Mortality and Cardiovascular disease in patients with adrenal insufficiency

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DECLARATION OF ORIGINALITY

I declare that the following work presented in this thesis is my own work unless indicated in text where previous literature is explicitly acknowledged and a list of references is provided. No part of this thesis has been previously submitted for another degree at this or other institutions.

Some of the results presented here have been presented at an international conference and published as conference proceedings.

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ABSTRACT

Increased risks for mortality and cardiovascular disease in primary and secondary adrenal insufficiency, and pituitary disorders have been inconsistently reported. Risk estimations have traditionally used national statistics as reference, with no matching for precise age, and time and place of clinical care of the patients and the reference population. This study evaluated risks for mortality and cardiovascular disease in patients with adrenal insufficiency of any type and, separately, primary and secondary adrenal insufficiency, by comparing with controls individually matched for sex, age, and time and place of care, using as the source of data a UK primary care database (Clinical Practice Research Datalink, CPRD). Additionally, established cardiovascular risk factors were taken into account.

The risk for mortality was increased in patients with adrenal insufficiency (HR, 1.68 [95% CI, 1.58-1.77]) including primary (HR, 1.83 [1.66-2.02]) and secondary adrenal insufficiency (HR, 1.52 [1.40-1.64]). From the first year, the mortality risk was significantly increased, in accordance with an early increase in hospitalisations from adrenal crisis. Cardiovascular disease was the leading cause of death but infections posed the greatest relative mortality risk. Risk for cardiovascular events was increased but was dependent on the presence of cardiovascular risk factors (unadjusted HR, 1.28 [1.20-1.36]; adjusted HR, 1.07 [1.01-1.14]). However, specifically for cerebrovascular disease in secondary adrenal insufficiency, risk was independently increased. Concomitant cardiovascular disease was associated with adrenal crisis-related death.

In conclusion, infections and adrenal crisis could account for the increased risk for mortality in adrenal insufficiency observed at the beginning of disease course. The risk for cardiovascular disease was also increased and could further contribute to adrenal crisis-related mortality. The interaction of the three factors: adrenal crisis, infections and cardiovascular disease, probably plays a part in the increased mortality of patients with adrenal insufficiency.

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LIST OF ABBREVIATIONS

11β-HSD	11β-hydroxysteroid dehydrogenase
11β-HSD1	11β-hydroxysteroid dehydrogenase subtype 1
11β-HSD2	11β-hydroxysteroid dehydrogenase subtype 2
95% CI	95% confidence interval
ALD	Alcoholic liver disease
ACTH	Adrenocorticotropic hormone
APS	Autoimmune polyglandular syndrome
BMI	Body mass index
CBG	Cortisol-binding globulin
CNT&RA	Connective tissue disease and Rheumatoid arthritis
CPRD	Clinical Practice Research Datalink
CRD	Current registration date
CRH	Corticotropin-releasing hormone
CVD	Cardiovascular disease
CYP3A4	Cytochrome P450 3A4
DM	Diabetes mellitus
GCR	Glucocorticoid receptor
GDPR	General Data Protection Regulation
GP	General practitioner
GPRD	General Practice Research Database
GU	Genitourinary system
HDL-c	High-density lipoprotein cholesterol
HES	Hospital Episode Statistics

HES APC	Hospital Episode Statistics Admitted Patient Care
HPA	Hypothalamic-pituitary-adrenal
HR	Hazard ratio
hs-CRP	high-sensitivity C-reactive protein
ICD-10	the 10th Revision of the International Classification of Diseases and Related Health Problems
ICD-9	the 9th Revision of the International Classification of Diseases and Related Health Problems
IHD	Ischaemic heart disease
IL-6	Interleukin 6
IMT	Intima-media thickness
IQR	Interquartile range
ISAC	Independent Scientific Advisory Committee
KIMS	Pfizer International Metabolic Database
LCD	Last collection date
LDL-c	Low-density lipoprotein cholesterol
LRI	Lower respiratory tract infection
MCCD	Medical Certificate of Cause of Death
MCR	Mineralocorticoid receptor
MHRA	Medicines and Healthcare products Regulatory Agency
NHS	National Health Service
NIHR	National Institute for Health Research
ONS	Office for National Statistics
OR	Odds ratio
PH test	Tests for departures from the proportional hazard assumption
POMC	Pro-opiomelanocortin
RR	Relative risk

SIR	Standardised Incidence Ratio
SMR	Standardised Mortality Ratio
TC	Total cholesterol
TG	Triglyceride
TNF-α	Tumour necrosis factor alpha
TOD	Transfer out date
TOR	Transfer out reason
UTI	Urinary tract infection
UTS	Up to standard date
VAMP	Value Added Medical Products
WC	Waist circumference
WHR	Waist to hip ratio

CHAPTER 1: INTRODUCTION

1.1 Background

Adrenal insufficiency is a state in which the adrenal glands are unable to produce sufficient glucocorticoids. Glucocorticoid replacement is the mainstay of treatment but the therapy appears to be unable to replicate physiology. Non-physiological doses of glucocorticoid may contribute to premature mortality and cardiovascular disease. Increased risks for mortality and cardiovascular disease have been reported in patients with primary adrenal insufficiency, and in pituitary disorders which are often concomitant with secondary adrenal insufficiency. However, there were also some inconsistent results. Almost all previous studies have evaluated the risks for mortality and cardiovascular events using 'Standardised Mortality Ratio, SMR' or 'Standardised Incidence Ratio, SIR', respectively. The number of deaths (or events) in the study patients is compared with that in the reference population. The number of deaths (or events) in the reference population is estimated from a national statistic of the general population having the same sex and age range as the study patients, over a specified period. In SMR (or SIR), there are discrepancies between parameters in the study patients and controls potentially interfering with the risk estimation. The discrepancies have included age and the geographical location and period of clinical care, as age was a major contributor to increased mortality and cardiovascular disease, and regional and temporal variation can affect the difference in the standard of care. In addition, using the SIR for cardiovascular disease is unable to take account of established cardiovascular risk factors such as previous cardiovascular disease, diabetes, and hypertension. Longitudinal studies using a matched reference population for correcting the discrepancies, and taking account of cardiovascular risk factors are needed to improve accuracy in the evaluation of risks for mortality and cardiovascular disease in patients with adrenal insufficiency.

1.2 Glucocorticoids

Glucocorticoids are steroid hormones produced by the adrenal cortex to control energy supply, fuel metabolism, blood pressure homeostasis and immune function, which are essential for survival. Glucocorticoids serve many basal functions during the resting state and also regulate various organ systems to respond to various stimuli. Glucocorticoids are regarded as the main homeostatic hormone responding to stress. The most biologically active endogenous glucocorticoid is cortisol.

1.2.1 Cortisol production and control

The hypothalamic-pituitary-adrenal axis (HPA axis) operates as a complex system consisting of: the hypothalamus, pituitary, and adrenal glands. The HPA axis regulation initially occurs at the hypothalamus which secretes corticotropin-releasing hormone (CRH) in a circadian rhythm. CRH plays a major role to stimulate the production of pro-opiomelanocortin (POMC), a peptide from the anterior pituitary where POMC is cleaved by prohormone convertase enzyme to generate a smaller peptide, adrenocorticotropic hormone (ACTH or corticotropin). ACTH then stimulates its target endocrine gland, the adrenal cortex, to produce and secret cortisol (Figure 1.1). ACTH is also essential for the maintenance of the adrenal cortex (tropic hormone for the adrenal cortex). ACTH secretion is pulsatile and, normally, the HPA-axis acts in a circadian fashion, resulting in a peak of plasma ACTH pulsatility and cortisol concentrations between 06.00-10.00h and a nadir of ACTH pulsatility at 18:00-24.00h (1, 2). Independently of the circadian rhythm, the HPA axis is activated by physical and emotional stresses such as hypoglycaemia, hypotension, an intercurrent illness, fear, or pain, which can abruptly increase cortisol to higher than normal levels (3, 4).

In addition to downward regulation from the hypothalamus, the adrenal cortex is able to upwardly control the HPA axis by a feedback loop involving both negative and positive

feedbacks (Figure 1.1). The negative feedback occurs when there is an excess of glucocorticoids, which can be administered exogenously or produced by the adrenal gland. Glucocorticoid excess inhibits hypothalamic CRH and pituitary ACTH production and secretion, which consequently decreases adrenal cortisol production. The positive feedback occurs when there is glucocorticoid depletion. This state stimulates CRH and ACTH production and secretion, thereby enhancing adrenal cortisol production. The feedbacks are a natural mechanism to control adrenal cortisol production and secretion, and maintain appropriate cortisol levels when various stresses are encountered.

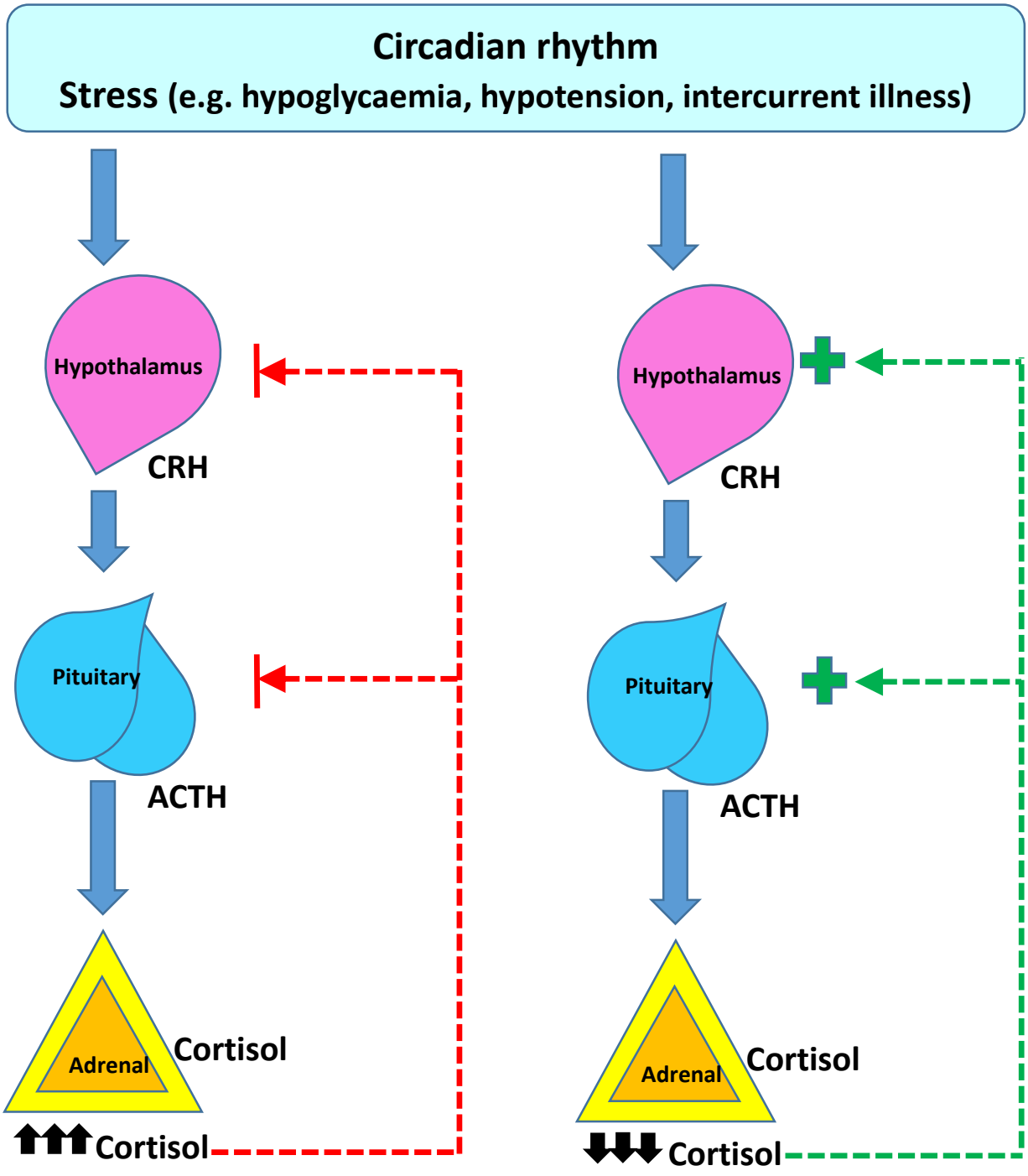


Figure 1.1: Regulation of the hypothalamic-pituitary-adrenal axis.

Note: CRH, corticotropin releasing hormone; ACTH, adrenocorticotropic hormone

1.2.2 Cortisol transport and metabolism

Similar to other steroid hormones, cortisol is lipophilic and requires binding proteins for transport via the bloodstream. The principal binding protein of cortisol is cortisol-binding globulin (CBG), synthesised by the liver. Although CBG comprises only a minor proportion of plasma proteins, it binds up to 90% of circulating cortisol with a high-affinity conformation (5). Cortisol binding to albumin accounts for 10-15% of cortisol, and 2.5-5% of cortisol is in free, i.e. unbound, form (5). CBG plays a vital role in transporting and releasing cortisol to its target tissues. Only the released, free cortisol is able to enter the target cells and stimulate the glucocorticoid receptor (Figure 1.2).

Cortisol metabolism and action are critically controlled by the activity of the 11β-hydroxysteroid dehydrogenase (11β-HSD) enzyme. 11β-HSD is located in the cytoplasm to modulate the action of cortisol on its nuclear receptor. 11β-HSD consists of two isoforms: subtype 1 (11β-HSD1) and subtype 2 (11β-HSD2) (6, 7). 11β-HSD1, principally produced in the liver, converts cortisone, an inactive glucocorticoid, to cortisol (Figure 1.2). 11β-HSD1 is also widely expressed in adipose tissue (8), enabling cortisol to act locally in a specific fashion; for example, by stimulating omental adipocyte differentiation (9, 10). Local 11β-HSD1 activity facilitates cortisol actions on tissues at the pre-glucocorticoid receptor level (9-11). Because of the synergistic action of 11β-HSD1, serum cortisol level may not be the only indicator of cortisol actions. 11β-HSD1 can also convert other inactive glucocorticoids to active glucocorticoids, such as prednisone to prednisolone (12) and the active glucocorticoids can act on the glucocorticoid receptor (3, 13). Meanwhile, 11β-HSD2, widely expressed in tissues containing the mineralocorticoid receptor (MCR), such as the kidney, acts in opposition to 11β-HSD1 by changing cortisol into inactive cortisone. This action inhibits cortisol from binding to the MCR and thus enables aldosterone to stimulate the MCR (Figure 1.2). Although blood

concentrations of cortisol are approximately 1000 times higher than aldosterone, and cortisol and aldosterone have a similar affinity for the mineralocorticoid receptor, mineralocorticoid effects of cortisol are minimised by the deactivating action of 11β-HSD2 (3).Therefore, this can be considered to be a 'life-protection' mechanism from the overstimulation of mineralocorticoid receptors by cortisol (6, 7). Accordingly, both 11β-HSD subtypes are important regulators of cortisol actions at the pre-receptor level.

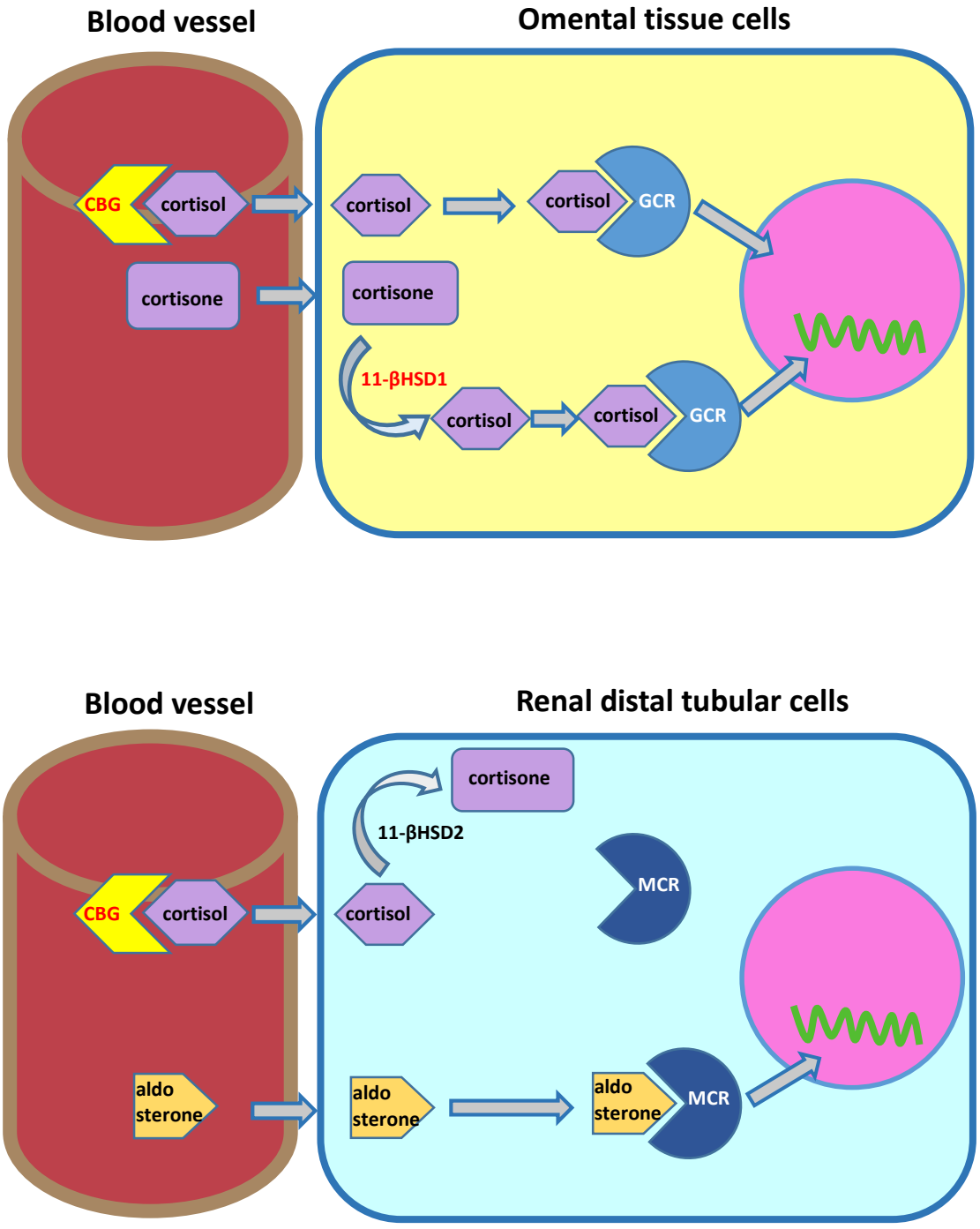


Figure 1.2: Cortisol action and target tissues

Note: CBG, cortisol binding globulin; GCR, glucocorticoid receptor; MCR, mineralocorticoid receptor; 11-βHSD1, 11-β hydroxysteroid dehydrogenase type 1; 11-βHSD2, 11-β hydroxysteroid dehydrogenase type 2

1.2.3 Glucocorticoid actions

Cortisol and other glucocorticoids affect various tissues by binding to the glucocorticoid receptor, which acts in concert with its various gene transcription co-repressors and co-activators. The most important glucocorticoid actions, which are essential for life, are the regulation of fuel metabolism and the cardiovascular system.

Metabolically, cortisol elevates and maintains blood glucose by stimulating hepatic glucose output and inhibiting glucose consumption from peripheral tissues (3, 4). Glucocorticoids directly stimulate hepatic gluconeogenesis (3, 4) and also increase the amount of substrates for hepatic gluconeogenesis by promoting the release of amino acids and glycerol from peripheral tissues such as skeletal muscle and adipose tissues (3, 4). Glucocorticoids indirectly increase hepatic glucose output by promoting hepatic glycogen storage to prepare for glycogenolysis. Glycogenolysis, stimulated by glucagon and epinephrine in response to acute stress, is another mechanism for hepatic glucose output (4). In addition to increasing hepatic glucose output, glucocorticoids inhibit glucose uptake from the peripheral tissues (3, 4). All these mechanisms promote increasing blood glucose levels.

Another vital glucocorticoid action is raising and maintaining blood pressure. Glucocorticoids affect numerous cells of the cardiovascular system such as vascular smooth muscle cells and the myocardium by improving their sensitivity to intrinsic and extrinsic vasopressors such as catecholamines and angiotensin II (3, 4). These effects contribute to vasoconstriction and increased cardiac output (positive inotropic effect), thereby increasing blood pressure.

These glucocorticoid actions are considered to be a permissive effect, in which glucocorticoids prime various tissues and organ systems for maintaining normal homeostasis under normal condition and promptly responding to stressful conditions (3, 4). The strength of the effect

depends on glucocorticoid tissue concentrations (14). Individuals whose HPA axis fails to increase appropriate glucocorticoid levels are unable to overcome stresses and can suffer from hypoglycaemia or hypotension (details in section 1.5.5 Adrenal crisis).

1.3 Adrenal insufficiency

Adrenal insufficiency (Adrenal failure, Hypocortisolism, or Hypoadrenalism) is an uncommon disorder in which the adrenal glands are unable to produce sufficient glucocorticoids. The most important glucocorticoid is cortisol, which is vital for regulating metabolism and hemodynamic function. Adrenal insufficiency is classified into two types: primary and secondary adrenal insufficiency, which depend on the location of the defect and mechanism of disorder.

Primary adrenal insufficiency (or Addison's disease) is caused by an adrenal gland defect that renders the adrenal glands unable to produce sufficient glucocorticoids despite being stimulated by ACTH. Primary adrenal insufficiency is characterised by elevated CRH and ACTH, caused by the response of the hypothalamus and pituitary to low glucocorticoid levels (positive feedback). Since there is a defect in the adrenal glands, primary adrenal insufficiency is accompanied by deficiencies in mineralocorticoids and adrenal androgens. Common causes of primary adrenal insufficiency are autoimmunity in developed countries and tuberculous adrenalitis worldwide (3, 15). Prevalence and incidence rates of primary adrenal insufficiency have been estimated at 82-140 per million and 2-6.5 per million per year, respectively (16-20).

Secondary adrenal insufficiency is caused by disruption of the HPA axis resulting in ACTH levels that are too low or inappropriately normal. Inadequate ACTH results in failure to stimulate adrenal glucocorticoid synthesis or its trophic effect on the adrenal cortex. Although both primary and secondary adrenal insufficiency are associated with inadequate glucocorticoid levels, there are many ways in which the secondary condition differs from primary adrenal insufficiency. First, secondary adrenal insufficiency is associated with hypothalamic-pituitary disorders and is often accompanied by deficiency in other pituitary hormones such as growth hormone, gonadotropins, thyrotropin, or vasopressin. Second, patients with secondary adrenal insufficiency can produce some glucocorticoids after the administration of a high dose of ACTH especially in the early course of disease before the

adrenal glands become atrophied (3, 15), which is in contrast to primary adrenal insufficiency. Third, the production and secretion of aldosterone remain intact in secondary adrenal insufficiency since the hormone is primarily regulated by the renin-angiotensin-aldosterone system, independently of the HPA axis. The most common cause of secondary adrenal insufficiency is from suppression of the HPA axis signalling by prolonged use of exogenous glucocorticoids. In this condition, neither anatomical pathology of the hypothalamus or pituitary gland nor deficiency in other pituitary hormones is evident. Other common causes are pituitary adenoma and craniopharyngioma (21, 22). Prevalence and incidence rates of secondary adrenal insufficiency, estimated from the studies of patients with hypopituitarism and pituitary adenoma, have been estimated at 290-455 per million and 6-11 per million per year, respectively (23, 24).

Because glucocorticoids regulate several systems, both primary and secondary adrenal insufficiency patients usually experience general and non-specific symptoms such as fatigue, weakness, tiredness, loss of appetite, and weight loss. Some symptoms and signs are observed solely in patients with primary adrenal insufficiency, such as salt craving and hyperpigmentation as a result of mineralocorticoid deficiency and ACTH/ POMC excess, respectively. Non-specific laboratory findings can also be observed such as anaemia, eosinophilia, hypercalcaemia, and hyponatremia (3, 15). Hyponatremia can result from low total body sodium and water as a result of mineralocorticoid deficiency (observed in primary adrenal insufficiency) or dilutional hyponatremia from decreasing glomerular filtration rates and free water clearance from glucocorticoid deficiency (observed in both primary and secondary adrenal insufficiency) (3, 15).

Although the progression and severity of symptoms are determined by the cause of adrenal insufficiency and the extent of the underlying pathology, these symptoms generally worsen

gradually, but there may be partial compensation such that the condition is not recognised for months or years (3, 15). Under diagnosis is aggravated by the low incidence of adrenal insufficiency, such that it may only become apparent much later in the context of a life-threatening condition such as shock, hypoglycaemia, or hypovolemia (3, 15, 25-27) (details in section 1.5.5 Adrenal crisis).

1.4 Physiological glucocorticoid replacement therapy remains unachievable

Glucocorticoid replacement therapy is the standard treatment for patients with adrenal insufficiency, the majority of whom require lifelong use. However, current glucocorticoid replacement appears unable to replicate healthy HPA axis function. Physiological cortisol production and secretion exhibit uniquely dynamic oscillations according to circadian rhythms that are themselves superimposed on ultradian rhythms (1, 2). The healthy HPA axis is also able to adapt to various stresses (3) but standard day to day glucocorticoid replacement does not replicate this. Beyond these physiological factors, clinical factors contribute to shortcomings in the treatment of adrenal insufficiency. These factors include variation in glucocorticoid types and doses, and in frequency and time of synthetic glucocorticoid ingestion (compounded by the short half-life of some synthetic glucocorticoids); interactions with other medications and other hormone replacement therapy; and the lack of robust markers for monitoring of glucocorticoid adequacy.

1.4.1 Types of glucocorticoids

To date, available synthetic glucocorticoids that have been used for replacement therapy are cortisone acetate, prednisolone, and hydrocortisone (28), which have different chemical properties. Their different properties can affect glucocorticoid bioavailability, transportation and metabolism and can lead to differences in glucocorticoid action.

Cortisone acetate, the first available synthetic glucocorticoid has been decreasingly used in clinical practice since it is biologically inactive and needs to be converted to active cortisol by the 11-βHSD1 enzyme (9-11, 29). Consequently, with cortisone acetate, glucocorticoid action may be delayed and suboptimal depending on the availability and biological activity of 11-βHSD1. This can cause poor treatment response in some adrenal insufficiency patients (30, 31).

Independently of 11-βHSD1, prednisolone can directly stimulate the glucocorticoid receptor and the glucocorticoid potency of prednisolone is four times higher than that of hydrocortisone (3, 32). In addition, prednisolone has a binding affinity for CBG lower than cortisol especially in long-term use and this can alter the glucocorticoid transportation (3, 32) and eventually its tissue effects. However, prednisolone is inactivated by the 11-βHSD2 enzyme at a higher rate than cortisol (12, 33). In tissues with high expression of 11-βHSD2, glucocorticoid action in patients using prednisolone may, therefore, be suboptimum (12, 33) and the glucocorticoid action of prednisolone may differ from tissue to tissue.

Hydrocortisone, the synthetic glucocorticoid identical to endogenous cortisol, has become the standard choice for glucocorticoid replacement therapy (34, 35). Hydrocortisone has been shown to have high oral bioavailability with rapid absorption such that plasma cortisol levels peak after only an hour following hydrocortisone ingestion (36).

1.4.2 Doses, frequency, and time of glucocorticoid administration

Although hydrocortisone has been widely used (37-39), optimisation of dose, frequency and time of administration remains elusive. The appropriate hydrocortisone dosages should be 10-20 mg per day on the basis of physiological studies, which have shown the physiological cortisol production rates of healthy individuals of 5-8 mg/m^2/day (40-43). However, many real-world studies have reported that some adrenal insufficiency patients received hydrocortisone at doses of >25-30 mg per day (28, 44-46), raising the possibility of adverse effects from over-

dosing. In patients with primary adrenal insufficiency, a positive correlation has been reported between glucocorticoid dose and incidence of hypertension, although not type 2 diabetes or hyperlipidaemia (47). In patients with secondary adrenal insufficiency, hydrocortisone doses of 20 mg per day or more have been associated with increased waist circumference, LDL-cholesterol, and triglyceride levels (44) and doses of 25-30 mg per day or more have been associated with increased all-cause mortality (45, 46, 48, 49).

Attempts to reproduce the highly variable diurnal profile of cortisol levels have been confounded by the conflicting factors of the short half-life of hydrocortisone, the need to minimise cortisol exposure and the need to achieve an effective response. Cortisol levels remain out of the physiological range because of the short half-life of hydrocortisone. After the first dose on awakening, in a twice-daily regimen, cortisol levels in patients with adrenal insufficiency can surge to a supraphysiologic peak in a few hours and later drop in 4-6 hours to the subphysiologic or undetectable levels in the afternoon (50, 51). To minimise the undesirable peaks and troughs of cortisol levels, hydrocortisone has been administered 3-4 times a day (51). However, even with thrice daily dosing, cortisol levels in many patients remain suboptimal throughout the day (52).

1.4.3 Altering glucocorticoid effects by other medications

Co-administration of other medications with glucocorticoids can affect the levels of glucocorticoids. Glucocorticoids are metabolised in the liver (3) by an important family of enzymes, cytochrome P450 3A4 (CYP3A4), the activity of which can be affected by other medications. Patients using strong CYP3A4 inducers such as carbamazepine, phenytoin, rifampicin and mitotane can have reduced cortisol levels and may require higher glucocorticoid replacement doses (32, 53). Strong CYP3A4 inhibitors such as macrolides and nondihydropyridine calcium channel blockers can increase cortisol levels (53). Therefore, in patients with adrenal insufficiency using these medications cortisol levels should be monitored.

1.4.4 Altering glucocorticoid effects by other hormonal replacements

Co-administration of other hormones can also influence glucocorticoid metabolism, and this is an important consideration in patients with secondary adrenal insufficiency who frequently have other hormone deficiencies. In patients commencing growth hormone replacement therapy, the urine cortisol to cortisone metabolite ratio may be decreased (54, 55), indicating a reduction of 11β-HSD1 activity (56). Growth hormone therapy can also uncover mild secondary adrenal insufficiency (57). Signs and symptoms of worsening adrenal insufficiency should be closely monitored and glucocorticoid replacement doses may need to be increased in patients with secondary adrenal insufficiency initiating growth hormone therapy (35). In patients with hypothyroidism, decreased cortisol clearance has been demonstrated in the absence of changes in endogenous cortisol production, cortisol circadian rhythmicity, or CBG levels; however, impaired cortisol clearance was reversible after initiating levothyroxine (58). Thyroid hormone replacement therapy can also precipitate adrenal crisis in untreated adrenal insufficiency patients (59-61). It is therefore recommended that, in patients with adrenal insufficiency accompanied by hypothyroidism, glucocorticoid replacement should be established before commencing thyroid hormone replacement (35). However, it is not known whether glucocorticoid doses need to be increased in known adrenal insufficiency patients who are later treated with levothyroxine. Oral administration of oestrogen can increase hepatic production of CBG (62, 63), which can interfere with the accurate assessment of glucocorticoid availability on the basis of serum cortisol levels. No such interference is observed in patients using transdermal oestrogen (64, 65).

1.4.5 Limitations of the assessment of glucocorticoid levels and effects

Assessment of glucocorticoid adequacy on the basis of, for example, a serum cortisol day curve or 24 hour urine free cortisol, has been used in some centres (51). However, no monitoring approach is fully reliable and monitoring may be unfeasible in routine clinical practice (26).

Measuring serum total cortisol is inadequate since only free cortisol is active. Moreover, spot measuring of serum cortisol or a cumulative measure of 24-hour urine free cortisol are inadequate since they cannot evaluate variation in cortisol production and secretion throughout the day. Furthermore, cortisol action on target tissues is critically controlled by 11-βHSD, which is mainly expressed in glucocorticoid target cells (7, 8, 11, 12, 29, 33). The activity of 11β-HSD1 of patients with adrenal insufficiency may not be equivalent to healthy individuals and exogenous administration of hydrocortisone could increase the activity of local 11β-HSD1 in glucocorticoid sensitive tissues such as adipocytes (66). Consequently, glucocorticoid action in patients using glucocorticoid replacement therapy cannot be precisely evaluated. In normal practice, it is recommended that the adequacy of glucocorticoid replacement should be evaluated by the clinical assessment of symptoms and signs of under or over-replacement (34, 35). However, clinical assessment is subjective and determined by doctor's clinical experience. Also, patients have frequently reported feeling better with higher glucocorticoid doses and this might have contributed to overdosing.

Although attempts have been made to replicate a healthy HPA-axis by prescribing weight-based (67) and multiple daily doses (51, 67) of hydrocortisone, patients often experience symptoms of excess and/or inadequate glucocorticoid action. These symptoms are associated with low quality of life (68, 69), sleep disturbance (70), compromised work and social life (37), and increased risk of affective depressive disorders (71). Long-term exposure to inadequate glucocorticoid replacement can cause symptoms and signs of adrenal insufficiency such as malaise, postural hypotension, loss of appetite, and weight loss. In addition, inadequate glucocorticoid during acute severe stress can lead to a life-threatening condition, adrenal crisis (details in section 1.5.5 Adrenal crisis). Long-term exposure to excessive glucocorticoids can cause symptoms and signs of Cushing syndrome, which include osteoporosis, weight gain, central and visceral fat accumulation, insulin resistance, hypertension, hyperlipidaemia, and

eventually cardiovascular disease. Both adrenal crisis and cardiovascular disease can contribute to increased mortality in patients with adrenal insufficiency.

Difficulties in achieving physiological cortisol levels in patients with adrenal insufficiency have led some investigators to develop and assess the value of modified-release glucocorticoid preparations, but these have not been widely adopted in clinical practice. A detailed description of these preparations and their potential is beyond the scope of this thesis introduction.

1.5 Mortality in patients with adrenal insufficiency

Before glucocorticoid replacement therapy was widely available, 80% of patients with primary adrenal insufficiency died within two years and all patients died within five years after diagnosis (72). It has previously been assumed that the life expectancy of patients with adrenal insufficiency normalised after a synthetic glucocorticoid was used (72). However, population-based studies have reported increased mortality in patients with primary adrenal insufficiency (73-75) and hypothalamic-pituitary disorders, in which adrenal insufficiency is prevalent (23, 76-82).

Currently available information on mortality has mainly been based on derivation of a standardised mortality ratios (SMR) by comparing mortality among patients with adrenal insufficiency with mortality in a comparable population derived from national database information. An SMR is the ratio of observed deaths in the patient population to the expected number of deaths in the general population from which the patients were drawn (83, 84). The expected number of deaths is given by the summation of the expected numbers of deaths in the general population with equivalent proportions according to sex and number of patients in each age range. An SMR of over one indicates an increased mortality risk relative to the reference population.

1.5.1 All-cause mortality in patients with primary adrenal insufficiency

In patients with primary adrenal insufficiency, all-cause mortality rates have been reported in four population-based studies conducted in Sweden and Norway (Figure 1.3). In 2006, the first population-based study of primary adrenal insufficiency included 1675 Swedish patients and showed the SMRs for all-cause mortality of 2.19 (95% CI, 1.91-2.51) and 2.86 (95% CI, 2.54-3.20) for men and women, respectively (73). In 2008, a larger Swedish study including 3299

patients with autoimmune primary adrenal insufficiency confirmed a similar SMR of 2.70 (95% CI, 2.60-2.80) (74). However, in 2009 a Norwegian study in 811 patients with primary adrenal insufficiency found a non-significantly increased SMR of 1.15 (95% CI, 0.96-1.35) (19). The inconsistencies in SMR results could not be accounted for by differences in place and time, because all studies were conducted in Scandinavia during a similar time period, in which similar standards of care would be expected. It should be noted that SMRs may not represent the actual mortality risks relative to the general population since regions and periods of care for the patient group might differ from those for the reference population.

Recently, in 2017 a Swedish population-based study found a considerably increased mortality risk among 226 patients with primary adrenal insufficiency who had diabetes mellitus compared with 1129 matched controls with diabetes (HR, 3.89 [95% CI 2.84-5.32]) (75). Although the study population was restricted to diabetes patients, it was conducted recently, during a period in which the quality of care would have been expected to have improved. The unexpectedly high hazard ratio emphasises that the mortality risks in patients with primary adrenal insufficiency need to be further evaluated.

Further limitations of previous studies include the lack of any evaluation of the influence of fludrocortisone replacement on mortality (19, 73-75), even though mineralocorticoid deficiency can worsen adrenal crisis in patients with primary adrenal insufficiency.

Another limitation of previous studies of primary adrenal insufficiency has been that all studies (19, 73-75) have used national database information in which biochemical testing to confirm a diagnosis of adrenal insufficiency was not recorded. Primary adrenal insufficiency is uncommon and, a large database, with prolonged follow-up is required to achieve sufficient

study power. Accordingly, inclusion based on hormonal testing at the time of diagnosis has not been practical in population-based studies. One small study reviewed hospital records and patients were further excluded if hormone levels at diagnosis were not compatible with adrenal insufficiency (19). However, among those diagnosed in the more distant past, hormonal evaluation was not performed and study inclusion was based on a record of signs and symptoms of adrenal insufficiency (19).

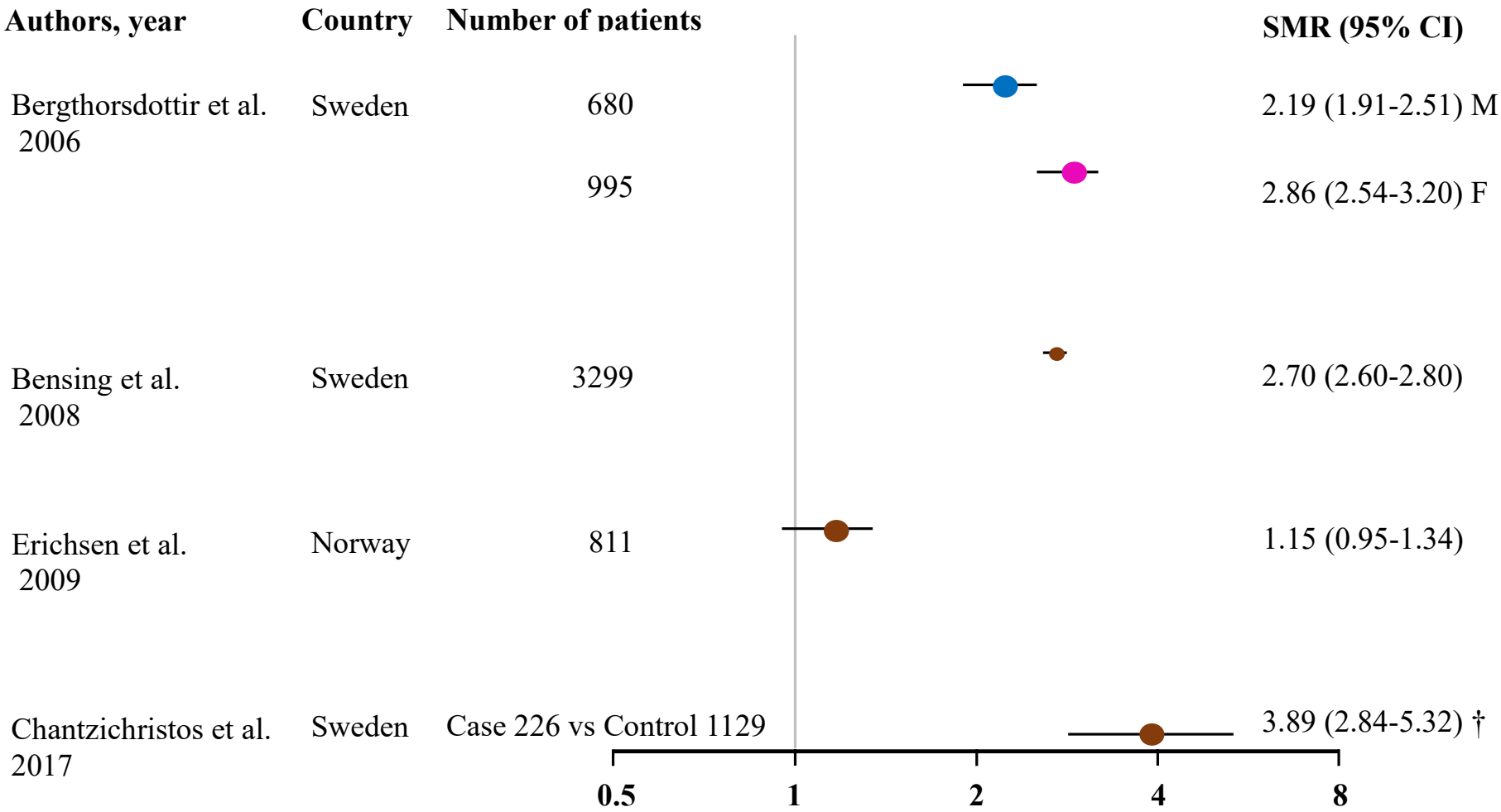


Figure 1.3: The studies of all-cause mortality in patients with primary adrenal insufficiency

Note: M-males; F-females; SMR-Standardised Mortality Ratio; † data reported in HR (95% CI), all participants had diabetes mellitus

1.5.2 All-cause mortality in patients with secondary adrenal insufficiency

Mortality risks associated with secondary adrenal insufficiency have been assessed mainly in patients with pituitary disorders (23, 49, 76-82, 85-90). The study populations varied, and could include patients with any pituitary hormone deficiency (76-78) - in particular growth hormone deficiency (79-81, 86, 89) - or hypothalamic-pituitary tumours (77, 85) - in particular pituitary adenoma (23, 49, 82, 87, 88, 90). The SMRs reported in these studies were 0.88-3.80 and, taken together, suggested a trend towards lower risk in recent years (Figure 1.4).

Four studies of mortality in patients with pituitary disorders have been conducted in the UK; however, the results were inconsistent (76, 78, 82, 85). In 1996, Bates et al. examined 172 patients with hypopituitarism (73% with adrenal insufficiency, 76% with pituitary tumours) treated in the metabolic unit of the North Staffordshire Hospital Center between 1967 and 1993 (76). The SMR (95% CI) for all-cause mortality was 1.73 (1.28-2.28) (76). In 1999, Bates et al. examined 348 patients with a sellar mass requiring pituitary surgery (94% with glucocorticoid replacement, 70% with at least one biochemically-confirmed pituitary hypofunction) from the Birmingham pituitary database between 1970 and 1992 (85). All-cause mortality after excluding perioperative death was not significantly increased (SMR, 1.2 [95% CI, 0.95-1.55]) (85). In 2001, Tomlinson et al. prospectively studied 1014 patients with hypopituitarism defined by at least one biochemically confirmed pituitary hypofunction (66% with non-functioning pituitary adenoma or prolactinoma, 76% biochemically-confirmed adrenal insufficiency) from the West Midlands Pituitary database between 1992 and 2000 (78). The all-cause mortality was reported with the SMR (99%CI) of 1.87 (1.62-2.16) (78). In 2016, Ntali et al. examined 546 patients with non-functioning pituitary macroadenoma requiring pituitary surgery (38% with biochemically-confirmed adrenal insufficiency) who were treated at the department of Endocrinology in Oxford during 1963-2011 (82). All-cause mortality,

including postoperative mortality, was markedly increased (SMR, 3.6 [95% CI, 2.9-4.5]) (82). This particularly high SMR was likely to have been caused by inclusion of patients with large pituitary masses who would have been at increased risk for postoperative death and treated during a period when pituitary surgery and care had yet to become well-established. In addition to the contradictory results, no UK study has reported the mortality risk of patients specifically with secondary adrenal insufficiency.

The mortality risks of patients with secondary adrenal insufficiency have been available in subgroup analyses of some studies (48, 49, 78, 81, 82, 86), although the reference information used differed between studies. Some studies reported SMRs by comparing with the general population (49, 78, 81, 82, 86) whereas another reported relative risk (RR) by comparing with study participants without adrenal insufficiency (internal comparison) (48).

In a comparison with the general population, the SMR in secondary adrenal insufficiency was not different from that in other patients with pituitary disorders who did not have hypoadrenalism in some (49, 78, 82) but not all studies (81, 86). Tomlinson et al. showed similar SMRs in patients with hypopituitarism who had and did not have secondary adrenal insufficiency (SMR, 1.82 vs 2.41; p for SMR difference, 0.3) (78). Ntali et al., primarily analysing patients with non-functioning pituitary macroadenoma, reported that the SMR (95% CI) of patients with secondary adrenal insufficiency was 4.0 (2.9-5.4), which was not different from the subgroup of patients without adrenal insufficiency (SMR, 3.3 [95% CI, 2.1-4.8]) (82). Recently, Hammarstrand et al. studied patients with non-functioning adenoma who received or did not receive glucocorticoid therapy and the SMRs of the two subgroups were not different (SMR, 0.88 [95% CI, 0.68-1.12] vs 0.87 [95% CI, 0.63-1.18]) (49). However, in the studies primarily examining the mortality of people receiving growth hormone therapy, the mortality

risk was further increased in those with accompanying adrenal insufficiency (81, 86). Among 6107 patients receiving growth hormone therapy for various reasons, 1419 had adrenal insufficiency and the SMR (95% CI) was 7.1 (6.2-8.2), which was higher than the total group (SMR, 3.8 [95% CI, 3.4-4.2]) (86). In 1286 patients with growth hormone deficiency receiving growth hormone replacement, the SMR (95% CI) of the subgroup of patients with secondary adrenal insufficiency was 1.53 (1.23-1.88), which was higher than that of those without adrenal insufficiency (SMR, 1.18 [95% CI, 0.80-1.68]) (81).

In an internal comparison, O'Reilly et al. compared the mortality risk of 318 patients with pituitary adenoma who had secondary adrenal insufficiency with 175 patients who had preserved HPA function (48). The mortality risk of adrenal insufficiency was significantly increased after adjustment for sex, age at diagnosis, attained age, surgery and radiotherapy (RR, 2.26 [95% CI, 1.15-4.47]) (48).

The mortality risk of patients with secondary adrenal insufficiency, available from the studies of patients with pituitary disorders, remain inconclusive, depending as they do on the primary study population. In the studies of pituitary disorders, the diagnosis of adrenal insufficiency has been defined in various ways, including biochemical testing (48, 78, 82), telephone interviews of glucocorticoid replacement (86), a medical record of signs and symptoms consistent with adrenal insufficiency (49), or not stated (81). In the studies using biochemical testing criteria, the number of participants was small, as adrenal insufficiency was a subgroup, not the primary population. Further analyses with a larger number of patients, exclusive to those with secondary adrenal insufficiency, are needed.

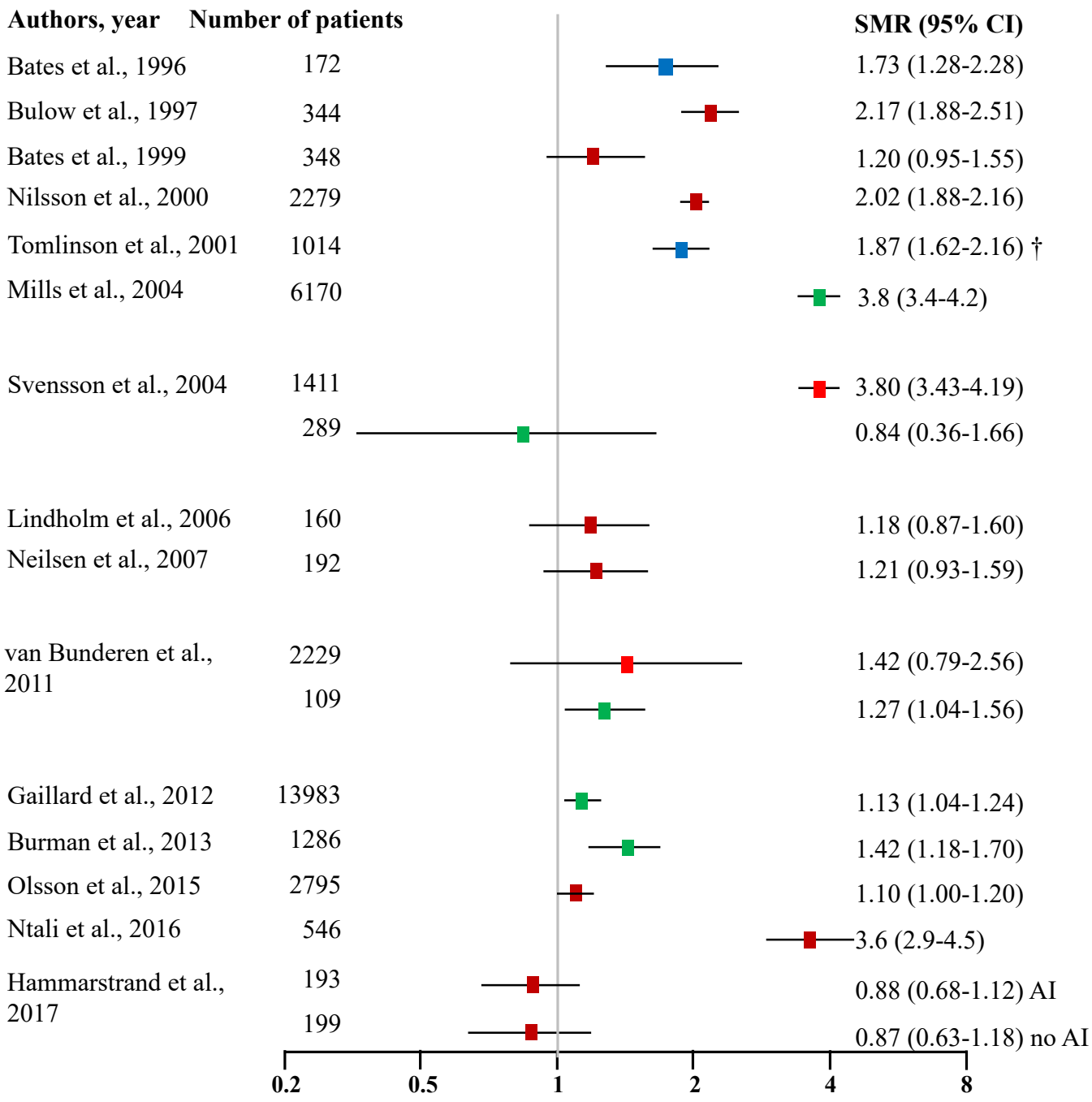


Figure 1.4: The studies of all-cause mortality in patients with pituitary disorders

Note: SMR-Standardised Mortality Ratio; AI-Adrenal insufficiency; no AI-no adrenal insufficiency; † range reported in 99%CI; colour codes for the primary study population: Green-growth hormone replacement; Red-no growth hormone replacement; Brown-Pituitary tumours; Blue-Hypopituitarism

1.5.3 Factors contributing to mortality risks in patients with adrenal insufficiency

Many factors have been reported to be associated with increased mortality in patients with primary adrenal insufficiency and hypothalamic-pituitary disorders. These include patients' age and sex, aetiology of adrenal insufficiency, other treatments for underlying causes of adrenal insufficiency, other hormonal deficiencies, prescribed glucocorticoid dosages, other comorbidities, and follow-up periods (duration of adrenal insufficiency). Moreover, one factor not related to patient characteristics is calendar time of study.

- ***Age***

In comparisons with the general population, the mortality risks of younger patients with primary adrenal insufficiency have been higher than those of older patients, although young and old age groups have been defined differently between studies (19, 74). Erichsen et al reported that the SMR of patients with primary adrenal insufficiency at age less than 40y was 1.50 (95% CI 1.09-2.01), which was higher than that of patients with adrenal insufficiency at any age (SMR, 1.15; [95% CI, 0.96-1.35]) (19). Bensing et al observed the highest mortality risk among patients with autoimmune primary adrenal insufficiency at age less than 15 but the number of deaths was low (74). However, as might be expected, in an internal comparison of patients with primary adrenal insufficiency, Quinkler et al reported the average age of those who died was higher than that of patients who survived (91).

In patients with pituitary disorders, the mortality risk by age relative to the general population has differed across studies. Some (77, 78, 80, 89, 90) though not all (23, 82, 91, 92) studies have reported that younger ages have greater all-cause mortality risk than older ages. Some studies observed that the SMRs for all-cause mortality were not significantly increased in patients over 45 (89) or over 60 years (78, 80). Olsson et al reported a lower SMR in older than younger patients, although risk remained relatively increased (90). Bulow et al also reported a lower SMR in older patients but this was observed only for cerebrovascular not cardiac death

(77). In contrast, Nilsson et al reported excess mortality in patients with age at diagnosis of 40-69y (SMR 4.0 [95% CI 3.7-4.4]), which was higher than that of any age (SMR 2.0 [95% CI 1.9-2.2]) (23). In an internal comparison of patients with pituitary adenoma, Ntali et al reported that, as might be expected, those diagnosed after age 50y had a higher mortality rate than those diagnosed at younger ages (82). In this study, increased age was an independent predictor of mortality (HR 1.1 [95% CI 1.07-1.13] per one-year increment of age at diagnosis) (82). Quinkler et al also reported, in an internal comparison of patients with secondary adrenal insufficiency, the average age of those who died was higher than that of survivors (91). In contrast, Brada et al, in an internal comparison of patients with pituitary adenoma, age at hypothalamic-pituitary irradiation was not associated with increased cerebrovascular mortality (92).

In comparisons with the general population, the available evidence suggests that mortality risks are greater in younger aged patients. In internal comparisons within patient groups, risks associated with increasing age may still be distinguished, although findings are inconsistent.

- ***Sex***

The mortality risk of patients with primary adrenal insufficiency relative to the general population was not different between sexes in some studies (73, 74). However, also in a population-based study, Erichsen et al reported that median age at death in men with primary adrenal insufficiency was 11.2 years earlier than expected life expectancy at diagnosis but only 3.2 years earlier in women (19). In an internal comparison within patients with primary adrenal insufficiency, Quinkler et al reported the proportion of men among those who died was similar to proportion of men who survived, suggesting no influence of sex on mortality in this patient group (91).

In patients with pituitary disorders, the all-cause mortality risk relative to the general population (SMR) in men was lower than women in most studies (23, 76-81, 87-90, 93). In

some of these studies, the risk in men did not differ from that in the general population (80, 87-90, 93). The SMR for cerebrovascular disease was also reported to be higher in women (92). In contrast, a study of patients with pituitary tumours undergoing surgery showed no difference between sexes in SMRs for all-cause mortality (85). In an internal comparison within patients, some studies observed that sex was not a predictor of death (48, 82). In an internal comparison between patients with secondary adrenal insufficiency, Quinkler et al reported the proportion of men was higher in those who died than that in those who survived (91).

Similar to the findings according to age, sex difference in mortality risk in patients with adrenal insufficiency differs across the studies. The findings depended on study methodology and reference populations. However, the majority of evidence supports increased mortality in women with pituitary disorders and a number of reasons have been proposed to explain this. Nielson et al noted that pituitary hormone deficiency was less frequently reported in women than in men (88), which suggested that a higher proportion of women might have missed appropriate hormone replacement (94). Oral oestrogen therapy reduces hepatic production of insulin-like growth factor I (IGF-I) (95), which can contribute to decreasing lean body mass (96). This can have an adverse effect in patients with pituitary defects because the low IGF-1 level cannot stimulate growth hormone secretion. Oral oestrogen administration has also been associated with increased central fat accumulation in patients with growth hormone deficiency (97) as a result of reducing lipid oxidation (98). These unfavourable effects on protein and lipid metabolism could be associated with increased cardiovascular disease. In addition, oral oestrogen can increase hepatic CBG production (62, 63) and thus interfere with assessment of glucocorticoid adequacy in patients with secondary adrenal insufficiency (details in section 1.4.4 Altering glucocorticoid effects by other hormone replacements). However, in principle, the adverse effects of hormonal interaction can be minimised by changing to non-oral

administration of oestrogen, monitoring IGF-1 levels, and adjusting growth hormone replacement doses accordingly.

- ***Aetiology of adrenal insufficiency***

Primary adrenal insufficiency is mainly caused by autoimmune disorders. To date, there is no information regarding the mortality risk specifically caused by other disease such as adrenal infection. Bensing et al evaluated the mortality risk of patients with autoimmune primary adrenal insufficiency (74). The SMR of patients with autoimmune polyglandular syndrome (APS) type I was significantly higher than that of those with APS type II (SMR, 4.6 [95% CI 3.5-6.0] vs 2.1 [95% CI 1.9-2.4]) (74). Patients undergoing bilateral adrenalectomy appeared to have a higher mortality risk compared with primary adrenal insufficiency from other causes, although the number was low (91).

In studies of patients with pituitary disorders, the SMR was higher in those with craniopharyngioma than in those with pituitary adenoma (78, 80, 89). Among these studies, some reported no increase in SMRs in patients with growth hormone deficiency caused by non-functioning pituitary adenoma (80, 89). However, more aggressive tumour lesions such as craniopharyngiomas or giant hypothalamic-pituitary tumours may be associated with increased risk, the SMR in a study evaluating this issue being 6.84 (95%CI 5.28-8.71) (80). Craniopharyngiomas are usually of greater size than pituitary adenomas. Craniopharyngiomas or giant hypothalamic-pituitary tumours are more likely to be treated by extensive surgery and/ or radiotherapy, so these more aggressive tumours may have been associated with other pituitary hormone deficiencies. In addition, aggressive tumours may involve the hypothalamus, at which the thirst centre and/or a production of anti-diuretic hormone can be disrupted and lead to severe hypovolemia. All these factors could contribute to the increased mortality risks observed in patients with craniopharyngioma or giant tumours.

- ***Other treatments for underlying causes of adrenal insufficiency***

In contrast to patients with primary adrenal insufficiency, those with pituitary disorders, in whom the major underlying cause is pituitary tumours, frequently have to undergo pituitary surgery and/ or irradiation. Although these interventions are the mainstay of treatment, they may themselves have an adverse effect on survival.

Type of pituitary surgery and the number of occasions on which it is carried out may affect mortality in patients with pituitary masses. The mortality risk relative to the general population of patients undergoing trans-cranial surgery has been reported to be higher than that of patients undergoing trans-sphenoidal surgery (78, 80, 81). Among those undergoing trans-sphenoidal surgery, mortality risk may even be reduced to that of the background population (80, 81). Debulking surgery was also associated with increased cerebrovascular mortality (92). In one study, however, no statistical difference in the SMR between different types of surgery has been reported but the numbers in each subgroup population was low (trans-sphenoidal surgery n=160; trans-cranial surgery n=32) (88). Regarding possible effects of multiple surgery, one study has suggested that patients having recurrent surgery had a higher SMR than those with a single surgery (90). In an internal comparison among patients, the extent or number of surgeries was not associated with increased mortality in patients with non-functioning pituitary adenoma (82).

Cranial irradiation might also influence mortality in patients with pituitary tumours. Some studies have observed higher all-cause mortality risks in patients with radiotherapy compared with those without (45, 80, 90). Cerebrovascular death appears to contribute most to the increased mortality risk associated with radiotherapy (78, 89). However, some studies reported no difference in SMR according to whether or not patients received radiotherapy (81, 82, 88). In an internal comparison among patients with pituitary tumours, cranial irradiation was not independently associated with increased mortality (48, 85).

The majority of the patients undergoing trans-cranial surgery or radiotherapy had large hypothalamic-pituitary masses; consequently, mass effects could have contributed to their increased mortality risks. These interventions can also cause pituitary hormone deficiencies, which may influence mortality.

- ***Other associated hormonal deficiencies and their replacements***

Patients with autoimmune primary adrenal insufficiency can have dysfunction of other endocrine glands, as in autoimmune polyglandular syndrome (APS). Bensing et al reported that the SMR was higher in patients with APS type I than type II (see section 1.5.3 Factor contributing to mortality risks in patients with adrenal insufficiency) (74). In this study, patients with APS type I had a higher proportion of hypoparathyroidism but lower proportions of hypothyroidism and type 1 diabetes (74). However, to date no data compared the mortality risks of primary adrenal insufficiency between those with and without hypothyroidism, hypoparathyroidism, or type 1 diabetes.

In patients with pituitary disorders, deficiencies in growth hormone, gonadotropins, thyrotropin, and anti-diuretic hormone including their replacement therapy can be responsible for the increased mortality. Among those with growth hormone deficiency, mortality risk (SMR) has been described as being higher than among those with intact growth hormone secretion, although the difference in SMRs was not statistically significant (78). Svensson et al. reported that mortality risk among patients receiving growth hormone replacement was no higher than in the background population, whereas it was significantly increased in those not receiving replacement (79). Some studies, mainly deriving from an international pharmaco-epidemiological registry (KIMS) (99), found that mortality risk in patients receiving growth hormone replacement remained elevated (80, 81, 89), although risk in men was not higher than in the background population (80, 89). The SMRs of patients with large non-functioning pituitary adenomas were reported to be similar between those treated and untreated with growth

hormone in some small studies (82, 87), although one study reported both groups had similarly increased SMRs (82) whereas another reported similarly low SMRs (87). Accordingly, growth hormone deficiency may be associated with increased mortality in patients with pituitary disorders but the survival benefit of growth hormone replacement has not been clearly demonstrated.

In pituitary disorders, hypogonadal patients had similar SMRs to those with eugonadism, observed in most (45, 76-78, 81, 85) but not all studies (48). In these analyses both hormone-treated and untreated hypogonadal patients were combined. However, in an additional analysis, one study specifically distinguished untreated hypogonadism and noted a higher mortality risk than eugonadism (78). One other study also specifically distinguished untreated hypogonadism but found risk increased only in women (87). In treated hypogonadal patients, the mortality risk has been reported to be similar to risk in eugonadism and lower than in untreated hypogonadism (78). However, some studies reported similar mortality risks whether or not the patients received sex hormone replacement (48, 82). Since these studies have been based on heterogenous study populations and the results were inconsistent, it remains unclear whether hypogonadism and/ or sex hormone replacement could affect mortality in patients with pituitary disorders.

Since thyroid hormone is essential to life, patients with thyrotropin deficiency generally receive thyroid hormone replacement. Most studies reported no increased mortality risk in those with hypothyroidism compared with those with normal thyroid function (45, 76, 78, 81, 82). However, in one study, lower doses of thyroid hormone replacement were associated with higher mortality risks in patients with non-functioning pituitary adenoma (48), patients receiving levothyroxine of less than 100 microgram per day having increased mortality whereas those receiving higher doses showing no increased risk (48).

In patients with pituitary disorders, mortality risks were increased in those having diabetes insipidus compared with those without (78, 80, 81, 90) and the risk appeared to be higher in women (90). However, one study reported no association between having diabetes insipidus and increased mortality (82). Many studies have shown increased mortality in patients with diabetes insipidus, although concomitant extensive pituitary masses and their treatment might have also contributed.

Regarding predictors of mortality in patients with non-functioning pituitary tumours, there are complex associations between aetiology of disease, other treatments for pituitary tumours, and other pituitary hormone deficiencies including their hormonal replacement. Underlying aetiology of pituitary disorders can reflect the size and extension of the mass. Other treatments for pituitary tumours such as methods of surgery and eligibility for radiotherapy are usually determined by the mass size and nature of disease. Degree of pituitary hormone deficiencies are also usually affected by the mass size and the extent of surgical and/ or radiological interventions. Also, deficiencies of pituitary hormone can occur long after the interventions, and doses and types of hormonal replacement can be later changed. Any or all of these factors might have contributed to the excess mortality of patients with pituitary disorders and real-world, observational study designs cannot isolate their effects. Accordingly, the independent contribution of any single factor remains uncertain.

- ***Other comorbidities***

In primary adrenal insufficiency, the mortality rate of patients with diabetes mellitus has been reported to be higher than in those without (73) but this could reflect the increased mortality risk associated with diabetes, independently of adrenal insufficiency. In an internal comparison among primary adrenal insufficiency patients, the proportion of those with concomitant diabetes was higher in the deceased than in survivors but this might have resulted from the higher average age in the deceased (91). An increased mortality risk was reported in primary

adrenal insufficiency patients with diabetes mellitus, compared with the diabetes patients with normal adrenal function (HR 3.89 [95%CI 2.84-5.32]) (75) and this risk was two times higher than that previously observed in patients with primary adrenal insufficiency in general (19, 73, 74). One explanation is that in this study the patients with primary adrenal insufficiency had a longer diabetes duration and a higher proportion of diabetic complications (75). Also, the risk of severe or life-threatening hypoglycaemia might be further increased in diabetes with adrenal insufficiency. Further studies are needed to confirm whether diabetes mellitus can additively or synergistically increase all-cause mortality risks in patients with primary adrenal insufficiency. To date no study has examined all-cause mortality risk associated with hypertension in patients with primary adrenal insufficiency. However, one study reported that the proportion of hypertension among primary adrenal insufficiency patients who died was higher than among those still alive (91).

In patients with pituitary disorders, no study has examined the association between concomitant diabetes and all-cause mortality. In patients with growth hormone deficiency having replacement, the mortality risk was higher in those receiving anti-hypertensive drugs than those without the drugs (RR 1.38 [95%CI 1.13-1.38]) (80).

Currently, it remains unclear to what extent, if any, the increased mortality risk of patients with adrenal insufficiency is modified by having concomitant diabetes or hypertension.

- ***Adrenocortical steroid dosages***

In patients with primary adrenal insufficiency, to date no data on the association with high steroid replacement dosages and increased mortality has been reported. Nonetheless, Skov et al. examined the risk of cardiovascular events associated with hydrocortisone and fludrocortisone doses, where high dose was defined as an average dose of hydrocortisone/ fludrocortisone of 37.6/ 0.11 and 42.9/ 0.12 mg per day in women and men, respectively (100). The risk of cardiovascular events was significantly increased in women using high doses of

hydrocortisone and/ or fludrocortisone but not in men, although no information on weight-based doses was reported (100). Accordingly, women might have been relatively over-dosed and uncertainty remains as to whether sex can modify the dose-dependent effect on cardiovascular disease.

In patients with pituitary disorders, high glucocorticoid doses were first reported to be associated with increased mortality in acromegaly (45). Mortality risk was increased in acromegaly patients who had adrenal insufficiency and were receiving steroids equivalent to hydrocortisone doses of more than 25 mg per day (45). In those receiving lower doses, risk was indistinguishable from risk in those without adrenal insufficiency (45). This finding has been confirmed by a few studies of patients with non-functioning pituitary adenoma, in which the mortality risk was increased in those using hydrocortisone higher than 20 (46, 49) or 30 mg per day (48) but was not increased at lower doses. The increased all-cause mortality related to high steroid doses was believed to be caused by increased cardiovascular disease. In patients with growth hormone deficiency, those using daily hydrocortisone of 20 mg or more had a higher level of cardiovascular markers, consisting of high waist circumference, total cholesterol, and triglyceride, compared with those without steroids (44). However, no study has demonstrated an association between high steroid doses and increased risk of cardiovascular disease or cardiovascular mortality in patients with pituitary disorders. The proportions of cardiovascular death (45, 46) and diabetes and hypertension (46) were not statistically different between patients with pituitary disorders using the different glucocorticoid doses and those without steroids. Unexpectedly, the proportion of patients with dyslipidaemia was lowest in those receiving the highest glucocorticoid doses (46).

High glucocorticoid doses were associated with increased all-cause mortality in patients with secondary adrenal insufficiency but there are no data in primary disease. However, it was not known whether cardiovascular disease contributed to the increased mortality risk. Another

possible explanation is that patients who used high glucocorticoid doses were likely to have a smaller reserve of HPA function and they might have had an increased risk of adrenal crisis and death. In addition, high glucocorticoid doses may increase the risk of infection as this has been observed in patients using steroids for other therapeutic reasons (101).

- ***Follow-up period (Duration of adrenal insufficiency) and calendar years of the study (Historical period of medical care)***

In patients with primary adrenal insufficiency, the mortality rate was observed to be high during the first few years of follow-up but no details of numbers of deaths nor of mortality risk were reported (73, 75). Bensing et al, however, reported the SMR remained increased until 19 years but provided no details of variation in magnitude of risk with time (74). Quinkler et al. reported the average duration of primary adrenal insufficiency was similar in deceased and alive patients (91).

In patients with pituitary adenoma, some studies reported increased all-cause mortality rates in those having a follow-up period of 10-15 years, compared with those having a shorter follow-up period (23, 90). The SMR (95%CI) was increased from 1.07 (1.03-1.54) to 1.69 (1.24-2.24) when the follow-up period increased from less than 5 years to more than 10 years but this was observed only in women (93). Some reported the risks of cerebrovascular mortality did not differ according to difference in follow-up periods (77, 92). In patients with secondary adrenal insufficiency, the average duration of disease in those who died was not different from those alive (91). The increased mortality rates and risks in patients with long follow-up periods may reflect a different standard of care between the calendar years. Patients with longer follow-up periods were likely to attend medical care in earlier years, when a lower standard of care may have been expected, compared with those attending recent care with shorter follow-up periods.

With regard to primary adrenal insufficiency, there appears to be no information as to whether or not mortality risk has varied according to historical period of care. However, in patients with pituitary adenoma, a lower mortality risk has been observed in those receiving their care in more recent years (93). The lower mortality risk may reflect an improvement in standard of care for adrenal insufficiency while standards of care have also improved in the general population. The SMRs derived from comparisons with the national database information did not match for calendar time of medical supervision and, therefore, may not represent the actual mortality risk.

1.5.4 Causes of death in patients with adrenal insufficiency

The causes of death in patients with adrenal insufficiency can be considered from two perspectives: the absolute mortality rates and the mortality risk relative to the reference population. The primary (principal) cause of death has been reported according to the organ systems, with major causes of death consisting of: 1) disease of the circulatory system, 2) neoplasm, 3) disease of the respiratory system, 4) infectious disease, and 5) endocrine system disorder.

- ***Circulatory system***

In patients with primary adrenal insufficiency, cardiovascular disease has been the leading cause of death in all mortality studies, comprising approximately 30-50% of total deaths (19, 73-75, 91). Cardiovascular disease was also the leading cause of death in the general population (19, 73) or controls (75). However, some (73) but not all studies (19, 75) reported that the risk of death from cardiovascular disease was increased relative to the general population (details in the section 1.6.4 Cardiovascular mortality in patients with adrenal insufficiency).

The majority of the studies in patients with pituitary disorders report the leading cause of death as cardiovascular disease (23, 48, 49, 76-78, 80-82, 85, 88, 90), similar to primary adrenal insufficiency. However, the risk of cardiovascular mortality relative to the general population, was increased only in some (23, 77, 90) rather than all studies (76, 80, 81, 85, 88, 89). One study reported that the risk of cardiovascular mortality was increased only in women (89). The relative risk was predominantly due to increased death from cerebrovascular disease (77, 80, 89, 92) (details in section 1.6.4 Cardiovascular mortality in patients with adrenal insufficiency).

- ***Neoplasm***

In patients with primary adrenal insufficiency, neoplasm was, if not the leading cause of death, then at least a contributor (19, 73-75), with approximately 20% of total deaths for any neoplasm (74) and 13-14% for malignancy (19, 73). The risks of death from any neoplasm (74) or malignancy (73), relative to the general population, were observed to be increased. There appeared to be no sex difference in the risk of death from malignancy (SMR, women, 1.47 [95%CI 1.03-2.02] vs men, 1.61 [1.13-2.23]) (73). However, in some studies the percentage of deaths from malignancy in patients with primary adrenal insufficiency appeared to be lower than that in the general population (19) or in matched controls with diabetes (75).

In patients with pituitary disorders, some studies reported that malignant neoplasm was among the leading cause of death, approximately 23-30% of total deaths (80-82, 85, 88, 89). The risk of death from malignancy was similar to the general population in most studies (78, 80, 81, 86, 88-90) but was increased in some studies with the SMRs (95%CI) of 1.71 (1.21-2.37) and 1.46 (1.23-1.72) (23, 77). In one study, the risk of death from malignancy in patients with non-functioning pituitary adenoma appeared to be decreased (SMR, 0.76 [95%CI 0.61-0.94]) (90). Another study reported increased risk of death from malignancy only in women (SMR, women, 3.21 [95%CI 1.46-6.11] vs men, 0.53 [0.11-1.54]) (76). When benign neoplasms were

separately considered, the risk relative to the general population was significantly increased (23, 81). Death from neoplasm, mainly pituitary tumours (23, 77), was likely to be recorded as the primary cause of death, resulting in a very high SMR in patients with known pituitary disorders (23, 80). However, cranial radiation might have also contributed to the increased mortality from neoplasm in the brain (92).

- ***Respiratory system***

In patients with primary adrenal insufficiency, studies of mortality due to disease of the respiratory system are fewer than for cardiovascular disease. Death from respiratory disease was approximately 9% of total deaths (73, 74). The mortality risk appeared to be increased (73, 74) but one study observed this only in women (SMR, women, 3.74 [95%CI 2.52-5.34] vs men, 1.74 [0.97-2.87]) (73).

In patients with pituitary disorders, death from respiratory disease was reported to be 3-19% of total deaths (23, 48, 49, 77, 78, 80, 81, 85). Pneumonia accounted for 6-7 in 10 deaths from disease of the respiratory system (81, 85). The relative risk of death from the respiratory system was increased with SMRs of 2.05 to 2.49 (77, 78, 81). However, the relative risk was similar to the general population in some studies (23, 80).

- ***Infectious disease***

In patients with primary adrenal insufficiency, 'infection' has been reported as being responsible for 2-10% of total deaths (19, 73, 75). However, in one study in which infections were distinguished according to identified infectious disease pathogen and organ system infection (e.g. pneumonia, infective diarrhoea, urinary tract infection), the number of deaths from infection was increased from 2% for pathogen-identified alone to 7% for pathogen-identified plus organ system infection; and the major cause was pneumonia (73). The risk of

death from infectious disease in patients with primary adrenal insufficiency was approximately 5 times higher than the general population (73, 74). No sex difference in the relative risk was observed (73).

In patients with pituitary disorders, infectious disease was reported to be 3-30% of total deaths (23, 48, 49, 80-82, 90). The difference in percentages might be due to the difference in the source with which the cause of death was established. Use of chart reviews and direct contact with primary care doctors could have increased the number of instances in which death was ascribed to infection (48, 82). In addition, including infections reported based on the organ system also increased the number of infection deaths (48, 81, 82), similarly to the finding in primary adrenal insufficiency. It was noted that almost all patients who died from infection had secondary adrenal insufficiency (80, 81). The relative risk was increased in some studies with the SMRs of 2.08 to 4.97 (80, 90) but the risk was not significantly increased in some studies (23, 81). However, the SMR was increased and became significant after infectious disease based on organ systems was combined with infection with an identifiable organism (SMR, 6.32 [95%CI 3.36-10.8]) (81).

- ***Endocrine disease***

In patients with primary adrenal insufficiency, death recorded as being from disease of the endocrine system was approximately 8-13% of total deaths (73, 74). The relative risk of death from endocrine disease was up to ten times higher than the general population (SMR 10.9 [95%CI 9.1-12.9]) (74). A possible explanation for the high SMR was that the majority of recorded deaths in the endocrine system was from adrenal failure (19, 73). Recording death from adrenal failure was possibly influenced by the patients' underlying disease. Also, the term of 'adrenal insufficiency/ failure' might have been used, instead of 'adrenal crisis'. For example, Bergthorsdotti et al found that among 507 deceased patients with primary adrenal

insufficiency, no adrenal crisis was recorded but 15 patients were recorded as having died from adrenal failure (73). In addition, death from adrenal crisis might have not been distinguished from unknown or infectious causes of death, which were prevalent among deceased patients (75, 91). Therefore, adrenal crisis might have been under-recorded as a cause of death (details in section 1.5.5 Adrenal crisis). Regarding death from diabetes mellitus, the percentage of deaths in patients was not different from the general population (19). One study reported a higher mortality rate from diabetic complications in patients with primary adrenal insufficiency compared with controls who had diabetes, although at baseline the proportion of those having diabetic complications was higher in the patient group (75).

In patients with pituitary disorders, death from disease of the endocrine system was reported at 2-14% of total deaths (23, 77, 80, 81). The reported SMRs from disease of the endocrine system varied from 1.82 to 16.1 (23, 77, 80, 81). Similar to primary adrenal insufficiency, ascribing a cause of death might have been influenced by the established diagnosis of pituitary disorders. This was illustrated in a study of patients with pituitary adenoma receiving radiotherapy in whom mortality ascribed to pituitary and hypothalamic causes was substantially increased compared to mortality from a similar diagnosis in the general population (92). As for primary adrenal insufficiency, death from adrenal crisis in patients with pituitary disorders might have been overlooked or not been considered as the principal cause of death. Berman et al reported that secondary adrenal insufficiency might have been responsible for death in over a half of patients who were supposed to have died from infections (81). In addition, the death certificates of some patients inaccurately reported cardiovascular disease as the cause of death, but no evidence of the disease was found on the autopsy (81). Mills et al also reported that adrenal crisis might have contributed to a third of deaths in patients receiving growth hormone who had sudden and unexplained death (86).

In conclusion, from currently available evidence, precise all-cause and cause-specific mortality rates and risks of patients with adrenal insufficiency remained unclear. Most studies have used national database information from which actual mortality rates cannot be calculated. Furthermore, defining the cause of death for patients with adrenal insufficiency has been problematic, information having been obtained from death certificates, where the assigned cause of death was mainly based on clinical considerations, without post-mortem examination. Importantly, however, an autopsy is unable to confirm some causes of death, in particular adrenal crisis.

1.5.5 Adrenal crisis

Adrenal crisis (Addisonian crisis, acute adrenal failure, acute adrenal insufficiency) is a life-threatening condition of acute decompensation of hypocortisolism. Adrenal crisis can occur in patients with known adrenal insufficiency or in undiagnosed individuals and is usually precipitated by a stressful event such as accident, surgery, or intercurrent illness (102-104). To respond to the stress, higher glucocorticoid levels are required but patients with adrenal insufficiency are unable to raise sufficient endogenous hormone.

- ***Pathophysiology***

In patients with undiagnosed or untreated adrenal insufficiency, lack of glucocorticoid leads to a lack of the permissive effects of glucocorticoids, according to which glucocorticoids are necessary for normal homeostasis in various organ systems (3, 4). In patients with adrenal crisis, an inadequate permissive effect on the cardiovascular system and liver can cause hypotension or shock and hypoglycaemia (14, 25). Hypotension can be worsened in patients with primary adrenal insufficiency because of the lack of mineralocorticoids, important hormones for preserving salt and water balance (25, 27). Further salt and water may be lost in patients who have vomiting as a symptom of adrenal crisis or concomitant gastrointestinal infection (25, 27). In patients with known adrenal insufficiency who are using a basal glucocorticoid, the permissive effect may be preserved (25). However, in a stressful event, higher levels of glucocorticoid may be needed to moderate the stress-related (14, 25) surge of pro-inflammatory cytokines such as tumour necrosis factor alpha (TNF-α), interleukin-1, and interleukin-6, which can cause dysregulation of the immune system (14, 25, 27). A low level of glucocorticoids is unable to suppress these cytokines and this can worsen intercurrent illness especially in infection (14, 25).

- ***Diagnosis***

The diagnosis of adrenal crisis is based on clinical evaluation. Some diagnostic criteria have been proposed (25, 27, 103) but none of these have been widely accepted. Typical clinical symptoms and signs include nausea, vomiting, abdominal pain, fever, severe fatigue, dehydration, hypotension or shock, and impaired consciousness (3, 15, 25, 27, 105, 106). All of these symptoms are non-specific and, often, cannot be differentiated from the symptoms of acute illnesses such as infection (81) and cardiovascular disease (81, 107-109), which are usually concomitant with adrenal crisis. Associated laboratory findings include unexplained hypoglycaemia, hyponatremia, azotemia, hypercalcaemia, hyperkalaemia, and eosinophilia (3, 15, 25, 27, 105, 106), all of which are also non-specific to adrenal crisis. For this reason, adrenal crisis might have been overlooked and under-reported (81, 110), leading to inappropriate diagnosis and treatment, increased morbidity, and eventually death. Dramatic improvement of the signs and symptoms after administration of high doses of glucocorticoids suggests the diagnosis and this can be used to retrospectively define adrenal crisis.

- ***Prevalence of adrenal crisis and adrenal-crisis-related death***

In patients with adrenal insufficiency of any cause, adrenal crisis has been reported in 21-42% of cases (104, 111-113), of which 12-51% had recurrent events (104, 111, 113, 114). In one prospective study there was also a positive association between a history of adrenal crisis and incidence of further adrenal crises (103). The reported proportion of patients experiencing adrenal crisis was 20-47% in primary (104, 111, 113, 115-118) and 17-35% in secondary adrenal insufficiency (104, 111, 113). The proportion of patients with adrenal crisis was up to 58% in those with congenital adrenal hyperplasia (119). Calculated prevalence of adrenal crisis was 4.4-15 per 100 patient-years for adrenal insufficiency of any cause (103, 104, 113), 3.8-17 for primary (20, 104, 112, 119, 120), and 3.6-5.8 for secondary adrenal insufficiency (104,

112). The lower prevalence of adrenal crisis in secondary adrenal insufficiency can be explained by the preservation of mineralocorticoid secretion and residual adrenocortical function in some patients (106). Study methodology can also affect the reported prevalence of adrenal crisis. The prevalence was higher in studies defining adrenal crisis by patients' reports or questionnaires than those using hospital records (103, 119).

Retrospective reviews suggest that adrenal crisis may have contributed up to 40% of total deaths in patients with adrenal insufficiency, including those with congenital adrenal hyperplasia (19, 73, 110). However, if adrenal crisis was recognised and led to hospital admission, only 2.9-6.3% of patients died (103, 114). The higher mortality on retrospective review suggests that in many cases adrenal crisis might have been initially overlooked, resulting in inappropriate or delayed treatment and death. Accordingly, if adrenal crisis is recognised and the appropriate treatment provided, nearly all patients can survive.

- ***Treatment and Prevention***

Adrenal crisis is responsible for increased mortality and morbidity in patients with adrenal insufficiency but it is treatable with an excellent outcome if this is timely treated. Clinical awareness leading to the early detection is vital. More importantly, prevention of adrenal crisis remains the mainstay of care for patients with known adrenal insufficiency. Since adrenal insufficiency is a chronic disease, it usually requires lifelong glucocorticoid therapy. As with other chronic diseases, adherence to treatment is essential. Specifically, patients with adrenal insufficiency should be educated in sick-day rules. Education on self-increasing glucocorticoid doses and self-injection of hydrocortisone, if needed, is very important to prevent adrenal crisis during an acute stress. The education should not be limited to the patients but also their families and family doctors. Seeking timely medical attention when developing acute illnesses should be emphasised. Patients and their relatives can play a role in informing healthcare providers of

the past medical history of adrenal insufficiency in acute illnesses or emergency conditions or elective surgery. All of these measures can help prevent adrenal crisis and reduce mortality and morbidity in patients with adrenal insufficiency.

1.6 Cardiovascular disease in patients with adrenal insufficiency

Evidence of increased cardiovascular morbidity and mortality including cardiovascular risk factors has been observed in patients with Cushing syndrome where there is a long-term exposure to inappropriately high glucocorticoid levels (121, 122). Also, in the general population an association between high urinary cortisol and cardiovascular mortality has been reported (123). These observations have been considered relevant to patients with adrenal insufficiency receiving replacement therapy, since the administration of exogenous glucocorticoid is unable to completely mimic physiological endogenous glucocorticoid secretion (details in section 1.4. Physiological glucocorticoid replacement therapy remains unachievable). In association with glucocorticoid replacement, in patients with primary adrenal insufficiency or pituitary disorders there have been reports of (1) increased prevalence of the classic cardiovascular risk factors: diabetes, hypertension, and dyslipidaemia, and (2) increases in other predictors of atherosclerosis including adiposity and proinflammatory markers.

1.6.1 Classic cardiovascular risk factors

- ***Diabetes***

Up to 38% of patients with autoimmune primary adrenal insufficiency associated with APS type II had type 1 diabetes (74) whereas 12-14% of patients with primary adrenal insufficiency had diabetes of any kind (73, 124). The relative risk of diabetes of any kind was also increased compared with matched controls (OR 1.75 [95%CI 1.35-2.25]) (125). In a small study, after excluding patients with baseline diabetes, the proportion of those having impaired glucose tolerance was higher in patients with primary adrenal insufficiency than in controls (8% vs 0%) (126). The increased occurrence of diabetes might have resulted from the association of autoimmune primary adrenal insufficiency and type 1 diabetes. However, use of high-dose glucocorticoids may precipitate type 2 diabetes in susceptible individuals, including those with

primary adrenal insufficiency. Nevertheless, a population-based study reported no significantly increased risk of type 2 diabetes in patients with primary adrenal insufficiency (OR 1.48 [95%CI 0.93-2.37]) (47). Failure to detect increased risk in this study might have resulted from diabetes prevalence in patients and controls having been obtained from different sources (47). Another study reported that mean haemoglobin A1c and the proportions of those with diabetes were higher in patients with primary than in secondary adrenal insufficiency (38), which could be explained by the association between primary adrenal insufficiency and type 1 diabetes. Available evidence has suggested that patients with primary adrenal insufficiency have increased risk of diabetes, although type of diabetes was not distinguished. On the basis of the link between autoimmune diseases, it is suggested that type 1 diabetes might have played a major role in the increased diabetes in primary adrenal insufficiency.

In patients with pituitary disorders, prevalences of diabetes of 2-16% have been reported (46, 49, 77, 81). In a comparison with healthy controls, pituitary disorder patients, among whom the majority had secondary adrenal insufficiency, had a higher proportion of impaired glucose tolerance and diabetes (127), although another, similar, study reported a lower mean blood glucose level with a similar insulin level, compared with controls (128). However, these findings were against a background of untreated growth hormone deficiency in the patient group, which may have confounded discrimination of any effect of adrenal insufficiency. Subsequently, in a larger study in which a majority of patients had secondary adrenal insufficiency, and growth hormone-deficiency in the patient group was treated, there was increased risk of diabetes relative to controls, but only in women (OR, women, 2.53 [95%CI 1.54-4.13] vs men, 1.07 [95%CI 0.68-1.68]) (129). Another study, also in growth hormone-treated patients, observed that the proportion of newly developed diabetes in patients with secondary adrenal insufficiency was higher than those without adrenal insufficiency (0.7% vs 0%, p=0.02) (44). Accordingly, available evidence suggests that pituitary patients with

secondary adrenal insufficiency and growth hormone deficiency have no increase in diabetes risk but if growth hormone was replaced, the risk of diabetes (relative to the general population) appeared to be increased.

In patients with non-functioning pituitary adenoma, the risk of diabetes relative to the general population was also increased (Standardised Incidence Ratio, SIR 2.44 [95%CI 2.16-2.75]) (130). There was also a report of the increased diabetes risk in patients with secondary adrenal insufficiency relative to controls (OR 1.87 [95%CI 1.72-2.04]) (125). In a comparison with other patients who had pituitary disorders but sufficient HPA function, those using glucocorticoid replacement had similar diabetes occurrence (46, 49). In patients with a non-functioning pituitary adenoma, the frequency of diabetes was not different between those with and without secondary adrenal insufficiency (49) and between those receiving different doses of glucocorticoid (46).

In summary, the risk of diabetes in patients with secondary adrenal insufficiency appeared to be increased when compared with the normal population but did not differ from risk in other pituitary patients who had an intact HPA axis. Overall, other pituitary hormone deficiencies and their treatments, especially growth hormone, were likely to have contributed to the increased risk of diabetes observed in many pituitary studies.

- ***Hypertension***

In primary adrenal insufficiency, 15-44% of patients had a clinical record of hypertension (91, 124, 125, 131). Compared with controls, patients with primary adrenal insufficiency had similar systolic and diastolic blood pressures (131) and 24-hour blood pressure patterns (126). Furthermore, the 24-hour blood pressure patterns were not different between those using different doses of fludrocortisone (126). Dalin et al reported the risk of hypertension in patients with primary adrenal insufficiency was lower than controls (OR 0.73 [95%CI 0.55-0.97]) (47).

A contributor to this lower OR might have been the lower body mass index in patients and the different approach to define hypertension between patients and unmatched controls (47). However, an increased risk of hypertension (OR 1.53 [95%CI 1.25-1.88]) (125) and a higher proportion of anti-hypertensive drug users in primary adrenal insufficiency compared with matched controls (131), especially in those with age less than 40 (132), has been reported. Accordingly, the reported risks of hypertension relative to controls in patients with primary adrenal insufficiency are inconsistent.

In pituitary disorders, 9-58% of patients were reported to have hypertension (49, 77, 81). In patients with growth hormone deficiency where the majority had adrenal insufficiency, the systolic (128, 133), diastolic (133) blood pressure, and the proportion of anti-hypertensive users (129) were not different from matched controls. However, in a study of patients with secondary adrenal insufficiency, the risk of hypertension relative to matched controls was doubled (OR 2.24 [95%CI 2.10-2.40]) (125). In a comparison with growth hormone deficiency but intact HPA function, patients with secondary adrenal insufficiency had a similar level of systolic and diastolic blood pressure (44). However, a small study reported that the percentage of those having hypertension increased with increasing glucocorticoid dose, although this did not reach statistical significance (46). In a comparison with primary adrenal insufficiency, patients with secondary adrenal insufficiency had higher systolic blood pressures in conjunction with higher body mass indexes (38).

On the basis of observational studies, whether primary or secondary adrenal insufficiency can increase hypertension remains debatable. A possible reason for the inconsistent findings is that the studies have used only one of the different methodologies for defining hypertension such as measuring blood pressure, physician diagnosis, patient report, or use of anti-hypertensive drugs.

- ***Dyslipidaemia***

In primary adrenal insufficiency, the proportions of patients using lipid-lowering agents have varied between 12-21%, with the majority taking statins (131, 134, 135). However, a population-based study reported up to 41% of patients with a diagnosis of dyslipidaemia (125). In a comparison with controls, the OR (95% CI) for a diagnosis of dyslipidaemia was 1.53 (1.25-1.88) (125) and for lipid-lowering agent use 1.31 (1.15-1.48) (132). However, another study found no significant increase in risk of dyslipidaemia (OR 1.13 [95%CI 0.83-1.54]) (47). The proportions of use of a lipid-lowering agent (132) and a diagnosis of dyslipidaemia (47) were similar to controls when patients with primary adrenal insufficiency were over 50 or 65 years of age. The reported abnormalities of lipids included increased triglyceride (TG) (124, 126, 131), decreased high-density lipoprotein cholesterol (HDL-c) (124, 131), increased total cholesterol (TC) (126), increased low-density lipoprotein cholesterol (LDL-c) (126), decreased LDL-c (131), and increased small dense LDL-c (124).

In pituitary disorders, 14-23% of patients used lipid-lowering agents (91, 129) whereas other studies reported 35-72% of patients as having dyslipidaemia (46, 49, 136). In patients receiving growth hormone replacement where the majority had adrenal insufficiency, the proportion of lipid-lowering users was higher than controls, only in women (OR, women, 2.11 [95%CI 1.44-3.08] vs men, 0.94 [95%CI 0.67-1.32]) (129). The reported abnormality of lipids in patients with hypopituitarism included increased TC (127, 136, 137), LDL-c (127, 136, 137), TC to HDL-c (137) and LDL-c to HDL-c ratios (128); decreased HDL-c (128); and increased TG (137). Some studies observed lipid changes only in women, including increased TG (127, 136) and decreased HDL-c (137). In sub-analysis, the lipid abnormalities observed in women were not different between those with or without secondary adrenal insufficiency (136). It is noteworthy that all studies reporting lipid abnormalities obtained data from patients with untreated growth hormone deficiency (127, 128, 136, 137), only some of whom had adrenal

insufficiency. Among patients with pituitary adenoma, those with adrenal insufficiency had a similar percentage of dyslipidaemia to those without. (49). However, in a comparison with matched controls, the risk of dyslipidaemia was increased in patients with secondary adrenal insufficiency, although some participants might also have had growth hormone deficiency (OR 1.98 [95%CI 1.84-2.12]) (125). With regard to glucocorticoid-dose dependent dyslipidaemia, findings have been inconsistent. In a study of patients receiving growth hormone replacement, the blood levels of TC, TG, and LDL-c in patients using high glucocorticoid doses were higher than those with the intact HPA axis and those using lower doses (<20 mg of hydrocortisone per day) (44). In contrast, one study of pituitary adenoma with secondary adrenal insufficiency observed that the proportion of dyslipidaemic patients was not increased in those using higher glucocorticoid doses (46). In addition, patients with secondary adrenal insufficiency have been reported to have higher TG and lower HDL-c than those with primary disease (38).

Regarding the diagnosis of dyslipidaemia or use of lipid-lowering agents, as with hypertension, the assessment of risks was difficult using the real-world studies. Again, as with hypertension, there were many criteria used to define dyslipidaemia, although all criteria would have been associated with cardiovascular disease. Lipid-lowering agents, especially statins may have been more readily-prescribed than anti-hypertensive drugs because of perceived lower adverse effects. Use of lipid-lowering agents would, conventionally, be taken to indicate adverse cardiovascular risk from dyslipidaemia, but more ready availability of lipid-lowering agents could instead have had a protective effect.

1.6.2 Other predictors of atherosclerosis

In a UK study, up to 65% of patients with primary adrenal insufficiency had a body mass index (BMI) more than 25 kg/m^2 (134). However, a Swedish study reported that after adjustment by age and sex, patients with primary adrenal insufficiency had a mean BMI (95%CI) of 1.28

(0.82-1.66) kg/ m^2 lower than that of unmatched controls (47). In patients with pituitary disorders, the mean BMI was higher than controls in some (133, 137, 138) but not all studies (139). All this information was, however, obtained from patients with untreated growth hormone deficiency. In patients treated with growth hormone, those with secondary adrenal insufficiency had a similar BMI to those without (44). In a comparison between types of adrenal insufficiency, patients with secondary disease had a higher BMI than primary disease but this might have been explained by a higher proportion of men in the secondary adrenal insufficiency group (38).

Both waist circumference (WC) and waist to hip ratio (WHR) have been used as an index of central fat accumulation in studies of primary adrenal insufficiency and pituitary disorders. The WC in patients with primary adrenal insufficiency has been reported to be higher than that of controls who had a similar BMI (126). However, visceral adipose tissue evaluated by computed tomography in patients with primary adrenal insufficiency was not different from age-sex-BMI matched controls (131). Among patients with untreated growth hormone deficiency, the WHR was higher than controls (133, 137, 139), especially in females (127). In a study of patients receiving growth hormone replacement, those with secondary adrenal insufficiency had higher WC but similar WHR if treated with a higher dose of glucocorticoids, compared to those with the intact HPA axis (44).

Proinflammatory biomarkers, known to be associated with atherosclerosis, have also been examined in patients with primary adrenal insufficiency and pituitary disorders. In patients with primary adrenal insufficiency, high-sensitivity C-reactive protein (hs-CRP) was higher than controls, although only age and sex were matched (124). When BMI and smoking habits were also matched, the hs-CRP of primary adrenal insufficiency was not different from controls but still an increase was observed in other proinflammatory biomarkers such as interleukin-6 (IL-6) and also a decrease in a vasodilatory marker (131). In patients with hypopituitarism,

there was also an increase in hs-CRP and IL-6, relative to controls but growth hormone deficiency and increased BMI may have contributed to this difference (138).

Intima-media thickness of common carotid arteries (IMT) has also been evaluated. In a small study of patients with primary adrenal insufficiency, IMT was not different from controls (126). In patients with pituitary disorders, evidence of increased IMT (127) and loss of distensibility and compliance of carotids (140) has been reported, but another study found no difference in IMT between the patients and controls (128, 133). These studies showed contradictory results despite untreated growth hormone deficiency being a common factor (127, 128, 133, 140).

In conclusion, atherosclerosis risk factors in patients with adrenal insufficiency of any kind could have been influenced by many factors such as age, sex, and adiposity. In patients with secondary adrenal insufficiency, there is little reliable information on predictors of atherosclerosis, since the available evidence is likely to have been confounded by the effects of growth hormone deficiency.

1.6.3 Cardiovascular events in patients with adrenal insufficiency

- ***Cardiovascular events in patients with primary adrenal insufficiency***

There appears to be only a single study in patients with primary adrenal insufficiency, reporting the risk of a cardiovascular event (100). In this study, Skov et al evaluated patients with autoimmune Addison's disease by matching with controls for age, sex, time of study, and area of residence. Follow-up periods were 8807 and 80163 person-years in patients and controls, respectively. Cardiovascular disease was defined by using diagnostic codes describing ischaemic heart disease and cerebrovascular disease. The cardiovascular disease event rate for first events was higher in the patients than in the controls (10.7 vs 7.0 per 1000 person-years) and the unadjusted HR (95%CI) was 1.52 (1.12-1.89) (100). After adjustment for diabetes and chronic obstructive pulmonary disease, the HR was no longer increased (adjusted HR 1.20 [95%CI 0.95-1.51]). However, when the analysis was restricted to ischaemic heart disease events, the risk remained significantly increased (adjusted HR 1.61 [95%CI 1.22-2.12]) specifically in women (adjusted HR, women, 2.15 [95%CI 1.49-3.10] vs men, 1.16 [0.75-1.78]). The risk of cerebrovascular events was not significantly increased either before or after adjustment. This study, however, did not consider the influence of other established cardiovascular risk factors. Smoking status was merely taken to be signified by chronic obstructive pulmonary disease and there was no consideration of hypertension and dyslipidaemia, which have previously been shown may be increased in primary adrenal insufficiency (125). Also, over a half of participants entered the study before 2000, in a period during which cardiovascular disease prevention was believed to be improving. It was suggested that a predisposition to autoimmune disease might have contributed to the increased risk of cardiovascular disease (100). However, the prevalence of other autoimmune diseases was not different between men and women with autoimmune primary adrenal insufficiency (47). Therefore, no priori reason can explain the sex difference in the risk of ischaemic heart disease

in patients with primary adrenal insufficiency. The increased risk of ischaemic heart disease only in women with primary adrenal insufficiency needs to be confirmed.

- ***Cardiovascular events in patients with secondary adrenal insufficiency***

In patients with pituitary disorders, more evidence of increased cardiovascular events has been reported. For cardiovascular disease of any kind, the incidence rates for first events in a study restricted to women with hypopituitarism and matched controls were 15.3 and 4.6 per 1000 person-years, respectively but the relative risk did not reach statistical significance (RR 3.3 [95%CI 0.9-12.0]) (139). When recurrent events were included, the RR (95%CI) was 3.7 (1.2-11.3) but this was evaluated only in 33 women with untreated growth hormone deficiency (139).

For ischaemic heart disease, larger groups of patients with pituitary disorders have been studied (79, 129, 130). Svensson et al reported the risk of myocardial infarction relative to the Swedish general population (RR; 95% CI) in 1411 patients with untreated growth hormone deficiency as 1.40 (1.10-1.75) but this was significantly increased only in women (RR, women, 1.87 [95%CI 1.27-2.65] vs men, 1.20 [0.88-1.60]) (79). This study also reported a lower RR of myocardial infarction in patients with treated growth hormone deficiency but the sample size of this patient sub-group was small (79). In a larger study of patients treated with growth hormone replacement, the risk of non-fatal cardiac events relative to matched controls was not increased in either sex (RR, women, 0.92 [95%CI 0.39-2.13] vs men, 0.81 [0.52-1.26]) (129). In patients with pituitary adenoma, the standardised incidence ratio (SIR) for myocardial infarction was reported to be slightly increased overall (SIR 1.18 [95%CI 1.01-1.36]), the increase being specifically in women (SIR, women, 1.66 [1.30-2.09]) vs men, 0.98 [0.80-1.19]) (130). The risk was further increased in women with concomitant hypopituitarism (SIR 1.93 [1.41-2.58]) (130).

For cerebrovascular events, an increased risk among patients with pituitary disorders has been consistently reported (79, 129, 130, 141). In patients with untreated growth hormone deficiency, the RR (95%CI) for cerebrovascular disease, relative to the general population, was 2.74 (2.21-3.35) and this was more prominent in women (RR, women, 3.46 [95%CI 2.53-4.61] vs men, 2.27 [1.71-3.02]) (79). However, in the sub-group of patients treated with growth hormone, the risk was not significantly increased but the number of participants was very low in this sub-analysis (79). In a larger study of patients with pituitary disorders treated with growth hormone replacement, the risk of cerebrovascular disease relative to matched controls was increased in both sexes but more so in women (RR, women, 2.94 [95%CI 1.65-5.25] vs men, 1.81 [1.15-2.86]) (129). In patients with pituitary adenoma, the SIR for cerebrovascular disease was also increased (SIR 1.66 [95% CI 1.44-1.89], more obviously in women (SIR, women, 2.28 [95%CI 1.86-2.76] vs men, 1.32 [1.08-1.59]) (130). In addition, the risk of cerebrovascular events was associated with radiotherapy (130, 141). In a study of patients with pituitary adenoma, the SIR for cerebrovascular disease appeared to be higher in those with than those without radiotherapy but the number in this patient subgroup were low and the difference was not significant (130). In a study of patients with pituitary adenoma in which all participants underwent radiotherapy, the risk of cerebrovascular disease relative to the general population (RR [95%CI]) was 4.1 (3.6-4.7) (141). The risk was higher in women, in the patients with debulking cranial surgery, and in those receiving high-dose radiation (141). Cerebrovascular events were continuously increased throughout the follow-period, in which the cumulative incidences at 5, 10, and 20 years after radiotherapy were 4, 11, and 21%, respectively (141), suggesting a long-term effect of radiation.

In conclusion, the risk of cardiovascular events in patients either with primary adrenal insufficiency or pituitary disorders appeared to be particularly increased in women. However, available information on the risk of cardiovascular events in patients with primary adrenal

insufficiency has been limited, and among patients with secondary disease the risk was assessed in those with growth hormone deficiency (79, 129) or pituitary adenoma (130, 141). In large studies, the increased incidences of classic cardiovascular risk factors including cardiovascular drug prescription have been reported in patients with primary (47, 125, 132) and secondary adrenal insufficiency (125) as well as in pituitary disorders (129, 130). More extensive studies of the risk of cardiovascular events in patients with primary and secondary adrenal insufficiency in conjunction with evaluation of the effects of classic risk factors in these contexts are clearly needed.

1.6.4 Cardiovascular mortality in patients with adrenal insufficiency

- ***Cardiovascular mortality in patients with primary adrenal insufficiency***

In patients with primary adrenal insufficiency, to date there has been one study reporting the estimated risk of death from cardiovascular disease relative to the general population (73). Bergthorsdottir et al reported that the SMR (95%CI) of cardiovascular disease was increased in both men and women (SMR, men, 1.97 [95%CI 1.61-2.93]) vs women, 2.31 [1.94-2.74]; Figure 1.5) (73). The SMR was derived from a comparison of the expected number of deaths in the general population, but without close matching for age, calendar time and geographical locations of study, all of which can affect the comparison of mortality risk. In addition, the study was conducted in patients undergoing care between 1987 and 2001 (73), during which cardiovascular disease prevention was improving. Also, the median dose of cortisone acetate used (73) was higher than currently recommended glucocorticoid replacement doses (3, 15, 34). Considering all these factors, the reported SMR might have misrepresented the actual risk of cardiovascular mortality. Subsequent studies observed similar proportions of death from cardiovascular disease in patients with primary adrenal insufficiency and the background population (19) or matched controls (75). However, the mortality rate and risk of

cardiovascular disease were not calculated in these studies (19, 75). Regarding mortality from specific cardiovascular diseases, a previous study observed that in patients with autoimmune primary adrenal insufficiency, the proportion of those having died within 30 days of an ischaemic heart disease event, and with death ascribed to "death from ischaemic heart disease", was higher than that in controls, whereas the proportion distinguished by "death from cerebrovascular disease" was not different between the patients and controls (100). However, no data specific for risk of cardiac or cerebrovascular death in primary adrenal insufficiency has been reported. With the limited evidence, further studies to estimate the risk of cardiovascular mortality, in particular ischaemic heart disease, in patients with primary adrenal insufficiency are needed.

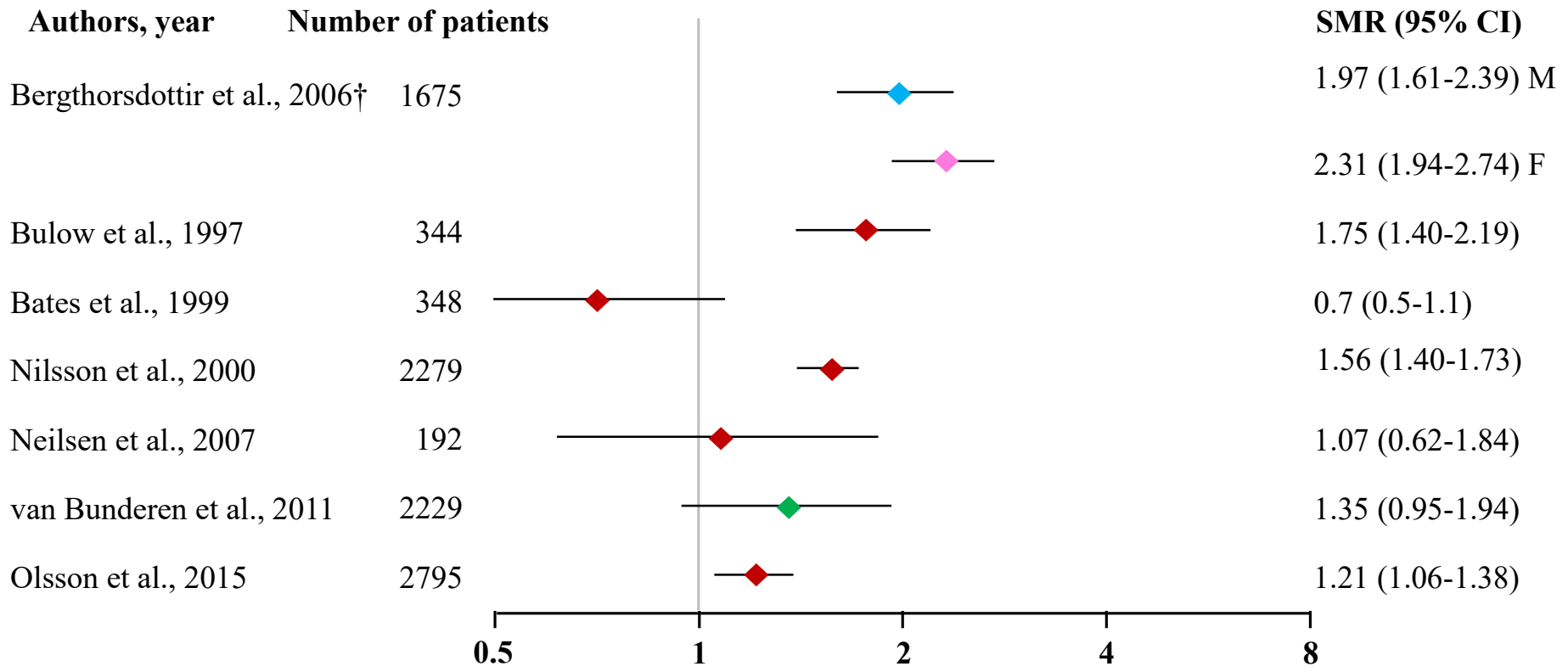


Figure 1.5: The studies of mortality from cardiovascular disease of any kind in patients with primary adrenal insufficiency and pituitary disorders

Note: M-Males; F-Females; SMR-Standardised Mortality Ratio; † the study of patients with primary adrenal insufficiency; colour codes for the primary study population: Green-growth hormone replacement; Brown-Pituitary tumours

- ***Cardiovascular mortality in patients with secondary adrenal insufficiency***

In patients with secondary adrenal insufficiency, the risk of cardiovascular death of any kind, relative to the general population, has been estimated in patients with pituitary tumours (23, 77, 85, 88, 90) or growth hormone deficiency (89) (Figure 1.5). In patients with pituitary tumours, the risk of death from cardiovascular disease was increased in most (23, 77, 90) but not all studies (85, 88). The significantly increased SMRs were between 1.21 and 1.75 (23, 77, 90). Women with pituitary tumours appeared to have a higher risk of death from cardiovascular disease with SMRs of between 1.42 and 2.39 whereas in men the range was 1.10-1.54 (77, 90). However, some studies of pituitary tumours showed no difference between sexes in the cardiovascular mortality risk (23, 85, 88). Nilsson et al reported that the risk of cardiovascular mortality in patients aged 40-69y (SMR 3.6 [95%CI 3.2-4.1]) was higher than the risk of all ages (SMR 1.56 [95%CI 1.40-1.73]) (23) and this was in line with the all-cause mortality risk reported in the same study (details in section 1.5.2 All-cause mortality in patients with secondary adrenal insufficiency). In a study of patients treated with growth hormone replacement, the SMR for death from cardiovascular disease was increased overall (SMR 1.21 [95%CI 1.06-1.38]) but when sex was categorised, the SMR was increased only in women (SMR, women, 1.42 [95%CI 1.14-1.75] vs men, 1.10 [0.92-1.31]) (90). The SMR for cardiovascular disease was further increased if the women had hypopituitarism or diabetes insipidus (SMR 1.66 [95%CI 1.23-2.18]) (90). A small study of patients with non-functioning pituitary adenoma reported that death from cardiovascular disease in patients with and without adrenal insufficiency was 44% and 36% of total deaths, respectively but cardiovascular mortality rate or risk was not evaluated (49). Also, the proportion of deaths from cardiovascular disease did not increase with increasing steroid doses (49). From the current evidence, it remains uncertain whether secondary adrenal insufficiency is associated with the increased

mortality from cardiovascular disease of any kind and the risk for specific cardiovascular mortality needs to be separately evaluated.

The risk of death specifically from cardiac disease relative to the general population was investigated in patients with pituitary tumours (23, 77, 90), growth hormone deficiency (80, 81), and hypopituitarism (78). The risk of death from cardiac disease was increased in some (23, 77, 78) but not all studies (80, 81, 90) (Figure 1.6). Initially, the reported risk for cardiac death was 1.36-1.82 times higher than the general population (23, 77, 78), with no sex difference in risk (23, 77). Subsequent studies found no increase in risk of cardiac death relative to the general population, either in patients with treated growth hormone deficiency (80, 81) or in those with non-functioning pituitary adenoma (90).

The risk of death from cerebrovascular disease relative to the general population was also investigated in patients with pituitary tumours (23, 77, 90, 92), growth hormone deficiency (80, 81, 89), and hypopituitarism (78). All (23, 77, 78, 80, 89, 90, 92) but one study (81) reported a significantly increased risk of death from cerebrovascular disease with SMRs of between 1.73 and 4.41 (Figure 1.7). Women appeared to be at greater risk than men, with an SMR of 3.37 and 4.91 reported in women (77, 89) whereas in men one study reported a significant but lower SMR of 2.64 (77) and the other, a non-significantly increased risk (SMR 1.97 [95%CI 0.82-2.96]) (89). The sex difference in risk of cerebrovascular death was also observed in patients undergoing radiotherapy (SMR, women, 6.93 [95%CI 4.29-10.60] vs men, 2.40 [1.24-4.20]) (92). However, no sex difference in the SMRs for cerebrovascular death was also observed in some studies (23, 90). Younger age at diagnosis of pituitary adenoma increased the risk of cerebrovascular death in one study (SMR, age <55y, 6.67 [95%CI 3.38-12.1] vs age ≥ 55y, 2.52 [1.47-4.26]) (77) but another showed no difference in the risk of cerebrovascular death according to age at radiotherapy (92).

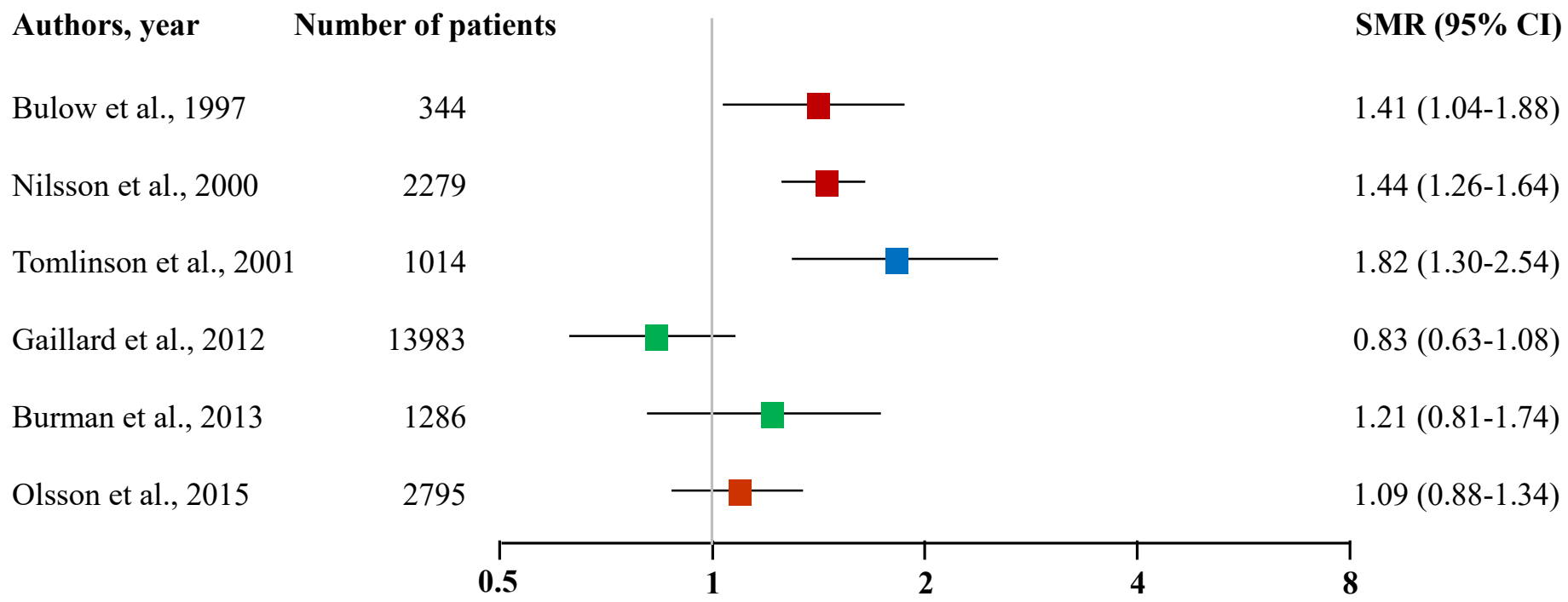


Figure 1.6: The studies of mortality from cardiac disease in patients with pituitary disorders

Note: SMR-Standardised Mortality Ratio; colour codes for the primary study population: Green-growth hormone replacement; Blue-Hypopituitarism; Brown-Pituitary tumours)

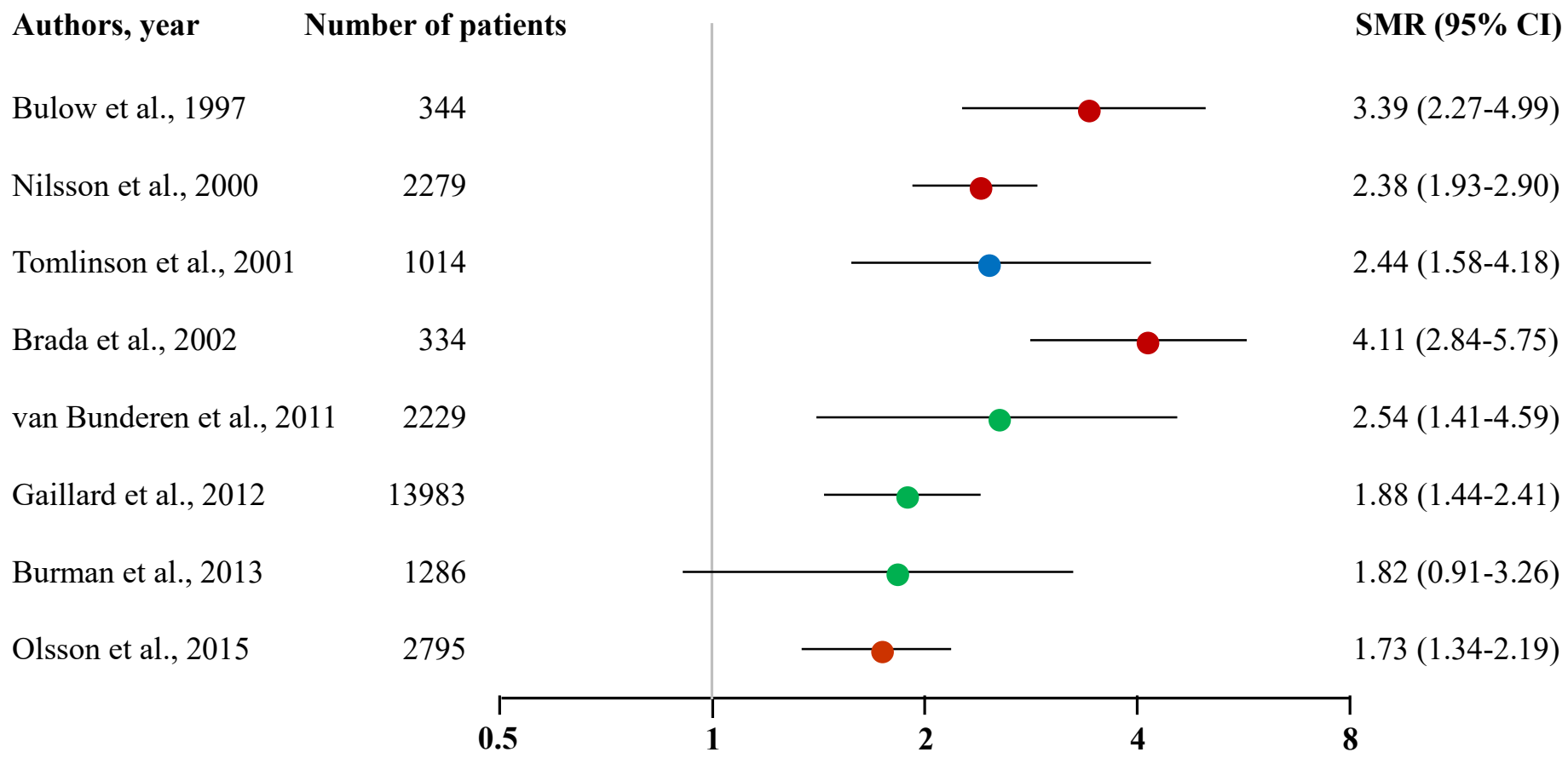


Figure 1.7: The studies of mortality from cerebrovascular disease in patients with pituitary disorders

Note: SMR-Standardised Mortality Ratio; colour codes for the primary study population: Green-growth hormone replacement; Blue-Hypopituitarism; Brown-Pituitary tumours

As reported for all-cause and cardiac mortality, one study showed a considerably increased risk of cerebrovascular death in patients with age at diagnosis of 40-69y (SMR 6.9 [95%CI 5.3-8.5]), compared with that in all ages (SMR 2.38 [1.93-2.90]) (23). Patients with a history of radiotherapy had 4 to 5 times higher risk of cerebrovascular death than the general population (78, 90, 92) whereas in those without radiotherapy the risk was 1.5 to 1.6 times (78, 90). The increased risk of cerebrovascular death was in accord with that of cerebrovascular events and radiation-induced vasculopathy may have been responsible, as observed in patients with other brain tumours (142). However, this mechanism was not the sole factor since the increased cerebrovascular events and deaths appeared to be higher in women.

1.7 Summary: Currently available evidence of the risk of all-cause mortality and cardiovascular disease in patients with primary and secondary adrenal insufficiency

1.7.1 All-cause mortality

In patients with primary adrenal insufficiency, the majority of studies estimated risk using the SMR, but findings have been inconsistent. One study matched the study patients with controls but the population was limited to patients with diabetes and an exceptionally high mortality risk was reported. This finding was not in accord with the previous studies. With few studies, it was unclear whether primary adrenal insufficiency can increase the mortality risk.

In patients with secondary adrenal insufficiency, more evidence has been forthcoming but nearly all studies concerned patients with pituitary tumours or growth hormone deficiency or unspecified hypopituitarism (the dysfunction of any pituitary axis). Although the mortality risk associated with secondary adrenal insufficiency was reported in subgroup analysis in some studies, the findings were inconsistent. More importantly, all estimated risks were reported using the SMR.

Since the SMR is obtained from a comparison between the observed (actual) number of deaths in the study patients and the expected number of death in the background population, attempts were made to match sex and age-range of the study patients to the reference population in order to estimate the expected number of deaths. However, if age appeared to be a major factor in modifying mortality risk, the SMR was unlikely to represent the actual risk. Furthermore, the expected number of deaths was estimated in a particular period during which the standard of care was improving and this could have been a confounding factor in studies requiring a long-term follow-up period to demonstrate a chronic outcome such as cardiovascular disease or mortality. In addition, the expected number of deaths was usually estimated from the background population living in the same country but the standard of care can be different in different geographical regions of a single country and this can further distort the estimated risk.

Therefore, mortality studies with well-matched controls are required for reliable estimation of all-cause mortality risks associated with either primary or secondary adrenal insufficiency.

Currently, no study has compared the mortality risk of patients with primary and those with secondary adrenal insufficiency. Given that both have glucocorticoid deficiency, the mortality risk related to non-physiologic glucocorticoid replacement might have been expected to be similar. However, as patients with primary adrenal insufficiency were likely to have lesser reserve of adrenocortical function and concomitant mineralocorticoid deficiency, they might be expected to be at a higher risk for adrenal crisis and death. On the other hand, patients with secondary adrenal insufficiency usually have hypothalamic-pituitary pathology and concomitant deficiencies in other pituitary hormones, these comorbidities and their treatments might also be expected to increase mortality. Therefore, studies that include both primary and secondary adrenal insufficiency with separate evaluation of mortality risk are needed to improve understanding of the similarities and differences in mortality risk between types of adrenal insufficiency.

1.7.2 Cardiovascular disease

In patients with primary adrenal insufficiency, one study reported risk of cardiovascular disease with matching of controls for sex, age, calendar time, and place of residence. However, this study did not take into account a representative range of cardiovascular risk factors and the reported risk was increased only in women.

In patients with secondary adrenal insufficiency, as for mortality studies, risks of cardiovascular disease were again evaluated in patients with pituitary tumours or growth hormone deficiency or unspecified hypopituitarism and these populations might not well represent patients with secondary adrenal insufficiency. In addition, the estimated risks were mainly based on comparisons with the expected number of events as reported in an SIR. The

SIR has the same limitations as the SMR. In addition, using the SIR does not take a representative range of cardiovascular risk factors into account.

To rigorously estimate the risk of cardiovascular disease in patients with primary and secondary adrenal insufficiency, further studies using a closely-matched reference population are needed, with consideration of a broad range of cardiovascular risk factors.

In previous studies of patients with primary adrenal insufficiency or with pituitary disorders, the risks for cardiovascular morbidity and mortality were increased, even though heterogenous populations were evaluated in the different studies. However, evaluation of risk differences between cardiovascular morbidity and mortality, and between primary and secondary adrenal insufficiency, has been rare. In patients with adrenal insufficiency, risk of cardiovascular mortality might have been augmented beyond the increased risk for cardiovascular events as a result of adrenal crisis. Therefore, analyses that evaluate cardiovascular morbidity and mortality in patients with different types of adrenal insufficiency within the same study population using the same methodology may advance understanding of variation in risk according to different defined outcomes and types of adrenal insufficiency.

In the present study, risks of all-cause mortality and cardiovascular disease were evaluated using individually matched controls and existing cardiovascular risk factors were also taken into account. Accordingly, the study aims to improve understanding of (1) differences in all-cause mortality risk between types of adrenal insufficiency; (2) differences in the risk of cardiovascular disease between types of adrenal insufficiency; and (3) differences in the risk of cardiovascular morbidity versus cardiovascular mortality in patients with adrenal insufficiency.

1.8 Hypothesis

Risks for all-cause mortality and cardiovascular disease are not increased in patients with adrenal insufficiency.

1.9 Aims

In patients with adrenal insufficiency of any cause, and with primary and secondary adrenal insufficiency separately

- To compare with matched controls the all-cause mortality rate
- To investigate whether the all-cause mortality risk changes according to sex, age, cardiovascular disease comorbidities, and calendar time of study
- To investigate the all-cause mortality rate according to years of study entry and years of diagnosis of adrenal insufficiency
- To compare with matched controls the principal cause of death regarding organ system-specific and disease-specific death, illustrated in cause-specific mortality rates
- To investigate endocrine-related causes of death as the principal and associated causes of death
- To investigate the rates of death and hospitalisation from adrenal crisis
- To compare with matched controls the occurrence of hospital admissions including emergency hospital admissions
- To compare with matched controls the event rates of cardiovascular disease of any kind and, specifically, of ischaemic heart disease, and cerebrovascular disease, taking into account previous cardiovascular disease, diabetes mellitus, hypertension, dyslipidaemia, and smoking as a confounding factor

- To investigate whether the risks of cardiovascular disease change according to sex, age, cardiovascular disease comorbidities, and time of study
- To compare with matched controls the rates of hospital admission from cardiovascular disease of any kind and, specifically, ischaemic heart disease, and cerebrovascular disease
- To investigate the association between cardiovascular disease and adrenal crisis-related death
- To investigate the association between radiotherapy and cerebrovascular disease in patients with secondary adrenal insufficiency

CHAPTER 2: MATERIALS AND METHODS

2.1 Study design

This is a retrospective cohort study using the database from Clinical Practice Research Datalink (CPRD) to identify adrenal insufficiency patients and their matched controls. All participants who have their data in CPRD between the 1st January 1987 and 31st December 2017 were investigated.

2.2 Source of data and Characteristics of the database

2.2.1 Primary care database

Clinical Practice Research Datalink (CPRD) is a research service providing anonymised primary care data in the UK, and funded by the Medicines and Healthcare products Regulatory Agency (MHRA) and the National Institute for Health Research (NIHR). CPRD collects longitudinal health data from general practices across the UK, comprising 45 million people of which 13 million are currently registered and alive (143). The database has been established in London since 1987, when it was called the small Value Added Medical Products (VAMP) dataset. It then became the General Practice Research Database (GPRD) in 1993 (144). Because of further data expansion, the database was developed into the CPRD in 2012 (144). It was considered to be one of the world's biggest databases of longitudinal primary care records with a median follow-up of 9.4 years (IQR, 3.4-13.9) for all and 5.1 years (IQR, 1.8-11.1) for currently active patients (144).

The CPRD collected and processed electronic health records of the patients from routine general practitioner (GP) consultations in which two general practice software systems were used: Vision® and EMIS®. Depending on which software systems the data derived from,

CPRD provided two separate databases: CPRD GOLD and CPRD Aurum (145). In this study the CPRD GOLD was used.

Characteristics of the CPRD GOLD database

CPRD GOLD database has been established since 1987 and included patient information from general practices in England, Wales, Scotland, and Northern Ireland that have participated in the scheme (144). The patients in the CPRD dataset are a representative population of the UK population with respect to age, sex, and ethnicity. The recorded data included demographics, diagnosis, clinical signs and symptoms, tests, immunisation, prescriptions, specialist referrals, hospital admissions, survival status, and the date of death (144, 146). Since the data was routinely collected in every GP consultation, the data input into the general practice software was normally on a daily basis. The data is later extracted and built into the CPRD and made available for researchers every month (147). Therefore, the data may be updated and changed on a monthly basis. For analytical precision, only one monthly CPRD database has been recommended for use in each study (146).

Structure of the CPRD GOLD database

The data structure, providing patient and practice information, consists of ten files: Practice, Patient, Staff, Consultation, Clinical, Therapy, Referral, Test, Immunisation, and Additional files. All information is encoded and can be decoded by using dedicated dictionaries and lookups provided by the CPRD. Important files and variables used in this study are listed in Table 2.1

CPRD GOLD data files	Example of variables (originally named by CPRD) that were used in this study
Practice	Practice identifier, Last collection date (LCD), Up to standard date (UTS)
Patient	Patient identifier, Patient gender, Birth year, Birth month, Current registration date (CRD), Transfer out date (TOD), Transfer out reason (TOR), Death date
Clinical	Patient identifier, Medical code, Event date, System date, Additional details identifier
Additional clinical details	Patient identifier, Entity type, Additional details identifier
Referral	Patient identifier, Medical code, Event date, System date, NHS specialty
Immunisation	Patient identifier, Medical code, Event date, System date
Test	Patient identifier, Medical code, Event date, System date, Entity type
Therapy	Patient identifier, Product code, Event date, System date, Total quantity, Number of Days, Dosage identifier

Table 2.1: A list of CRPD GOLD files and their variables that were used in this study

Practice file

Practice file provides practice-level information. There are four variables: practice identifier, region, the last collection date (LCD), and up to standard date (UTS). Practice identifier is a set of numbers, unique to each participating practice and is a pseudo-identifier according to deprivation status and geographical location (region) of each practice. Region comprises encoded areas representing 13 regions of the UK, ten in England (North East, North West, Yorkshire & The Humber, East Midlands, West Midlands, East of England, South West, South Central, London, and South-East Coast) and one each in Wales, Scotland, and Northern Ireland. LCD is the most recent date at which the practice has provided health information to CPRD. LCD corresponds to the date that the most recent data has been uploaded from each practice on a monthly basis. UTS is the earliest date after which the CPRD considers that the practice has provided research-standard data.

Patient file

Patient file provides the patient-level information, which includes variables such as patient identifier, demographic data, registration details, and acceptable patient flag.

Patient identifier is a set of numbers, each one unique for each patient in the CPRD GOLD. Each number is unidentifiable and cannot be mapped back to patients' NHS numbers. However, the last three digits of patient identifier of each participant are identical to a practice identifier of the corresponding practice.

Demographics consists of gender, the year of birth (birth year), and the month of birth (birth month) in cases of patient aged under 16. In this study, birth month was used when participants had age at the start of follow-up of less than 1 year.

Registration details include the current registration date (CRD), transfer out date (TOD), transfer out reason (TOR), and the date of death (CPRD death date).

CRD is the date at which a given patient has registered to the current practice.

TOD is the date at which if the patient has moved to another practice or died. TOD is missing if the patient remains in the practice.

TOR is the reason for that the patient having moved from the current practice and includes death as an option.

CPRD death date is the date of death, established according to the CPRD death algorithm (see Quality control of data in CPRD GOLD) (148). CPRD death date is identified from the earliest date of (1) the date at which the patient's record had been closed with the transferred out reason of death, (2) the date at which death had been recorded in the practice structured data area of death administration in Vision®, and (3) the date at which codes relating to death, suicide, postnatal or neonatal death were recorded in the patient's medical history (148).

Acceptable patient flag is a binary variable indicating that the information of a given participant has met CPRD quality standards (Details in section: Quality controls of data in CPRD GOLD).

Clinical file

Clinical file provides details of any specific clinical event for a given patient. The file includes variables such as patient identifiers, medical code, event date, system date, and additional details identifiers.

Medical code is a set of numbers representing clinical presentation, diagnosis, test, or treatment received. Medical code is exclusively used in CPRD and can be matched to Read code, which is a code routinely used by UK general practitioners for describing a wide spectrum of clinical details (clinical terms) such as symptoms, signs, diagnoses, investigations and therapeutic procedures. During a consultation, GPs can enter a key word of a clinical term and select the appropriate Read term paired with its Read code that is relevant to the patient's clinical detail from the interface. In each consultation, more than one Read term can be recorded if there are

more than one clinical conditions (146). CPRD provides a specific code browser including a dictionary that provides clinical terminology (Read term) for each Read code and enables mapping back to the equivalent medical code. A single medical code is matched to one particular Read code. However, one clinical condition can often be described by more than one clinical term and this results in more than one Read code and medical code. For example, 'adrenal crisis' has up to four medical codes (Read terms, Read codes): 21539 (Acute adrenal insufficiency, C154000), 42873 (Adrenal crisis, C154012), 12227 (Addisonian crisis, C154600), and 4042 (Addisonian crisis, C154011). In normal practice, Read code can be entered to a general practice software system, Vision®, by staff in the practice other than GPs such as nurse, practice manager, or administrator.

Event date is the date at which a patient had a consultation with a practice (an event) and this date was entered by the practice. The consultation record comprises all clinical encounters including telephone, mail, and home visit. System date is the date at which the practice entered the consultation information into Vision®. The definition of system date is constant across the different files provided in CPRD GOLD. In this study, system date was used to replace event date in the case that event date was missing. Additional details identifier is a code for an event that has further clinical details. The code is used to link with detailed clinical data in the additional clinical details file. Additional details identifier is recorded as zero if the event does not contain additional clinical details.

Additional clinical details file

Additional clinical details include variables such as patient identifiers, entity type, and additional details identifier. Entity type is a code representing clinical information in details such as blood test or other investigation that had been performed. It also includes death

administration and the date of death. Additional details identifier is used to map back with the specific event in clinical file.

Referral file

Referral file provides details for a specific event for which a given patient was referred from the practice. The file includes variables such as patient identifier, event date, system date, medical code, and NHS specialty. Event date in the Referral file is the date at which a patient has been referred to a specialty. Medical code is medical terminology selected by the practice, which may not be relevant to the referral. NHS specialty is classified into 35 specialties including endocrinology.

Immunisation file

Immunisation file provides a specific event in which an immunisation has been advised or administered to a given patient. This file includes variables such as patient identifier, event date, system date, and medical code. Event date is the date which is associated with an event, which in this file is the event when an immunisation had been administered or advised to a patient. Medical code is medical terminology selected by the practice, which may not be relevant to the given immunisation.

Test file

Test file provides a specific event in which a test has been planned, advised, or performed for a given patient. The file includes variables such as patient identifier, event date, system date, medical code, and entity type. Event date is the date which is associated with an event, which in this file is the event when there had been a test entered by the practice. Medical code is

medical terminology selected by the practice, which may not be relevant to the test. Entity type is a code for describing a specific test entered by the practice.

Therapy file

Therapy file provides a specific event in which a drug was prescribed to a given patient. The file includes variables such as patient identifier, event date, system date, product code, total quantity, number of days, and dosage identifier.

Product code is a unique code established by the CPRD for a specific drug. Product code can be mapped back using the CPRD code browser (see details below) to obtain drug name, strength, formulation, and route of administration.

Total quantity is a number of tablets (or millilitres) of a drug that has been prescribed in one prescription.

Number of days is the duration in days during which a drug was intended to be used in a prescription.

Dosage identifier is the code used for linking a given drug to its anonymised dosage text by using a CPRD Lookup file: the common dosage file. The common dosage file provides information on daily dose (daily dose), amount in each dose (dose number), and the number of times that the drug was taken per day (dose frequency).

Specific dictionaries in CPRD GOLD

CPRD provides specific dictionaries for decoding detailed information from ten CPRD GOLD files. The dictionaries used in this study are CPRD code browser and the lookup text files.

CPRD code browser

CPRD code browser consists of two dictionaries providing detailed information related to a particular clinical diagnosis and drug. For clinical diagnosis, the browser can be used to identify

a medical code from a specific clinical term (Read term) or Read code, and conversely identify a clinical term (Read term or Read code) from a given medical code. For drug information, the browser can be used to identify a product code by searching a full or a part of a drug name and conversely identify a full drug name from a product code. Additionally, the browser allows a function for building a personal set of clinical terms or drug list and for exporting the associated dataset to a well-known database software such as Excel, which can be transported to statistical software such as STATA.

CPRD Lookup files

CPRD lookup files are a collection of dictionaries for decoding data (usually encoded in three characters) from ten CPRD GOLD files to obtain more detailed data including some text descriptions. The examples of detailed data are entity file (providing information such as quantitative laboratory result including its normal range and death administration status) and common dosage file (providing dose number, dose frequency, and daily dose of a given drug).

Quality control of data in CPRD GOLD

In England, data quality in general practice is controlled by the Quality and Outcome Framework, which is an incentive programme rewarding GPs that recorded health data for key patients or key health data for any patients (149). In addition, CPRD has provided two quality criteria for selecting and confirming patients with research-standard data: 1) acceptability and 2) up-to-standard time criteria (144, 146). The acceptability criterion is to select an individual patient who had valid age and gender, valid registration and transferred-out dates, continuous follow-up, and not registered as a temporary patient (144). The up-to-standard time (UTS) is the earliest date after which each practice has continuously recorded its patient data and recorded a number of death cases that accords with the number expected from geographic and seasonal variation in mortality rates (144, 146). CPRD has recommended that all study

participants should meet the acceptability criteria and the start of the study should begin on or after the up-to-standard date (144, 146).

To identify all deaths in the CPRD population and best approximate the date of death, CPRD has developed the CPRD death algorithm (148). The algorithm consists of identifying a death record from three sources of the Vision® management system: 1. death administration structured data area; 2. patient registration status; and 3. clinical record. The three sources correspond to the information provided in three CPRD GOLD files: 1. Additional clinical detail file; 2. Patient file; and 3. Clinical file (Table 2.2). In 'Additional clinical detail file', the death status can be found from identifying 'entity type' with the code number of 148 and this file also provides the correlated date of death. In 'Patient file', death can be recorded as being from a specific cause (TOR) for a given patient, if they transferred out from the practice with the transferred out date being considered as the date of death. In 'Clinical file', there are four types of medical codes describing death: 3.1) codes indicating that a given patient has died; 3.2) suicide codes indicating a complete suicide, suicide attempt, or a patient's family member committing suicide; 3.3) codes indicating neonatal death, which can be recorded in the parents', sibling's, or baby's record; and 3.4) codes indicating postnatal death, which can be recorded in the mother's or the baby's record.

Since one death might have been recorded in more than one CPRD patient (e.g. the one who died and a close family member affected by the death), the medical codes recorded in 'Clinical file' is considered to be valid according to the following conditions: For a suicide code, it is valid if the patient's registration status (in 'Patient file') was also recorded as transferred out with the reason of death (TOR = death). For a code related to neonatal death, it is valid if it was recorded in a patient having age less than 2 years on the recorded date. For a code related to postnatal death, it is valid if it was recorded in a patient having age 12 years or more on the recorded date.

In addition, the CPRD death algorithm also defines the valid date of recorded death (Death-associated date) by excluding the following five dates. 1. Death-associated date from 'Additional clinical detail', 'Clinical' or 'Patient' files that was recorded before 1st January 1987; 2. Death-associated date from 'Additional clinical detail', 'Clinical' or 'Patient' files that was recorded before the date that the patient had been registered to the practice; 3. Death-associated date from 'Additional clinical detail', 'Clinical' or 'Patient' files that occurred after the latest date at which the practice had sent the data to CPRD (LCD); 4. Death-associated date from 'Clinical' file that was recorded more than 95 days prior to the date at which the patient moved from the practice (TOD); and 5. Event date from 'Clinical' file of a given patient for whom the death in 'Patient' file (TOR = death) is not recorded or the death in 'Additional clinical detail' file is not recorded.

To establish CPRD death date in 'Patient' file, CPRD selects the most recent date of the death recorded from three file sources: 1. The date of death recorded in 'Additional clinical detail' file, 2. TOD with death as the transferred out reason from 'Patient' file, and 3. the date of death recorded in 'Clinical' file.

	Original Vision® data source	CPRD GOLD files	CPRD GOLD variable name	Death-associated date in CPRD GOLD files
1.	Death administration structured data area	Additional clinical detail	Data 1 (entity type 148)	Event date
2.	Patient registration status	Patient file	Transfer out reason (TOR) = death	Transfer out date (TOD)
3.	Clinical record	Clinical file	Medical code	Event date

Table 2.2: Sources of data used to valid death recorded in CPRD GOLD in the death algorithm

2.2.2 Other databases: CPRD linked data

Data from patients in CPRD GOLD can be individually linked to other health care datasets. The linked data provides a further understanding of patient's health information beyond that in primary care such as patients' hospital data, death registration data, area level deprivation, and cancer registration. However, the linked data is available only in a subgroup of patients in CPRD GOLD, who were registered to the practices in England and did not opt out of sharing information to CPRD (145, 150). These practices in CPRD must have consented to participate in the CPRD linkage scheme and an individual GP practice has a right to cancel at any time its participation in the linkage scheme (145, 150). The linkage data include information for around ten million patients from 411 practices, which approximates to 54% of total UK practices or 75% of English practices who are participating in CPRD GOLD (145).

Linked datasets used in this study are Hospital Episode Statistics Admitted Patient Care (HES APC or HES) data and Death registration data from the Office for National Statistics (ONS). Before being linked to the CPRD dataset, the linked HES and ONS datasets are processed by the trusted third party, NHS Digital (150), which is legally responsible for standardising, collecting, and publishing information from the health and social care system in England (145). There are two sources from which NHS Digital receives identifiable data: 1) primary care and 2) secondary care or external sources (150). Identifiable data consists of NHS number, gender, date of birth, and current postcode of patients. For primary care, NHS Digital receives the identifiable data of patients together with pseudonymised patient and practice identifiers from general practice software suppliers. For secondary care and external sources including death registration data, NHS Digital receives the identifiable data together with a pseudonymised patient record identifier from external data custodians. NHS Digital then matches identifiable data of individual patient from the primary care source to that from the secondary care and external sources. For an individual who is well-matched, identifiable data is removed and the

pseudonymised identifiers from the primary care source (patient and practice identifiers) are paired together with the pseudonymised patient record identifiers from the secondary care and external source (150). NHS Digital subsequently generates a linker file which contains HES and ONS datasets with paired pseudonymised identifiers and sends the file to CPRD (150). CPRD can then merge the linker file with the CPRD cohort to generate a standard CPRD linked dataset such as HES APC and ONS. The linked HES and ONS data is provided to researchers alongside CPRD patient identifiers to allow researchers to match the linked data with the primary care data from CPRD GOLD.

Hospital Episode Statistics Admitted Patient Care (HES APC)

HES APC data contains information of all admissions including day case admissions to hospital at all English NHS healthcare providers including acute hospital trusts, primary care trusts, and mental health trusts (151). HES APC also includes the data of private patients and residents outside of England, who were treated by NHS healthcare providers or by independent providers that are funded by the NHS (151). The data has been collected since 1989 but CPRD only links data from 1997 onwards since it is the year that the NHS number was initiated.

HES APC data provides the diagnosis recorded during hospital admissions, which includes primary diagnosis (diagnosis that leads to hospitalisation), other diagnosis including comorbidities, and disease occurring during the hospitalisation. The HES diagnosis information is recorded in three files by: 1) primary diagnosis across a hospital admission which consists of one diagnosis for each admission (hes_primary_diagnosis), 2) hospital admissions (hes_diagnosis_hospital), and 3) episode of a given patient being transferred from one consultant to another during one hospital stay (hes_diagnosis_episode). All diagnoses are encoded using the 10th Revision of the International Classification of Diseases and Related Health Problems (ICD-10) and have the date at which the care related to a diagnosis has started

(date of admission or start date of episode of care) and ended (date of discharge or date of the end of episode). In addition, linked HES APC provides encoded information on the method of admission such as elective or emergency admission. For decoding the method of admission a HES data dictionary is available via an NHS digital website (152).

Office for National Statistics (ONS) mortality data

The linked ONS dataset contains information for deceased patients including the date of death, and the underlying cause and other contributing causes of death, which have usually been recorded in the Medical Certificate of Cause of Death (MCCD) alongside patient identifiers (151). In a death certificate, there are two parts for recording the causes of death: Part I the underlying causes of death in sequence (Ia, Ib, and Ic) and Part II other significant conditions (which can contribute to death but are not related to the diseases in Part I). The underlying (principal) cause of death in the linked ONS data is derived from the lowest completed line of part I (Ic), which is the disease or condition that has caused all the conditions of the above lines (Ib and Ia) (153). Additionally, the linked ONS dataset provides information on the causes of death that have been recorded other than the lowest line of part I for up to 15 diseases or conditions (151). The guidance for registering the causes of death is provided by the HM Passport Office (153). Specific text terms for the causes of death recorded in a death certificate were selected and converted to codes by automatic cause coding software using computer algorithms and if the software was unable to code from the free text, the coding was done by an experience coder (154). The codes are in the format of ICD-10 codes for the death registered from January 2001 onwards and ICD-9 (the 9th Revision of the International Classification of Diseases and Related Health Problems) for the death registered before 2001 (151).

In addition to the causes of death, the linked ONS dataset provide the ONS date of death and variables that can be used to link to the primary care data, which are CPRD patient identifiers and practice identifiers.

2.2.3 Strengths and weaknesses of CPRD GOLD and available linked databases

CPRD GOLD is one of the largest primary care databases in the world, thus enhancing study power while at the same time providing real world information. The quality of data is systematically controlled with regular checks to minimise errors of data recording. Data are made available for researchers encoded, enabling reproduction of analyses in a particular area by use of the same set of codes-of-interest. However, as the data is derived entirely from routine GP visits, there remain gaps in the data, in particular information generated at secondary or tertiary care centres, including hormonal evaluations of adrenal insufficiency and deficiencies in and replacement of other pituitary hormones. In reality, not only a GP but also other practice staff may be responsible for recording clinical information in the practice interface, which could generate inconsistences in recording. Moreover, it should be noted that frequency of GP visits and consequent ascertainment of co-morbidities are not controlled for in recording information in CPRD GOLD, which could result in so-called 'informed presence bias' (Details in section 5.4.1 and 6.8). In contrast, randomised controlled trials can avoid some biases of real life data, but would have difficulty generating such large amounts of information and have their own biases in that they recruit individuals who are willing to participate in long-term follow-up.

Although information generated in secondary and tertiary care may be missing from CPRD GOLD, linkage to hospital episode statistics (HES) can overcome this shortcoming to some extent, even though HES data is only available for 50% of participants in CPRD GOLD. Importantly, as in the present analysis, HES linkage data can be used to validate the diagnosis of adrenal insufficiency and cardiovascular disease in CPRD GOLD. It should be noted,

however, that the ICD-10 disease codes used in HES are not identical to Read codes used in CPRD GOLD and this might cause some inconsistencies in any validation. In addition, hormonal evaluation, which was mainly performed in out-patient settings of hospitals, was not available in the HES dataset. Similarly, linkage to ONS data for death certificate causes of death enables evaluation of the accuracy of death records in CPRD GOLD. However, few such records are based on rigorous autopsy information, raising the possibility of random inaccuracies in the ONS-recorded causes of death (Random bias).

2.3 Study population

This study used the CPRD GOLD database version April 2018, which contains the primary care information for 15,354,125 participants from a total of 734 UK practices. All participants met CPRD acceptability criteria (Details in section: quality control of data in CPRD GOLD). For the analyses related to the causes of death and hospital admissions, this study also used a subset of CPRD GOLD data linked with basic HES APC and ONS datasets (linkage eligibility set 16); the subset contains data for 8,444,946 participants registered to 411 practices in England. The population of 'cases' selected for the present study consists of patients who were diagnosed as having adrenal insufficiency (study patients) and their matched controls.

2.3.1 Study patients

To select study patients, inclusion and exclusion criteria were established. The initial criteria were based on medical codes and product codes. Detailed information for the study patients was subsequently used to further refine exclusion of the study patients.

Inclusion criteria- CPRD participants were eligible to be study patients if all the following were present:

1. Ever recorded: medical codes for any diagnoses of conditions related to adrenal insufficiency: adrenal insufficiency, Addison’s disease, adrenal crisis, hypopituitarism,

pituitary hormone deficiency, pituitary adenoma, Sheehan's syndrome, craniopharyngioma, congenital absence of the pituitary gland, or intervention on the pituitary gland (Appendix, Suppl. Table 2.1)

2. Ever prescribed: the oral form of any of hydrocortisone, cortisone acetate, prednisolone, or prednisone, as recorded using product codes (Appendix, Suppl. Table 2.2).

Exclusion criteria based on medical codes were initially established for use, in combination with the codes of inclusion criteria, for selection of study patients from the CPRD GOLD dataset.

Initial exclusion criteria- CPRD participants were ineligible to be study patients if any of the following medical codes were recorded at any time in the CPRD GOLD dataset:

1. Medical codes for any diagnoses of conditions that might have contributed to increased mortality and/or cardiovascular disease: Cushing syndrome, Cushing disease, acromegaly, gigantism, carcinoma / primary malignant neoplasms/ secondary malignant neoplasms of the pituitary gland, or carcinoma / primary malignant neoplasms / secondary malignant neoplasms of the adrenal glands (Appendix, Suppl. Table 2.3)
2. Medical codes for describing the diagnosis of congenital adrenal hyperplasia or related conditions: congenital adrenal hyperplasia and precocious puberty with adrenal hyperplasia (Appendix, Suppl. Table 2.3)

All medical codes and product codes for the inclusion and exclusion criteria were rigorously listed, given that one particular condition (or medication) is often described by many medical codes (product codes). The listed codes were sent to a data manager to extract eligible study patients from clinical, referral, test, and therapy files in the CPRD GOLD dataset. All extracted study patients had to have medical codes of conditions related to adrenal insufficiency (Inclusion criterion #1) and product codes of oral glucocorticoids (Inclusion criterion #2), along

with not having medical codes of conditions stated in the initial exclusion criteria (#1 or #2). The number of extracted study patients by this method was 8043 and this preliminary number was used to determine the feasibility of the study in the application to access the CPRD GOLD dataset (Appendix, Suppl. Material 2.4). Details of the feasibility were also demonstrated in the section below: Sample size consideration.

After access to the CPRD GOLD dataset was approved, detailed information of the extracted study patients and their practices was then available. This included UTS, CRD, LCD, TOD, and dates at which glucocorticoids had been prescribed, all of which variables were to be found in practice, patient, clinical, test, referral, immunisation, and therapy files (Details in sections: Structure of the CPRD GOLD database and Follow-up period). These variables were then used to further refine exclusions for extracted study patients.

Subsequent exclusion criteria: the extracted study patients were excluded if <u>any of</u> the following were <u>absent</u>:

1. Having one or more glucocorticoid prescriptions within 90 days after the first record of adrenal insufficiency
2. Having a follow-up period of 30 days or more
3. Having age at the start of follow-up of less than 100

Subsequent exclusion criterion #1 was established to ensure that the glucocorticoid prescription of each patient was related to the treatment of adrenal insufficiency. Subsequent criterion #2 was established to ensure that if the follow-up period of a study patient ended because of death, this was unlikely to have been related to post-operative complications of hypothalamic-pituitary surgery.

In a total of 8043 extracted study patients, the subsequent exclusion criteria were applied step by step. For the subsequent exclusion criterion #1, the dates of all oral glucocorticoid prescriptions for each patient available in Therapy file were evaluated and cross-checked with

the first date at which the medical codes of conditions related to adrenal insufficiency appeared (Inclusion criterion #1). Thereby 671 extracted study patients were excluded and 7372 remained eligible. For the subsequent exclusion criterion #2, the follow-up periods of the remaining 7372 patients were evaluated and 547 patients were found to have a follow-up period of less than 30 days (Details in section: follow-up period). For the subsequent exclusion criterion #3, no patient was further excluded as all had age less than 100 at the start of follow-up. The final number of study patients, eligible for matching with controls, was 6825. These study patients were registered across 703 practices. The study patient profile is illustrated in Figure 2.1.

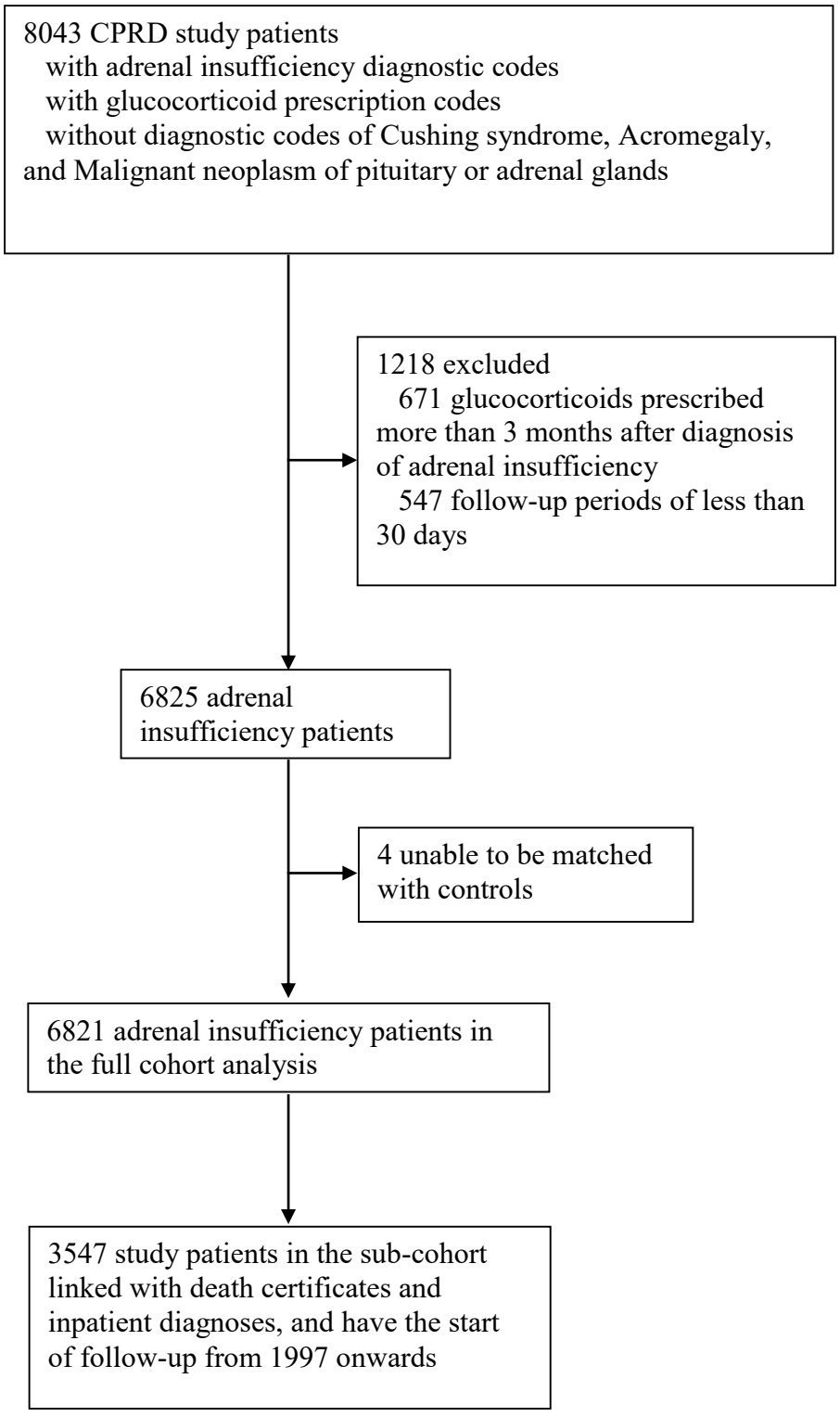


Figure 2.1: Study patient profile

2.3.2 Matched controls

Controls were selected from the participants in the same CPRD GOLD dataset (April 2018) who were not the intended study patients. A list of patient identifiers of potential controls was prepared before matching. A total of 15,347,300 participants were excluded step-by-step (Figure 2.2), if any of the following was present:

1. Not being registered with one of 703 practices, to which the 6825 study patients had been registered
2. Having a follow-up period of less than 30 days
3. Unknown sex

After the above exclusions, the number of potential controls was 12,527,940. Subsequently, up to ten of these participants were randomly matched with each individual study patient. The matched controls had the same sex, practice, 5-year strata of the year of birth, and 5-year strata of the year at start of follow-up, as their corresponding study patient. Matching practices indicated that study patients and matched controls had similar geographical locations. These criteria were used to match to ensure that the risks of mortality and cardiovascular disease were not likely to be confounded by differences between study patients and controls in sex, age, and period and place of care.

After individual matching, four study patients could not be matched with any control and each of 163 study patients could not be matched with fully ten controls. Thereby, the final number of study patients analysed in this study was 6821, matched with 67564 controls. Details of the number of study patients corresponding to the number of their matched controls (matching ratios) are given in Table 2.3.

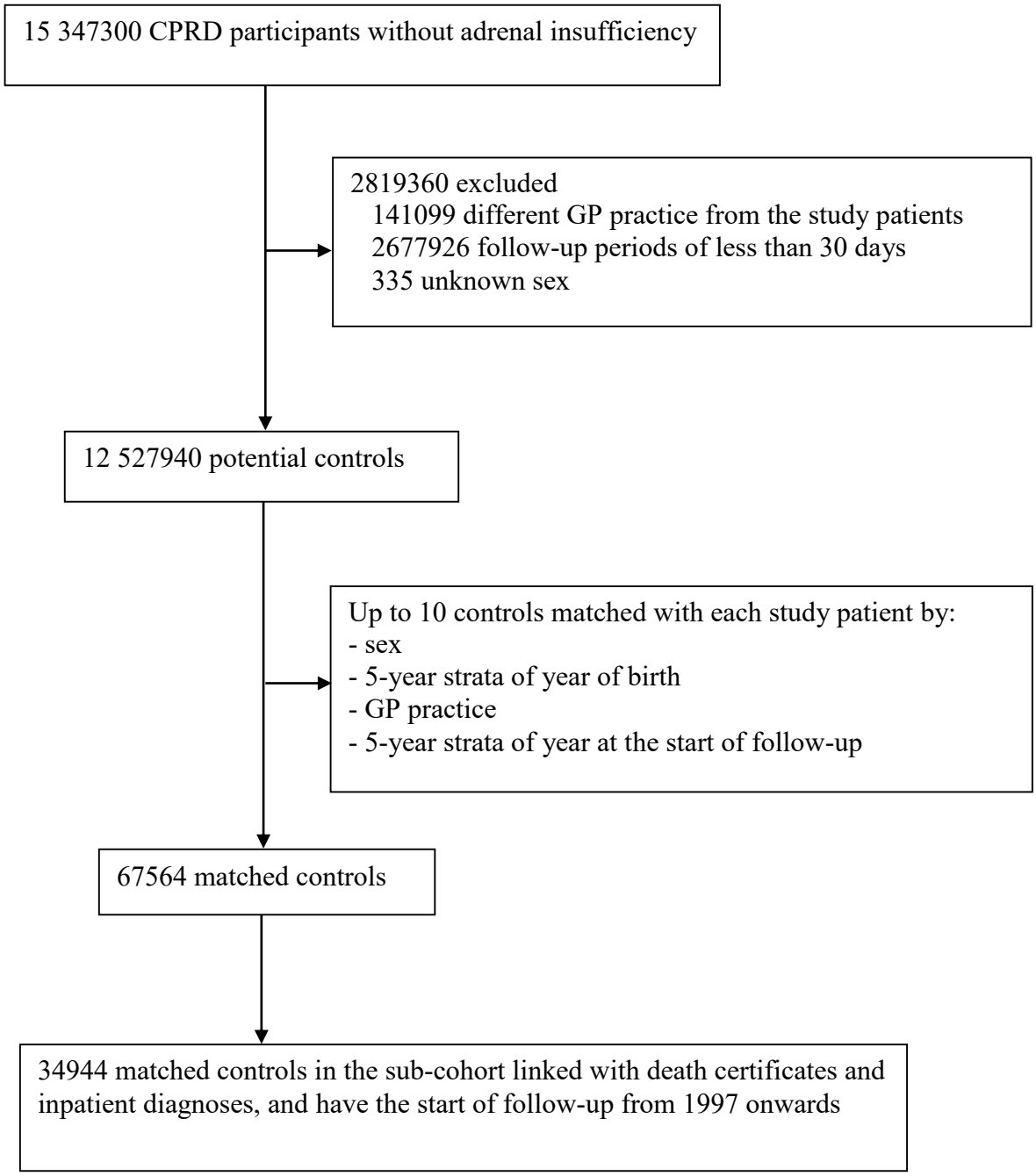


Figure 2.2: Control profile

Matching ratio (number of matched controls for each patient)	Number of corresponding study patients (%)	Number of corresponding matched controls (%)
10	6658 (97.61%)	66580 (98.54%)
9	27 (0.40%)	243 (0.36%)
8	28 (0.41%)	224 (0.33%)
7	27 (0.40%)	189 (0.28%)
6	17 (0.25%)	102 (0.15%)
5	21 (0.31%)	105 (0.16%)
4	10 (0.15%)	40 (0.06%)
3	19 (0.28%)	57 (0.08%)
2	10 (0.15%)	20 (0.03%)
1	4 (0.06%)	4 (0.01%)
Total*	6821 (100%)	67564 (100%)

Table 2.3: A number of study patients and their corresponding matched controls according to the matching ratio

Note: * Dedicate the final numbers of study patients and matched controls, analysed in this study.

2.3.3 Sample size consideration

Initially, this research was planned primarily to investigate the risk of cardiovascular disease in patients with adrenal insufficiency. The sample size calculation thus was based on the prevalence of cardiovascular events and this was used in the application to access to the CPRD data (Appendix, Suppl. Material 2.4). Subsequently, the sample size based on all-cause mortality rates was calculated. Both sample sizes were calculated according to the hypothesis that because of the improvement in the care for adrenal insufficiency and cardiovascular disease prevention, the rates of cardiovascular events and all-cause mortality in patients with adrenal insufficiency were not different from those of the general population, as represented by the matched controls in a 10:1 ratio.

Regarding cardiovascular disease, at the time of the sample size calculation, no data for the risk of cardiovascular events in adrenal insufficiency were available. The risk was, therefore, estimated using previous reports of risks of cardiovascular mortality as quantified by the SMR. The SMRs for cardiovascular mortality have been reported at 1.97 to 2.31 and 0.70 to 1.75 for patients with primary adrenal insufficiency (73) and pituitary disorders (23, 77, 85, 88-90), respectively. In a report from the British Heart Foundation, in 2011 the prevalence of cardiovascular disease of British men and women with age range of 45-64 years was 14.6% and 8.4%, respectively (155), giving an overall prevalence of 11.5% for both sexes combined. On the basis of these SMRs and reported cardiovascular events, it was estimated that the participant numbers of 3525 study patients and 35250 controls were sufficient to detect a 14% increased risk of cardiovascular disease in patients with adrenal insufficiency, providing 80% power and 5% level of significance.

Regarding all-cause mortality, the SMRs have been reported at 1.15 to 3.89 and 0.84 to 3.80 in patients with primary adrenal insufficiency (19, 73-75) and pituitary disorders (23, 49, 76-82, 85-90), respectively. In a report from the Office for National Statistics (ONS), in 2011 the age-

standardised mortality rates in England and Wales were 1159.6 and 842.1 per 100,000 for men and women, respectively (156), giving a mortality rate of 1.00085% for both sexes. On the basis of the reported SMRs and mortality rates, it was estimated that the participant numbers of 3960 study patients and 39600 controls were sufficient to detect a SMR of 1.50 for patients with adrenal insufficiency, providing 80% power and 5% level of significance.

The CPRD GOLD database was initially assessed to check the feasibility of the study by extracting the participants using the medical and product codes for inclusion and exclusion criteria (Details in section: study patients). The preliminary number of participants who were eligible to be the study patients was 8043. Assuming that the number of study patients would be decreased by 20% after applying the subsequent exclusion criteria, the feasible number of study was 6434, which remained higher than the numbers estimated from the sample size calculation for the outcomes of cardiovascular disease and all-cause mortality.

After the full CPRD GOLD dataset was available and matching was performed, the final numbers of study patients of 6821 and matched controls of 67564 also remained higher than the numbers estimated from the sample size calculation for both outcomes.

2.3.4 Agreement of matching parameters between study patients and matched controls

Study patients were individually matched with controls on the basis of sex, year of birth, practice identifier and year of the start of follow-up. These parameters of the study patients were individually compared with those of their corresponding matched controls. These parameters were changed to numeric variables and coded as to whether they were for the study patients or for the controls. For example, male sex (or female sex) in the study patients and in controls were recorded as ‘1’ (or ‘2’) in a variable name of case_gender and control_gender, respectively. The numeric differences between the parameters in the study patients and corresponding controls were calculated and the zero result indicated that the parameter was

identical between the study patients and controls. There was 100% matching of sex and practice identifier. The years of birth in matched controls were 85% identical to those in corresponding study patients with a 3-year maximum difference. The years of start of follow-up in matched controls were 52% identical to those in study patients with a 3-year maximum difference (Table 2.4).

Year differences*	Year of birth		Year of the start of follow-up	
	Number of matched controls	Percentage of matched controls	Number of matched controls	Percentage of matched controls
-3	366	0.54	1866	2.76
-2	850	1.26	3614	5.35
-1	4390	6.50	8975	13.28
0	57289	84.79	35024	51.84
1	3973	5.88	11943	17.68
2	696	1.03	6142	9.09
Total	67564	100.00	67564	100.00

Table 2.4: Number of matched controls of which their parameter years (years of birth and years at the start of follow-up) were different from the corresponding study patients

Note: * Minus value indicates that the parameter years of study patients occurred earlier than those of the corresponding matched controls.

2.3.5 Subcohorts of study participants

The study participants were subdivided according to types of adrenal insufficiency and whether or not they had linkage to the HES/ ONS datasets.

Types of adrenal insufficiency

The medical codes describing the conditions related to adrenal insufficiency (Appendix, Suppl. Table 2.1) were organised into three groups according to types of adrenal insufficiency: (1) Primary, (2) Secondary, and (3) Unknown type (specifically: adrenal crisis, Addisonian crisis, adrenocortical insufficiency.) Medical codes for adrenal insufficiency and primary adrenal insufficiency could be listed directly, since Read terms for these conditions are available. However, there is no specific Read terms for secondary adrenal insufficiency. Medical codes for secondary adrenal insufficiency were listed on the basis of Read terms describing pituitary or hypothalamic disorders (Appendix, Suppl. Table 2.1). All listed medical codes were examined in clinical, referral, test, and immunisation files, in order to categorise study patients into four groups: 1) Primary adrenal insufficiency, 2) Secondary adrenal insufficiency, 3) Unknown type, and 4) Uncertain type. Patients having 'unknown type' medical codes remained in the unknown type unless medical codes for primary (or secondary) adrenal insufficiency were later recorded and the patients were categorised accordingly. Patients of 'uncertain type' were those having medical codes for primary (or secondary) adrenal insufficiency and then later having medical codes for secondary (or primary) adrenal insufficiency. With this method, the numbers of classified patients were 2052 for primary adrenal insufficiency; 3948 for secondary adrenal insufficiency; 685 for unknown type, and 136 for uncertain type of adrenal insufficiency. Patients of 'unknown type' and 'uncertain type' were merged and classified as unspecified adrenal insufficiency, giving a total number of 821 for unspecified adrenal insufficiency.

As the study patients were individually matched with up to ten controls, there was a unique number for each set of a study patient with its matched controls (set identifier). Set identifiers were used to extract subcohorts of participants (study patients and matched controls) according to the assigned type of adrenal insufficiency. The subcohorts of participants used for further analyses included those with primary and those with secondary adrenal insufficiency. There were 2052 patients vs 20366 controls and 3948 patients vs 39134 controls, in primary and secondary adrenal insufficiency subcohorts, respectively.

Subcohort of participants with linked HES/ ONS datasets

There were 3839 study patients and 38455 controls, for which the linked HES/ ONS datasets were available. Only the participants with linked data having the start of follow-up from 1997 onwards were included in this subcohort to be consistent with the period at which CPRD GOLD had been linked with secondary care data. The numbers of participants included for the analysis of hospital admissions and causes of death were then 3547 and 34944 for the study patients and controls, respectively. Of these participants, 1015 patients vs 10025 controls and 2136 patients vs 20991 controls were assigned in primary and secondary adrenal insufficiency subcohorts, respectively.

2.4 Follow-up period

The start and end of follow-up were defined according to the recommendation from CRPD to ensure that the follow-up period had reliable clinical information. The start date was the most recent date of one of the following dates: (1) Current registration date (CRD), (2) Up to standard date (UTS), or (3) Index date (valid only in the study patients). Index date for a given study patient was the first date at which a condition related to adrenal insufficiency (Appendix, Suppl. Table 2.1) was recorded in the practice software system. Index date might have been earlier than the date that CPRD was established since the system allows GPs to flexibly record

according to the patients' previous medical history. Index date was thus presumed to be the date of diagnosis of adrenal insufficiency. The end date was the earliest date of one of the following dates: (1) Transfer out date (TOD), (2) Last collection date (LCD), or (3) the end of 2017. Possible follow-up periods are illustrated in Figure 2.3.

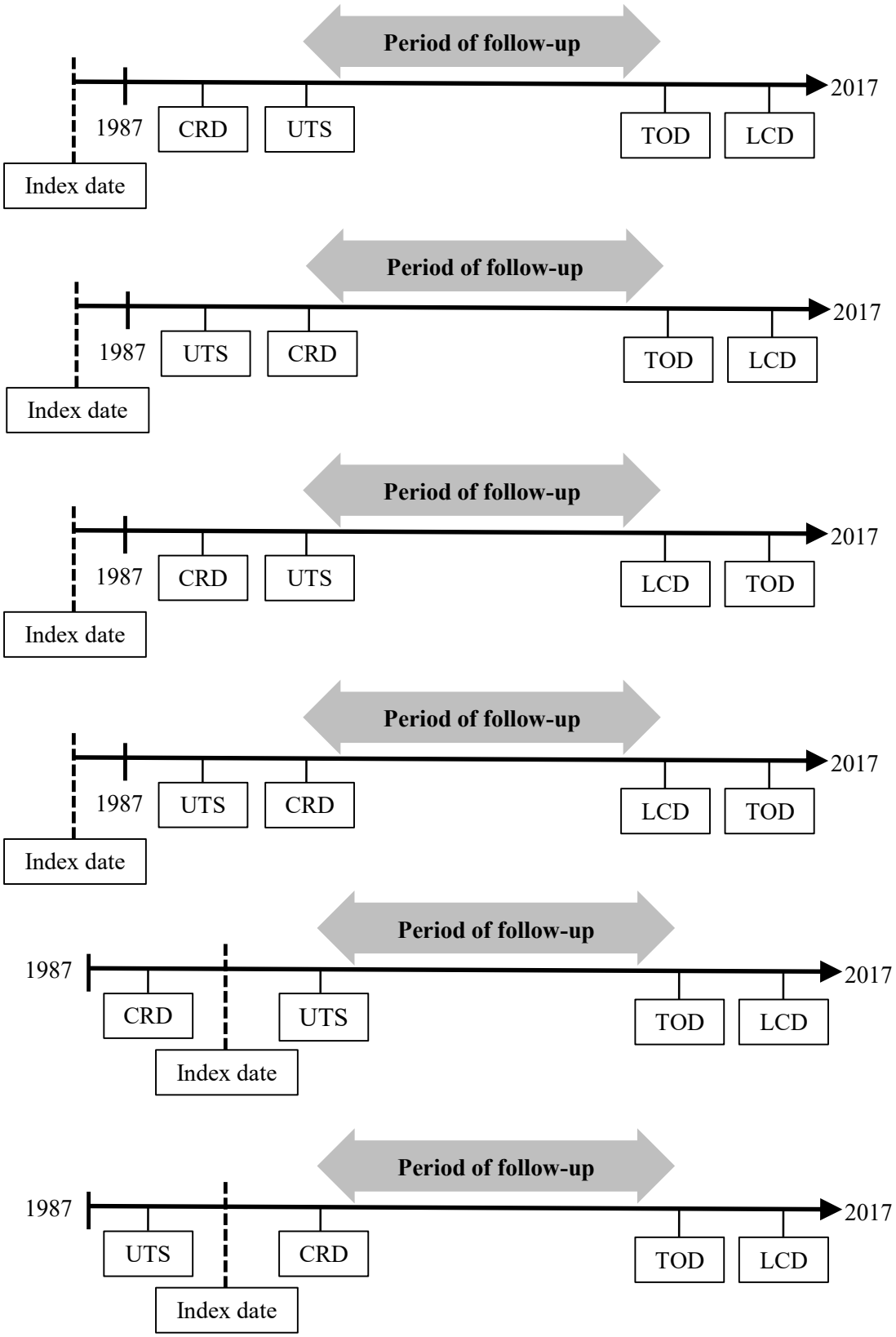


Figure 2.3: Possible follow-up periods of the participants

Note Index date or the date of diagnosis of adrenal insufficiency; CRD: Current registration date; UTS: Up to standard date; TOD: Transfer out date; LCD: Last collection date

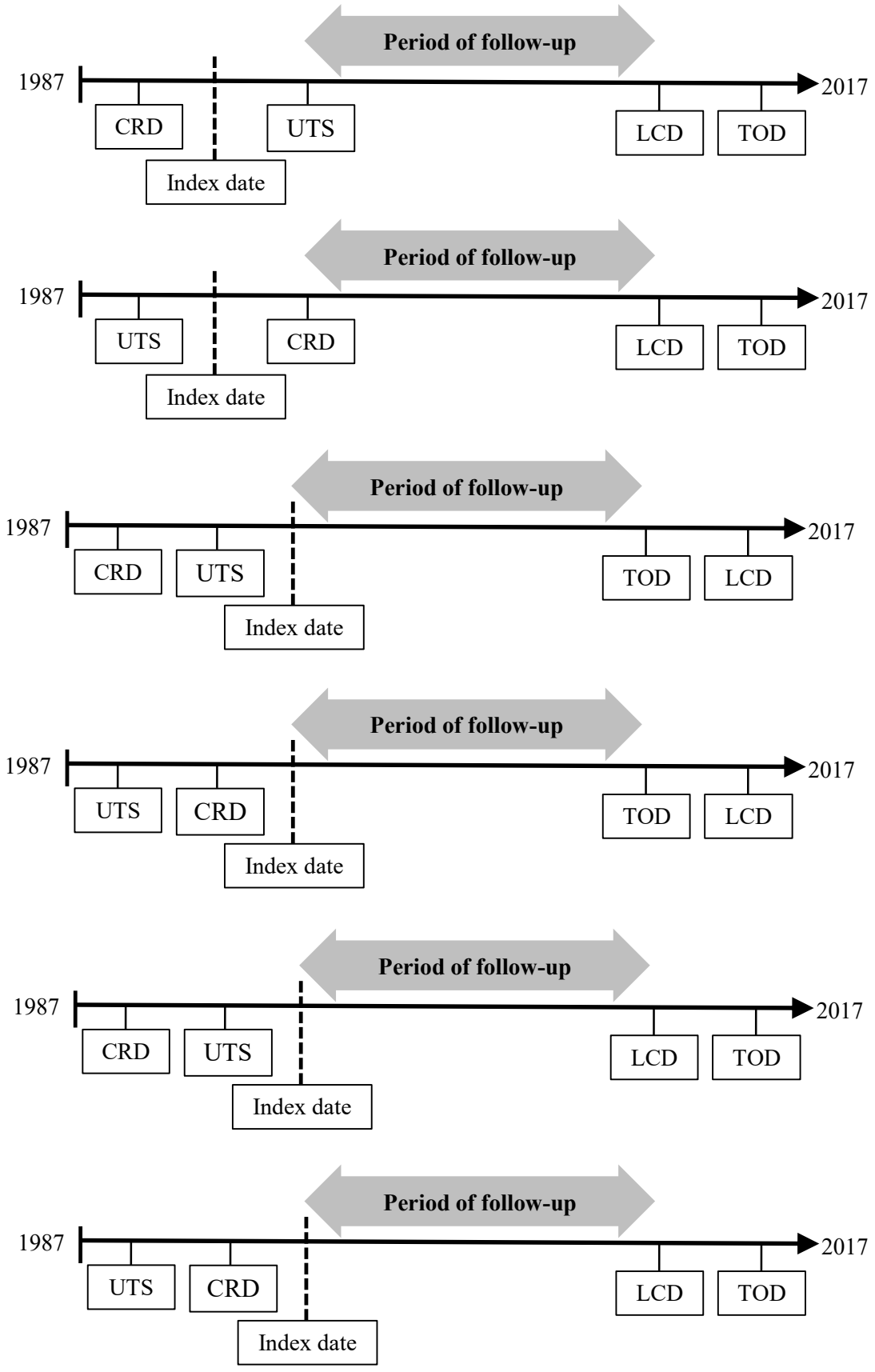


Figure 2.3 (continued): Possible follow-up periods of the participants

Note: Index date or the date of diagnosis of adrenal insufficiency; CRD: Current registration date; UTS: Up to standard date; TOD: Transfer out date; LCD: Last collection date

2.5 Study outcomes

2.5.1 Primary outcomes

Primary outcomes consisted of all-cause mortality and first cardiovascular mortality or morbidity, all of which were obtained from records in the CPRD GOLD dataset.

All-cause mortality was considered to be valid when the two conditions were met in a participant: (1) there was a record of transfer out (with the reason of death or not defined) and (2) there was the record of the date of death in CPRD GOLD dataset, which was within the follow-up period.

Cardiovascular disease was the first record of a fatal or non-fatal cardiovascular event during the follow-up period, consisting of (1) composite cardiovascular disease, (2) ischaemic heart disease, or (3) cerebrovascular disease. Composite cardiovascular disease included ischaemic heart disease, congestive cardiac failure, aortic dissecting, aortic aneurysm, atrial fibrillation, cerebrovascular disease, and peripheral arterial disease. Cerebrovascular disease included transient ischaemic attack or transient cerebral ischaemia. Medical codes related to these conditions were listed according to three defined cardiovascular outcomes (Appendix, Suppl. Table 2.5). Three code lists were individually examined in clinical, referral, test, and immunisation files.

2.5.2 Secondary outcomes

Secondary outcomes consisted of cause-specific mortality, mortality associated with adrenal crisis, incidence of adrenal crisis in hospital admissions, cardiovascular mortality, hospital admissions due to cardiovascular disease, and other detailed hospital admissions.

Cause-specific mortality was defined according to organ systems and specific disease, particularly the leading causes of death in each system. The cause of death was assigned according to the record of the principal cause in the ONS linked dataset, which was formatted using ICD-9 or ICD-10 codes (Appendix, Suppl. Table 2.6). A death was included in the

analysis of cause-specific mortality when the death recorded in ONS was concordant with that in CPRD GOLD and the ONS date of death occurred during the follow-up period.

Mortality associated with adrenal crisis was assigned whether adrenal crisis had been recorded as the principal or other causes of death. Adrenal crisis was defined by the ICD-10 code of E27.2; however, no ICD-9 code is available for the specific description of adrenal crisis.

Incidence of adrenal crisis in hospital admissions included any record of adrenal crisis (ICD-10: E27.2) as the primary diagnosis or among comorbidities, or conditions developing later during the hospital admissions. Only one record of adrenal crisis in each admission was assigned but other records of adrenal crisis in subsequent admissions were taken into account.

Cardiovascular mortality consisted of the principal cause of death recorded using the ICD-9 or ICD-10 codes. Cardiovascular mortality consisted of the principal cause of death from (1) disease of the circulatory system (2) ischaemic heart disease, and (3) cerebrovascular disease (Appendix, Suppl. Table 2.7). Disease of the circulatory system was defined in accordance to the ICD-9 and ICD-10 classifications for non-atherosclerotic cardiovascular diseases such as rheumatic heart disease. However, disease specific for atherosclerosis was also evaluated and defined as ischaemic heart disease and cerebrovascular disease. Cerebrovascular disease included ICD-9 and ICD-10 codes describing cerebrovascular disease (categorised in diseases of the circulatory system by ICD) and transient cerebral ischaemic attack (categorised in diseases of the nervous system).

Hospital admissions due to cardiovascular disease consisted of the primary diagnosis for a hospital admission, as suggested to be the main reason for hospitalisation. Hospital admissions due to cardiovascular disease consisted of admissions for (1) disease of the circulatory system, (2) ischaemic heart disease, and (3) cerebrovascular disease, in which the ICD-10 codes used were identical to those defining cardiovascular mortality (Appendix, Suppl. Table 2.7).

Hospital admissions from each subtype of cardiovascular disease was independently considered and valid only when recorded for the first time during the follow-up period.

Other detailed hospital admissions included hospital admissions from any diagnosis, emergency hospital admissions, and average length of stay. Hospital admissions from any diagnosis included all records of hospitalisation from HES APC linked data during the follow-up periods. Emergency hospital admission was an unpredictable admission or admission at short notice when there was clinical need. Emergency hospital admission was evaluated from the method of admission available from the HES APC hospital file, in which the method of each admission is encoded. The code used to define emergency admission was listed according to NHS digital recommendation (152). Average length of stay was the mean duration (in days) of hospital admissions in which the duration of admissions was completed during a year of follow-up. Hospital admissions where admitted date and discharge date were the same were excluded from the analysis of length of stay since it was considered to be a day case that could skew the calculated length of stay.

2.6 Other covariates

In addition to age, sex, calendar time and geographical location of care, other covariates might have affected the risk of developing cardiovascular disease and, possibly, mortality. Covariates considered in this study included previous cardiovascular disease, diabetes mellitus, hypertension, dyslipidaemia, and smoking, all of which are classical cardiovascular risk factors. Medical codes describing cardiovascular disease, diabetes mellitus, hypertension, and smoking were listed and used inclusively to search clinical, referral, test, and immunisation files. For cardiovascular disease, medical codes used were identical to those used for the primary outcome (Appendix, Suppl. Table 2.5). For diabetes, hypertension, and smoking, medical codes were also listed accordingly (Appendix, Suppl. Table 2.8-2.10). However, no medical code was available for describing the diagnosis of dyslipidaemia. Product codes for the prescription of lipid-lowering agents were used (Appendix, Suppl. Table 2.11) and the codes were available only in the therapy file.

Covariates were defined as baseline characteristics and comorbidity. Baseline characteristics were assigned when covariates were recorded before or at the start of follow-up, except for smoking. A participant was considered to have smoking as a baseline characteristic when a medical code describing smoker or ex-smoker was recorded at any time before the end of follow-up. This was based on the justification that those recorded as ex-smokers were less likely to quit smoking completely and the risk of cardiovascular disease associated with smoking remains for years. However, cardiovascular risk associated with smoking recorded before the start of follow-up was also compared with the risk associated with smoking recorded at any time (details in Chapter 5: Sensitivity analysis). These covariates at baseline were evaluated as 'confounding factors' that might have contributed to variation in risk of cardiovascular disease. In addition, co-morbid cardiovascular disease or diabetes were

evaluated as 'effect modifiers' that could further increase or decrease mortality risk. Risk differences in age and sex were also examined as effect modifiers.

Some covariates, which are considered to be cardiovascular risk factors, were not used as an ‘adjustment variable’ in multivariable Cox regression models. Variables not used included deprivation index, ethnicity, family history of premature cardiovascular disease and body mass index (BMI). Deprivation index was available only in participants with linked data (50% of participants) and the deprivation index was based on ‘practice level’. The present study has individually matched the study patients with controls using practice identifiers. Therefore, deprivation index was already taken into account in the study design. Ethnic variation in risk for cardiovascular disease has been distinguished in a number of studies but, again, ethnicity was available only in participants with linked data. Six codes in CPRD GOLD specify family details of cardiovascular disease, and one code specifies not having family history of cerebrovascular disease or stroke. However, no code specifies “prematurity” or “early onset” of cardiovascular disease in family members; therefore, these codes may not relate to the risk of cardiovascular disease in selected cases and controls. Moreover, for the majority of participants in CPRD GOLD, there was no positive indication as to whether there was or was not a family history of cardiovascular disease. BMI was unavailable for 29% (1964/ 6821) of patients with adrenal insufficiency and only 3% (209/ 6821) of the study patients had BMI data on the date of the start of follow-up. It should also be noted that the majority of covariates that were adjusted for were BMI related, especially histories of diabetes and of hyperlipidaemia, so some of the more pathological consequences of high BMI may, in any case, have been adjusted for.

In patients with pituitary disorders, radiotherapy has been reported to be a major factor associated with increased mortality (45, 78, 80, 89, 90), especially death from cerebrovascular disease (78, 89). In this study, history of radiotherapy was evaluated in a subgroup of patients

with secondary adrenal insufficiency to determine whether it was associated with mortality and cardiovascular disease.

2.7 Statistical analyses

2.7.1 Primary analyses

Mortality of patients with adrenal insufficiency and controls was calculated in rates per 1000 person-years using survival analysis and risk ratios (relative to controls) were expressed as hazard ratios (HRs) as derived from univariable and multivariable Cox regression models. Mortality rates were categorised according to years of follow-up, years of diagnosis (study patients only), age at start of follow-up, sex, co-morbid cardiovascular disease and co-morbid diabetes mellitus. HRs were also derived according to sex, age, co-morbid cardiovascular disease and diabetes. Interaction tests were used to evaluate whether these factors were acting as effect modifiers with respect to mortality risk. Cumulative mortality incidence was displayed in line graphs using the Kaplan-Meier failure function and this was estimated to a follow-up period of 10 years, as the number of remaining participants was low thereafter, especially when participants were categorised according to types of adrenal insufficiency and comorbidities.

Cardiovascular events in patients with adrenal insufficiency and controls were also expressed as incidence rates per 1000 person-years using survival analysis and risks relative to controls were evaluated as HRs according to univariable and multivariable Cox regression models. Classical cardiovascular risk factors (Details in section 2.5 Other covariates) were used for adjustments in multivariable Cox regression models. The rates of cardiovascular disease were also categorised by age at start of follow-up, sex, co-morbid cardiovascular disease, co-morbid diabetes mellitus, and statin use. HRs were also categorised according to sex, age, co-morbid cardiovascular disease, diabetes, and statin use. Interaction tests were used to evaluate whether these factors were acting as effect modifiers with respect to risk of cardiovascular disease.

For Cox proportional hazards models of all-cause mortality and cardiovascular events, tests for departures from the proportional hazard assumption were performed using the 'Schoenfeld residuals' method.

2.7.2 Secondary analyses

Cause-specific mortality of patients with adrenal insufficiency and controls was calculated in rates per 1000 person-years using survival analysis and risk ratios were demonstrated as HRs using univariable Cox regression models.

Mortality-associated with adrenal crisis was calculated as the proportion of the number of deaths associated with adrenal crisis to the total number of deaths in patients with adrenal insufficiency. Mortality rates per 1000 person-years were also calculated using survival analysis.

Incidence of adrenal crisis in hospital admissions was calculated as rates per 1000 person-year using survival analysis. Adrenal crisis in hospital admissions was assigned when it was recorded after index date (date of the diagnosis of adrenal insufficiency) and before or at end date. The incidence rate of adrenal crisis first recorded during this period was also categorised according to years after the diagnosis of adrenal insufficiency. With regard to patients having more than one episodes of adrenal crisis, the incidence rates were calculated using multiple failure analysis (Andersen-Gill model) (157). The number of patients having adrenal crisis in hospital admissions was calculated as a proportion to the number of those with linked HES data.

Similar to cardiovascular events, *cardiovascular mortality* and *hospital admission from cardiovascular disease* were calculated as rates per 1000 person-years using survival analysis and as HRs using univariable and multivariable Cox regression models. Classic cardiovascular risk factors were also used for adjustments in multivariable Cox regression models. HRs were also categorised according to sex, age, co-morbid cardiovascular disease and diabetes. Effect

modification was tested using interaction tests to evaluate whether risk of cardiovascular mortality was influenced by these factors.

Hospital admissions were expressed as the proportion of patients admitted to hospitals from any cause to those having CPRD-HES linked data. Likewise, emergency hospital admissions were also expressed as the proportion of patients admitted to hospital in a short notice to those having HES linked data and the proportion of patients admitted to hospitals in a short notice to all patients admitted to hospitals. These proportions in the study patients were compared with those of controls using Chi-square test. *Average length of stay (in days)* of study patients was compared with that of controls using rank sum test since it had non-normal distribution.

2.7.3 Other analyses

Baseline characteristics of study patients and controls were compared using Chi-square test for binary data (difference in proportions), independent t-test for quantitative data with normal distribution (difference in mean), and rank sum test for quantitative data with non-normal distribution (difference in median).

The association between radiotherapy and mortality or cardiovascular disease in patients with secondary adrenal insufficiency was evaluated and reported by odds ratios using logistic regression analysis.

All analyses in the subcohorts of primary and secondary adrenal insufficiency were also analysed as the whole cohort unless indicated otherwise. All analyses of risk ratios were reported with 95% confidence interval. All analyses were performed by using Stata SE version 15.1.

2.8 Ethical considerations

To protect patients' identity and confidentiality, all data were derived from a CPRD GOLD dataset and its HES/ ONS linkage, in which all identifiable data such as patients' names, addresses, date of birth, and NHS number were not available for researchers. In addition, all CPRD participants are able to opt out of sharing their health records to CPRD at any time by informing their general practitioners. Also, all UK practices have a right to not contribute their patients' data to CPRD.

To access anonymised patient level data of CPRD, all researchers must obtain ethical approval by submitting study protocols to an Independent Scientific Advisory Committee (ISAC). ISAC is a non-statutory group of experts established by the Secretary of State for Health that provides scientific advice on research-related requests to access data in CPRD (145). ISAC will confirm that the study protocol is feasible, that there are no ethical or governance issues, and that the investigation is of acceptable scientific standard. The protocol of this study was approved by ISAC on 27th July 2018 (Protocol number 18_179). Initially, all data should have been destroyed on 6th September 2019. As the analysis was then still ongoing, a request for retention of data was applied for and was grant until 6th September 2020, at which time all raw data and data management files will have to be destroyed.

To ensure that data were ethically handled and processed, at the start of conducting the study, self-training in Good Research Practice (from Medical Research Council) and Research Data and Confidentiality was undergone. In addition, yearly training requirements, including tests in Data Protection Awareness (under the General Data Protection Regulation-GDPR) and information security awareness, have been met.

CHAPTER 3: MORTALITY AND HOSPITAL ADMISSION DATA

MAIN FINDINGS

- All-cause mortality risks relative to controls were increased in patients with adrenal insufficiency of any type (HR, 1.68 [95%CI, 1.58-1.77], p<0.0001), including primary and secondary adrenal insufficiency (primary, HR, 1.83 [1.66-2.02] and secondary, HR 1.52 [1.40-1.64])
- The mortality risk in patients with primary adrenal insufficiency was greater than those with secondary disease (adjusted HR for age and sex, 1.27 [95% CI, 1.13-1.43], p<0.0001)
- The mortality risks relative to controls were increased to a similar extent, regardless of sex or co-morbid diabetes mellitus, in both primary and secondary adrenal insufficiency
- The mortality risks relative to controls were increased to a greater extent in younger patients than older individuals, in both primary and secondary adrenal insufficiency
- The mortality risks relative to controls were increased to a similar extent, independent of co-morbid cardiovascular disease, in adrenal insufficiency of any type and primary disease; however, in secondary adrenal insufficiency, the risk was higher in those without than in those with cardiovascular disease.
- The increased mortality risks relative to controls remained unchanged even for the patients attending recent clinical care in adrenal insufficiency of any kind and primary disease; however, in secondary adrenal insufficiency, the risk was lower in those with recent clinical care
- A maximum mortality rate was observed in the first year after diagnosis and yearly mortality risks were significantly increased after the first few years of follow-up in patients with adrenal insufficiency, in particular primary adrenal insufficiency

- Three leading causes of death in descending orders were diseases of the circulatory system, neoplasm, and respiratory system both in adrenal insufficiency patients and controls; however, the patients had significantly higher mortality rates from all these causes
- In patients with adrenal insufficiency of any kind including primary and secondary disease, the mortality risk from infectious disease relative to controls was considerably increased, although the mortality rate was low. When deaths from respiratory tract and urinary tract infections were combined, infection became among the leading causes of death in the patients.
- Patients with adrenal insufficiency had a higher proportion of hospital admissions and emergency hospitalisation, compared with controls
- Adrenal crisis contributed to one-tenth, one-third, and one percent of all deaths in patients with adrenal insufficiency of any kind, primary and secondary adrenal insufficiency, respectively
- Hospital admissions associated with adrenal crisis were greatest during the first year after diagnosis in patients with adrenal insufficiency of any type, including primary and secondary disease.
- Patients ever hospitalised for adrenal crisis had an increased risk of death associated with adrenal crisis

CHAPTER 3: MORTALITY AND HOSPITAL ADMISSION DATA

This chapter presents cohort baseline characteristics, a primary outcome of all-cause mortality, and secondary outcomes related to cause-specific mortality, adrenal crisis and hospital admissions.

3.1 Cohort baseline characteristics

Baseline characteristics, consisting of demographics, period of follow-up, calendar years of start and end of follow-up, and risk factors for cardiovascular disease, were evaluated in (1) the whole cohort of patients with adrenal insufficiency of any type and matched controls, and (2) subcohorts of patients with primary, secondary, and unspecified adrenal insufficiency and their matched controls. Statistical differences in baseline characteristics at the start of follow-up were compared between the study patients and matched controls (Table 3.1 and 3.2), and baseline characteristics at diagnosis and at the start of follow-up between the study patients having different types of adrenal insufficiency (Table 3.3 and 3.4). Also, an identical evaluation was performed in the subcohort of participants (study patients and controls) whose data have been linked with HES and ONS, and had the start of follow-up from 1997 onwards (Table 3.5 to 3.8).

3.1.1 Characteristics of the whole cohort of patients with adrenal insufficiency of any type, primary, secondary, and unspecified adrenal insufficiency, compared with their matched controls

- ❖ Patients with adrenal insufficiency of any type and their matched controls

From a total of 6821 patients with adrenal insufficiency of any type and 67564 matched controls, women accounted for approximately 54% of patients and controls (p=0.73). Both

groups had the same median age (53 years) at start of follow-up, similar median follow-up times (4.3 [Interquartile range, IQR, 1.7-8.8] years for patients vs 4.0 [1.6-9.0] years for controls; p =0.20) and the same calendar years of start – end of study from 2007 to 2014 (Table 3.1).

Regarding cardiovascular risk factors, the proportions of the patient group having a record of these factors at the start of follow-up were compared with those of the control group (Table 3.2). The proportions of previous cardiovascular disease, ischaemic heart disease, and cerebrovascular disease in the patient group were significantly higher than those in the control group. The proportions of diabetes of any type, type 1 diabetes, hypertension, dyslipidaemia, and statin use in the patient group were also higher than those in the control group. Notably, for dyslipidaemia, the proportions in the patient group relative to controls were approximately four-fold higher (20.5% vs 5.0%; p<0.001), which was markedly higher than for other cardiovascular risk factors, and this reflected a significant number of adrenal insufficiency patients using lipid-lowering agents. For smoking the proportion in the patient group relative to controls was increased when smoking was evaluated at the start of follow-up but this difference was no longer apparent when the evaluation period was extended until the end of follow-up.

CHARACTERISTICS	**Adrenal insufficiency of any type**			**Primary adrenal insufficiency**			**Secondary adrenal insufficiency**			**Unspecified adrenal insufficiency**		
	Patients N = 6821	Controls N = 67564	P	Patients N = 2052	Controls N = 20366	P	Patients N = 3948	Controls N = 39134	P	Patients N = 821	Controls N = 8064	P
Female, (%)	3648 (53.5)	36281 (53.7)	0.73	1192 (58.1)	11883 (58.4)	0.82	1977 (50.1)	19660 (50.2)	0.84	479 (58.3)	4738 (58.8)	0.82
Age at start; year, median (IQR)	53 (38-68)	53 (37-68)	0.20	51 (36.5-67)	51 (36-67)	0.56	54 (38-68)	53 (38-67)	0.36	59 (40-72)	58 (39-72)	0.43
Total follow-up time, year; median (IQR)	4.3 (1.7-8.8)	4.0 (1.6-9.0)	0.17	4.6 (1.7-9.6)	4.3 (1.7-10.0)	0.77	4.4 (1.8-8.9)	4.0 (1.6-8.9)	0.0042	3.1 (1.3-6.9)	3.4 (1.4-7.5)	0.061
Calendar year at start of follow-up; median (IQR)	2007 (2001-2012)	2007 (2001-2012)	0.59	2006 (2001-2011)	2006 (2000-2011)	0.81	2007 (2002-2012)	2007 (2002-2012)	0.72	2009 (2002-2013)	2009 (2002-2013)	0.63
Calendar year at end of follow-up; median (IQR)	2014 (2009-2017)	2014 (2009-2017)	0.15	2014 (2008-2017)	2014 (2009-2017)	0.61	2014 (2010-2017)	2014 (2009-2017)	0.0092	2014 (2009-2013)	2014 (2009-2017)	0.49

Table 3.1: Baseline characteristics of patients with adrenal insufficiency and controls at the start of follow-up

❖ Patients with primary adrenal insufficiency and their matched controls

In the analysis of primary adrenal insufficiency, 2052 study patients and 20366 matched controls were included. The proportion of women in the study group was similar to that of the control group (58.1% vs 58.4%, p=0.82). Both groups had the same median age of follow-up of 51. There was no statistical difference in the median follow-up times between patients and controls: (4.6 [IQR, 1.7-9.6] vs 4.3 [1.7-10.0] years; p =0.77) and calendar years of start – end of study were the same: from 2006 to 2014 (Table 3.1).

Regarding cardiovascular risk factors, similarly to the analysis of adrenal insufficiency of any type, the proportions in the patient group were higher than those in the control group (Table 3.2). For diabetes at baseline, particularly type 1 diabetes, the proportion in the patient group was up to 15 times higher than that in the control group (7.5% vs 0.5%, p<0.001). For smoking, as for adrenal insufficiency of any type, the difference in proportions between the patient and control groups was markedly reduced when the evaluation period was extended until the end of follow-up.

CHARACTERISTICS	**Adrenal insufficiency of any type**			**Primary adrenal insufficiency**			**Secondary adrenal insufficiency**			**Unspecified adrenal insufficiency**		
	Patients N = 6821	Controls N = 67564	P	Patients N = 2052	Controls N = 20366	P	Patients N = 3948	Controls N = 39134	P	Patients N = 821	Controls N = 8064	P
Cardiovascular disease, (%)	1190 (17.5)	7586 (11.2)	<0.001	318 (15.5)	2055 (10.1)	<0.001	680 (17.2)	4438 (11.3)	<0.001	192 (23.4)	1093 (13.6)	<0.001
Ischaemic heart disease, (%)	624 (9.2)	4230 (6.3)	<0.001	169 (8.2)	1136 (5.6)	<0.001	351 (8.9)	2505 (6.4)	<0.001	104 (12.7)	589 (7.3)	<0.001
Cerebrovascular disease, (%)	446 (6.5)	2608 (3.9)	<0.001	98 (4.8)	740 (3.6)	0.009	286 (7.2)	1481 (3.8)	<0.001	62 (7.6)	387 (4.8)	0.001
Diabetes mellitus, (%)	712 (10.4)	3217 (4.8)	<0.001	260 (12.7)	841 (4.1)	<0.001	358 (9.1)	1942 (5.0)	<0.001	94 (11.5)	434 (5.4)	<0.001
Type 1 diabetes mellitus, (%)	222 (3.3)	376 (0.6)	<0.001	153 (7.5)	99 (0.5)	<0.001	49 (1.2)	235 (0.6)	<0.001	20 (2.4)	42 (0.5)	<0.001
Hypertension, (%)	1508 (22.1)	9191 (13.6)	<0.001	349 (17.0)	2625 (12.9)	<0.001	938 (23.8)	5327 (13.6)	<0.001	221 (26.9)	1239 (15.4)	<0.001
Dyslipidaemia, (%)	1397 (20.5)	3407 (5.0)	<0.001	348 (17.0)	960 (4.7)	<0.001	858 (21.7)	1998 (5.1)	<0.001	191 (23.3)	449 (5.6)	<0.001
Statin use, (%)	1339 (19.6)	3305 (4.9)	<0.001	330 (16.1)	928 (4.6)	<0.001	828 (21.0)	1941 (5.0)	<0.001	181 (22.1)	436 (5.4)	<0.001
Ever smoked at the start of follow-up, (%)	2163 (31.7)	13882 (20.6)	<0.001	586 (28.6)	4040 (19.8)	<0.001	1279 (32.4)	8199 (21.0)	<0.001	298 (36.3)	1643 (20.4)	<0.001
Ever smoked before end date, (%)	2928 (42.9)	29114 (43.1)	0.79	832 (40.6)	8660 (42.5)	0.084	1721 (43.6)	17170 (43.9)	0.73	375 (45.7)	3284 (40.7)	0.006

Table 3.2: Baseline cardiovascular risk factors of patients with adrenal insufficiency and controls at the start of follow-up

❖ Patients with secondary adrenal insufficiency and their matched controls

In the analysis of secondary adrenal insufficiency, 3948 study patients and 39134 matched controls were included. The proportion of women in the study group was almost identical to that of the control group (50.1% vs 50.2%, p=0.84). The median ages [IQR] at the start of follow-up were not statistically different between the patient group and controls (54 [38-68] vs 53 [38-67], p=0.36). The median follow-up time [IQR] of the patient group was slightly longer than that of the control group (4.4 [1.8-8.9] vs 4.0 [1.6-8.9] years; p =0.0042) but both groups had the same calendar years of start – end of study: from 2007 to 2014 (Table 3.1).

Regarding cardiovascular risk factors, similarly to the analysis of adrenal insufficiency of any type and primary adrenal insufficiency, the proportions of these factors in the patient group were higher than those in the control group, even in the proportion of type 1 diabetes. As for the analysis of adrenal insufficiency of any type, the proportion of smokers in the patient group was no longer higher than that in the control group when the evaluation period was extended until the end of follow-up (Table 3.2).

❖ Patients with unspecified adrenal insufficiency and their matched controls

In unspecified adrenal insufficiency, the analysis included 821 study patients and 8064 matched controls. The proportion of women in the study group was similar to that of the control group (58.3% vs 58.8%, p=0.82). The median ages [IQR] at the start of follow-up were not statistically different between the patient group and controls (59 [40-72] vs 58 [39-72], p=0.43). The median follow-up times [IQR] for the patient group was slightly shorter than that of the control group (3.1 [1.3-6.9] vs 3.4 [1.4-7.5] years; p =0.061) but both groups had the same calendar years of start – end of study: from 2009 to 2014 (Table 3.1).

Regarding cardiovascular risk factors, similarly to the analysis in other cohorts, the proportions in the patient group were higher than those in the control group. For smoking, when the

evaluation period was extended until the end of follow-up, the difference between the proportions in the patient and control groups was reduced, compared with the difference evaluating at the start of follow-up (Table 3.2).

In summary, baseline demographic data was almost identical between study patients and controls in the whole cohort (overall), and the sub-cohorts of primary, secondary and unspecified adrenal insufficiency. However, for cardiovascular risk factors apart from ever-smoking, the proportions observed in the patient group were significantly higher than the control group in the overall and in the sub-cohorts.

3.1.2 Characteristics of the whole cohort of patients with adrenal insufficiency of any type, primary, secondary, and unspecified adrenal insufficiency at the diagnosis

In this analysis, baseline characteristics of only the study patients were evaluated at the time of a diagnosis of adrenal insufficiency and at the start of follow-up. Baseline characteristics were summarised for the overall group and compared within the three sub-groups of study patients: primary, secondary, and unspecified adrenal insufficiency. Also, characteristics were compared between patients with primary and secondary adrenal insufficiency.

- Sex

Women accounted for 54% of total patients. In primary adrenal insufficiency and unspecified adrenal insufficiency, the majority of patients were women (approximately 58%) but in secondary adrenal insufficiency, both sexes had no difference in the proportion. In a comparison between primary and secondary adrenal insufficiency, the proportion of women was significantly higher in those with primary adrenal insufficiency (58% vs 50%; $p<0.001$; Table 3.3).

CHARACTERISTICS	**Adrenal insufficiency of any type** N = 6821	**Primary adrenal insufficiency** N = 2052	**Secondary adrenal insufficiency** N = 3948	**Unspecified adrenal insufficiency** N =821	P†	P‡
Female, (%)	3648 (53.5)	1192 (58.1)	1977 (50.1)	479 (58.3)	<0.0001	<0.0001
Age at diagnosis; year; median (IQR)	52 (36-67)	50 (35-66)	53 (37-67)	57 (39-72)	0.0001	0.010
Age at start; year; median (IQR)	53 (38-68)	51 (36.5-67)	54 (38-68)	59 (40-72)	0.0001	0.047
Total follow-up time from diagnosis to end date, years; median (IQR)	5.2 (2.0-10.5)	5.6 (2.0-11.5)	5.4 (2.2-10.4)	3.5 (1.4-8.0)	0.0001	0.16
Total follow-up time from start to end date; years; median (IQR)	4.3 (1.7-8.8)	4.6 (1.7-9.6)	4.4 (1.8-8.9)	3.1 (1.3-6.9)	0.0001	0.72
Calendar year at diagnosis; median (IQR)	2006 (2000-2011)	2005 (1999-2011)	2006 (2000-2011)	2008 (2000-2013)	0.0001	<0.0001
Calendar year at start of follow-up; median (IQR)	2007 (2001-2012)	2006 (2001-2011)	2007 (2002-2012)	2009 (2002-2013)	0.0001	0.0001
Calendar year at end of follow-up; median (IQR)	2014 (2009-2017)	2014 (2008-2017)	2014 (2010-2017)	2014 (2009-2013)	0.0051	0.0011

Table 3.3: Baseline characteristics of patients with adrenal insufficiency of any type, primary and secondary adrenal insufficiency at the diagnosis and at the start of follow-up

Note: † P for difference between primary, secondary, and unspecified adrenal insufficiency; ‡ P for difference between primary and secondary adrenal insufficiency

❖ Age

The median age at diagnosis (IQR) was 52 (36-67) in patients with adrenal insufficiency of any type, which was one year lower than median age at the start of follow-up. At diagnosis, the median age (IQR) in those with primary adrenal insufficiency was 50 (35-66), which was significantly younger than in those with secondary adrenal insufficiency (53, IQR [37-67], p=0.010), although this was highest in those with unspecified adrenal insufficiency (57 [39-72]). Similar to patients overall, in those with primary and secondary adrenal insufficiency, the median ages of diagnosis were approximately one year lower than ages at the start of follow-up (Table 3.3).

❖ Follow-up time and calendar years of diagnosis and of the study

From the start of follow-up, the median follow-up time in years (IQR) was 4.6 (1.7-9.6), 4.4 (1.8-8.9), and 3.1 (1.3-6.9) in patients with primary, secondary, and unspecified adrenal insufficiency, respectively. Follow-up time was not significantly different between those with primary and secondary adrenal insufficiency (p=0.72). The median follow-up time from the start of follow-up (period of the study) was approximately one year shorter than the median follow-up time after the diagnosis in overall, primary, and secondary adrenal insufficiency. Similarly, the calendar year at diagnosis was approximately one year before the year at the start of the study (Table 3.3).

❖ Cardiovascular risk factors

At diagnosis, the proportion of previous cardiovascular disease was similar between patients with primary and secondary adrenal insufficiency (14% vs 16%; p=0.087) but this was higher in those with unspecified adrenal insufficiency (22%). Also, the proportion of ischaemic heart disease was similar between those with primary and secondary adrenal insufficiency (7.6% vs

8.3%; p=0.32) but this was higher in those with unspecified adrenal insufficiency (12%). Noticeably, the proportion of cerebrovascular disease in patients with secondary adrenal insufficiency was significantly higher than that in primary adrenal insufficiency (6.9% vs 4.5%; p=0.001) but the proportion was highest in those with unspecified adrenal insufficiency (7.1%). At diagnosis, the proportion of diabetes of any type in those with primary adrenal insufficiency was 12.1%, which was significantly higher than in those with secondary adrenal insufficiency (8.3%; p<0.001). In primary adrenal insufficiency, the proportion of type 1 diabetes was markedly higher than in secondary adrenal insufficiency (7.2% vs 1.2%; p<0.001). For hypertension, the proportion in secondary adrenal insufficiency was higher than in primary adrenal insufficiency (22% vs 15%; p<0.001) but the highest proportion was for unspecified adrenal insufficiency (26%). For dyslipidaemia, similarly to the finding in hypertension at the diagnosis, the proportion was highest in unspecified and lowest in primary adrenal insufficiency (primary, 15% vs secondary, 22% vs unspecified, 26%; p<0.001). In patients with each type of adrenal insufficiency, the proportions of statin users were not different from the proportions of dyslipidaemia observed in those with the same type of adrenal insufficiency. The similar proportion of statin users and patients with dyslipidaemia resulted from the fact that almost all treated participants have used statins as the lipid-lowering agent. For ever-smoking by the end of follow-up, the proportion in patients with unspecified adrenal insufficiency was slightly higher than in those with primary or secondary adrenal insufficiency (Table 3.4).

In summary, the majority of patients were women except among those with secondary adrenal insufficiency in whom women and men shared a similar proportion. Median age at diagnosis of primary adrenal insufficiency was consistent with the observations in previous studies. Patients with unspecified adrenal insufficiency were older, had a shorter period of follow-up, and higher proportions of cardiovascular risk factors, compared with those with secondary and primary adrenal insufficiency, except that type1 diabetes was more markedly observed in primary adrenal insufficiency.

CHARACTERISTICS	**Adrenal insufficiency of any type** N = 6821	**Primary adrenal insufficiency** N = 2052	**Secondary adrenal insufficiency** N = 3948	**Unspecified adrenal insufficiency** N =821	P†	P‡
Cardiovascular disease, (%)	1106 (16.2)	293 (14.3)	630 (16.0)	183 (22.3)	<0.0001	0.087
Ischaemic heart disease, (%)	581 (8.5)	155 (7.6)	327 (8.3)	99 (12.1)	<0.0001	0.32
Cerebrovascular disease, (%)	421 (6.2)	92 (4.5)	271 (6.9)	58 (7.1)	0.001	<0.0001
Diabetes mellitus, (%)	668 (9.8)	248 (12.1)	329 (8.3)	91 (11.1)	<0.0001	<0.0001
Type1 diabetes mellitus, (%)	214 (3.1)	148 (7.2)	48 (1.2)	18 (2.2)	<0.0001	<0.0001
Hypertension, (%)	1394 (20.4)	310 (15.1)	870 (22.0)	214 (26.1)	<0.0001	<0.0001
Dyslipidaemia, (%)	1269 (18.6)	315 (15.4)	776 (19.7)	178 (21.7)	<0.0001	<0.0001
Statin use, (%)	1221 (17.9)	300 (14.6)	751 (19.0)	170 (20.7)	<0.0001	<0.0001
Ever smoked, (%)	2021 (29.6)	533 (26.0)	1198 (30.3)	290 (35.3)	<0.0001	<0.0001
Ever smoked before end date, (%)	2928 (42.9)	832 (40.6)	1721 (43.6)	375 (45.7)	0.018	0.024

Table 3.4: Baseline cardiovascular risk factors of patients with adrenal insufficiency of any type, primary and secondary adrenal insufficiency at the diagnosis

† P for difference between primary, secondary, and unspecified adrenal insufficiency**;** ‡ P for difference between primary and secondary adrenal insufficiency

3.1.3 Characteristics of the subcohort of patients with linked HES and ONS data, compared with matched controls

The subcohort consisted of patients with adrenal insufficiency of any type, primary, secondary, and unspecified adrenal insufficiency and controls and included only participants having linked data and the start of follow-up from 1997 onwards (Table 3.5 and 3.6). Information for these participants was used to analyse the secondary outcomes such as cause-specific mortality and detailed hospital admissions.

- ❖ Patients with adrenal insufficiency of any type and their matched controls

From a total of 3547 patients with adrenal insufficiency of any type and 34944 matched controls, women accounted for approximately 54% of patients and controls (p=0.97). The median age at start of follow-up (IQR) in the patient group was slightly higher than that in the control group (53 [37-68] vs 52 [37-67]; p=0.42). The two groups exhibited no statistical difference in the median follow-up times (3.8 [IQR, 1.4-7.9] years for patients vs 3.5 [1.5.-7.7] years for controls; p =0.21) and the same calendar years of start – end of study from 2008 to 2014 (Table 3.5).

Regarding cardiovascular risk factors, similar to the whole cohort, the proportions of previous cardiovascular disease, ischaemic heart disease, and cerebrovascular disease in the patient group were significantly higher than those in the control group. As for the whole cohort, the patient group had a higher proportion of diabetes of any type, type 1 diabetes, hypertension, dyslipidaemia, and statin use than that of the control group. However, the proportion of ever smoking in the patient group was similar to that in the control group when it was evaluated at the end of follow-up (Table 3.6).

CHARACTERISTICS	**Adrenal insufficiency of any type**			**Primary adrenal insufficiency**			**Secondary adrenal insufficiency**			**Unspecified adrenal insufficiency**		
	Patients N = 3547	Controls N = 34944	P	Patients N = 1015	Controls N = 10025	P	Patients N = 2136	Controls N = 20991	P	Patients N = 396	Controls N = 3928	P
Female, (%)	1918 (54.1)	18885 (54.0)	0.97	605 (59.6)	5948 (59.3)	0.86	1082 (50.1)	10648 (50.7)	0.95	231 (58.3)	2289 (58.3)	0.98
Age at start; year, median (IQR)	53 (37-68)	52 (37-67)	0.42	51 (36-67)	51 (35-66)	0.70	53 (38-67)	53 (38-67)	0.50	57 (35.5-71.5)	57 (35-72)	0.83
Total follow-up time, year; median (IQR)	3.8 (1.4-7.9)	3.5 (1.5-7.7)	0.21	3.9 (1.4-8.3)	3.7 (1.5-8.4)	0.78	3.9 (1.6-8.0)	3.5 (1.5-7.6)	0.0042	2.8 (1.0-6.5)	3.0 (1.3-6.6)	0.061
Calendar year at start of follow-up; median (IQR)	2008 (2003-2012)	2008 (2002-2012)	0.83	2007 (2002-2011)	2007 (2002-2011)	0.85	2008 (2003-2012)	2008 (2003-2012)	0.91	2009 (2004-2013)	2009 (2004-2013)	0.53
Calendar year at end of follow-up; median (IQR)	2014 (2010-2016)	2014 (2010-2016)	0.073	2013 (2009-2016)	2013 (2009-2016)	0.73	2014 (2010-2016)	2014 (2010-2016)	0.010	2014 (2010-2016)	2014 (2010-2016)	0.95

Table 3.5: Baseline characteristics at the start of follow-up of patients with adrenal insufficiency and controls who had linkage

CHARACTERISTICS	**Adrenal insufficiency of any type**			**Primary adrenal insufficiency**			**Secondary adrenal insufficiency**			**Unspecified adrenal insufficiency**		
	Patients N = 3547	Controls N = 34944	P	Patients N = 1015	Controls N = 10025	P	Patients N = 2136	Controls N = 20991	P	Patients N = 396	Controls N = 3928	P
Cardiovascular disease, (%)	578 (16.3)	3822 (10.9)	<0.0001	140 (13.8)	952 (9.5)	<0.001	348 (16.3)	2344 (11.2)	<0.001	90 (22.7)	526 (13.4)	<0.001
Ischaemic heart disease, (%)	290 (8.2)	2120 (6.1)	<0.001	80 (7.9)	522 (5.2)	<0.001	165 (7.7)	1323 (6.3)	0.011	45 (11.4)	275 (7.0)	0.0020
Cerebrovascular disease, (%)	230 (6.5)	1320 (3.8)	<0.001	39 (3.8)	342 (3.4)	0.47	159 (7.4)	801 (3.8)	<0.001	32 (8.1)	177 (4.5)	0.0020
Diabetes mellitus, (%)	376 (10.6)	1873 (5.4)	<0.001	130 (12.8)	450 (4.5)	<0.001	206 (9.6)	1172 (5.6)	<0.001	40 (10.1)	251 (6.4)	0.0050
Type 1 diabetes mellitus, (%)	115 (3.2)	192 (0.6)	<0.001	77 (7.6)	47 (0.5)	<0.001	32 (1.5)	130 (0.6)	<0.001	6 (1.5)	15 (0.4)	0.0020
Hypertension, (%)	800 (22.6)	5194 (14.9)	<0.001	168 (16.6)	1374 (13.7)	0.013	530 (24.8)	3123 (14.9)	<0.001	102 (25.8)	697 (17.7)	<0.001
Dyslipidaemia, (%)	770 (21.7)	1933 (5.5)	<0.001	181 (17.8)	535 (5.3)	<0.001	496 (23.2)	1151 (5.5)	<0.001	93 (23.5)	247 (6.3)	<0.001
Statin use, (%)	738 (20.8)	1886 (5.4)	<0.001	171 (16.9)	520 (5.2)	<0.001	477 (22.3)	1125 (5.4)	<0.001	90 (22.7)	241 (6.1)	<0.001
Ever smoked at the start of follow-up, (%)	1184 (33.4)	7892 (22.6)	<0.001	309 (30.4)	2172 (21.7)	<0.001	718 (33.6)	4808 (22.9)	<0.001	157 (39.7)	912 (23.2)	<0.001
Ever smoked before end date, (%)	1555 (43.8)	15643 (44.8)	0.29	429 (42.3)	4386 (42.9)	0.36	930 (43.5)	9552 (45.5)	0.082	196 (49.5)	1705 (43.4)	0.020

Table 3.6: Baseline cardiovascular risk factors at the start of follow-up of patients with adrenal insufficiency and controls who had linkage

❖ Patients with primary adrenal insufficiency and their matched controls

In the analysis of primary adrenal insufficiency patients with liked HES/ ONS data, 1015 study patients and 10025 matched controls were included. Similar to the whole cohort of primary adrenal insufficiency in CPRD, most were women accounting for 59.6% and 59.3% of the patient and control groups, respectively (p=0.86). Both groups had the same median age of follow-up of 51. The two groups showed no statistical difference in the median follow-up times (3.9 [IQR, 1.4-8.3] years for patients vs 3.7 [1.5-8.4] years for controls; p =0.78) and the same calendar years of start – end of study: from 2007 to 2013 (Table 3.5).

Regarding cardiovascular risk factors, similarly to the whole cohort of primary adrenal insufficiency, the proportions of previous cardiovascular disease and ischaemic heart disease in the patient group were higher than those in the control group. However, the proportion of participants having previous cerebrovascular disease in the patient group was similar to that in the control group (3.8% vs 3.4%; p=0.47). For diabetes at baseline particularly type 1 diabetes, the proportion in the patient group was up to 15 times higher than that in the control group (7.5% vs 0.5%, p<0.001), consistent with the findings in the whole cohort of primary adrenal insufficiency. The proportion of ever smoking in the patient group was similar to those in the control group when it was evaluated at the end of follow-up (Table 3.6).

❖ Patients with secondary adrenal insufficiency and their matched controls

In the analysis of secondary adrenal insufficiency patients with liked HES/ ONS data, 2136 study patients and 20991 matched controls were included. Similar to the whole cohort of secondary adrenal insufficiency in CPRD, the proportion of women was 50% and 51% for the patient and control groups, respectively (p=0.95). The median ages [IQR] at the start of follow-up were identical between the patient and control groups (53 [38-67] vs 53 [38-67]; p=0.50). Similar to the whole cohort of secondary adrenal insufficiency, the median follow-up time

[IQR] of the patient group was slightly longer than that of the control group (3.9 [1.6-8.0] vs 3.5 [1.5-7.6] years; p =0.0042) but both groups had the same calendar years of start – end of study, from 2008 to 2014 (Table 3.5).

Regarding cardiovascular risk factors, similar to the whole cohort of secondary adrenal insufficiency, the proportions of these factors were higher in the patient group, compared with controls. Notably, the proportion of type 1 diabetes in patients with secondary adrenal insufficiency was higher than in controls, although the percentages were low (1.5% vs 0.6%; p<0.001). For ever-smoking, the proportion observed in the patient group was no longer different from that in the control group when the evaluation was extended to the end of follow-up (Table 3.6).

- ❖ Patients with unspecified adrenal insufficiency and their matched controls

In unspecified adrenal insufficiency, the analysis included 396 study patients and 3928 matched controls. The proportion of women in the study and control groups was identical (58.3% vs 58.3%; p=0.98). In the two groups, the median ages [IQR] at start of follow-up were also similar (57 [37.5-71.5] vs 57 [35-72]; p=0.83). The median follow-up time [IQR] for the patient group was slightly shorter than that of the control group (2.8 [1.0-6.5] vs 3.0 [1.3-6.6] years; p =0.061) but both groups had the same calendar years of start – end of study, from 2009 to 2014 (Table 3.5).

Regarding cardiovascular risk factors, similarly to the analysis in the whole cohort of unspecified adrenal insufficiency, despite the low number of participants the proportions in the patient group were higher than those in the control group. For smoking, when the evaluation period was extended until the end of follow-up, the difference between the proportions in the patient and control groups was reduced, compared with the difference evaluated at the start of follow-up (Table 3.6).

In summary, overall baseline data for demographics and cardiovascular risk factors of participants (the patient and control groups) in the subgroups with linked HES/ ONS data were very similar to those for all the participants. However, the follow-up periods in those with linked data were about one year shorter.

3.1.4 Characteristics of the subcohort of patients with linked HES and ONS data in comparisons between adrenal insufficiency of any type, primary, secondary, and unspecified adrenal insufficiency at the diagnosis

Similar to the analysis in the whole cohort, this analysis evaluated baseline characteristics of the study patients who had linked HES/ ONS data, at the time of a diagnosis of adrenal insufficiency and at the start of follow-up. Baseline characteristics were summarised for the overall group with linked HES/ ONS data and compared within the three sub-groups of study patients: primary, secondary, and unspecified adrenal insufficiency. Also, characteristics were compared between patients with primary and secondary adrenal insufficiency for those with linked HES/ ONS data.

- Sex

As for the full group of study patients, women accounted for 54% of total patients with linked HES/ ONS data. The majority of patients with primary and unspecified adrenal insufficiency were women but in secondary adrenal insufficiency no sex difference in proportions was observed. In a comparison between primary and secondary adrenal insufficiency, the proportion of women in patients was significantly higher in those with primary adrenal insufficiency (60% vs 51%; $p<0.001$; Table 3.7).

CHARACTERISTICS	**Adrenal insufficiency of any type** N = 3547	**Primary adrenal insufficiency** N = 1015	**Secondary adrenal insufficiency** N = 2136	**Unspecified adrenal insufficiency** N =396	P†	P‡
Female, (%)	1918 (54.1)	605 (59.6)	1082 (50.7)	231 (58.3)	<0.0001	<0.0001
Age at diagnosis; year; median (IQR)	51 (36-67)	48 (35-65)	52 (36.5-66)	56 (33.5-70.5)	0.0086	0.016
Age at start; year; median (IQR)	53 (37-68)	51 (36-67)	53 (38-67)	57 (37-67)	0.016	0.059
Total follow-up time from diagnosis to end date, years; median (IQR)	4.6 (1.8-9.6)	5.0 (1.8-10.1)	4.8 (1.9-9.6)	3.2 (1.1-8.0)	0.0001	0.41
Total follow-up time from start to end date; years; median (IQR)	3.8 (1.4-7.9)	3.9 (1.4-8.3)	3.9 (1.6-8.0)	2.8 (1.0-6.5)	0.0001	0.97
Calendar year at diagnosis; median (IQR)	2007 (2002-2011)	2006 (2001-2011)	2007 (2002-2011)	2009 (2003-2013)	0.0001	0.0001
Calendar year at start of follow-up; median (IQR)	2008 (2003-2012)	2007 (2002-2011)	2008 (2003-2012)	2009 (2004-2013)	0.0001	0.0013
Calendar year at end of follow-up; median (IQR)	2014 (2010-2016)	2013 (2009-2016)	2014 (2010-2016)	2014 (2010-2016)	0.0010	0.0003

Table 3.7: Baseline characteristics (at the diagnosis and at the start of follow-up) of patients with adrenal insufficiency of any type, primary and secondary adrenal insufficiency who had linkage

Note: † P for difference between primary, secondary, and unspecified adrenal insufficiency; ‡ P for difference between primary and secondary adrenal insufficiency

❖ Age

The median age at diagnosis (IQR) was 51 (36-67) in patients with adrenal insufficiency of any type, which was two years lower than median age at the start of follow-up. At the diagnosis, the median age (IQR) in those with primary adrenal insufficiency was 48 (35-65), which was significantly younger than in those with secondary adrenal insufficiency (52, IQR [36.5-66]; p=0.016), although the age of diagnosis was highest in those with unspecified adrenal insufficiency (56 [33.5-70.5]). The median age at diagnosis was three years younger than age at the start of follow-up in patient with primary adrenal insufficiency but only one year in secondary adrenal insufficiency (Table 3.7).

❖ Follow-up time and calendar years of diagnosis and of the study

From the start of follow-up, the median follow-up time in years (IQR) was 3.9 (1.4-8.3), 3.9 (1.6-8.0), and 2.8 (1.0-6.5) in patients with primary, secondary, and unspecified adrenal insufficiency, respectively. Follow-up time was not significantly different between those with primary and secondary adrenal insufficiency (p=0.97). Similar to the whole cohort, the median follow-up time from the start of follow-up among those with linked HES/ ONS data was approximately one year shorter than the median follow-up time after the diagnosis in overall, primary, and secondary adrenal insufficiency. The calendar year at diagnosis was approximately one year before the year at the start of follow-up in patients with primary and secondary adrenal insufficiency (Table 3.7).

❖ Cardiovascular risk factors

At the diagnosis, among those with linked HES/ONS data, the proportion of previous cardiovascular disease was similar between patients with primary and secondary adrenal insufficiency (13% vs 15%, p=0.061) but this was highest in those with unspecified adrenal

insufficiency (22%). Also, the proportion of ischaemic heart disease was similar between those with primary and secondary adrenal insufficiency (7.4% vs 7.2%, p=0.81) but it was higher in those with unspecified adrenal insufficiency (11%). Noticeably, the proportion of cerebrovascular disease in patients with secondary adrenal insufficiency and in those with unspecified adrenal insufficiency was higher than in primary adrenal insufficiency (primary, 3.7% vs secondary, 7.2% vs unspecified, 7.8%; p<0.001). At diagnosis, the proportion of diabetes of any type was highest in patients with primary adrenal insufficiency and type 1 diabetes was the major contributor. The proportion of type 1 diabetes in primary adrenal insufficiency was markedly higher than in secondary adrenal insufficiency (7.5% vs 1.5%, p<0.001). For hypertension, the proportion in secondary and unspecified adrenal insufficiency was higher than in primary adrenal insufficiency (primary, 15% vs secondary, 23% vs unspecified, 25%; p<0.001). For dyslipidaemia, similarly to the finding in hypertension at the diagnosis, the proportion was higher in secondary and unspecified adrenal insufficiency than in primary adrenal insufficiency (primary, 15% vs secondary, 20% vs unspecified, 21%; p=0.002). In patients with each type of adrenal insufficiency, the proportions of statin users were not different from the proportions of dyslipidaemia observed in those with the same type of adrenal insufficiency, as also observed in the whole cohort of study patients. For ever-smoking by the end of follow-up, the proportion in patients with unspecified adrenal insufficiency was slightly higher than among those with primary or secondary adrenal insufficiency (Table 3.8).

In summary, overall baseline characteristics for demographics and cardiovascular risk factors of the study patients in the subgroups with linked HES/ ONS data were virtually identical to the study patients in the whole cohort.

CHARACTERISTICS	**Adrenal insufficiency of any type** N = 3547	**Primary adrenal insufficiency** N = 1015	**Secondary adrenal insufficiency** N = 2136	**Unspecified adrenal insufficiency** N =396	P†	P‡
Cardiovascular disease, (%)	540 (15.2)	129 (12.7)	325 (15.2)	86 (21.7)	<0.0001	0.061
Ischaemic heart disease, (%)	269 (7.6)	75 (7.4)	153 (7.2)	41 (10.4)	0.085	0.81
Cerebrovascular disease, (%)	222 (6.3)	37 (3.7)	154 (7.2)	31 (7.8)	<0.0001	<0.0001
Diabetes mellitus, (%)	349 (9.8)	126 (12.4)	185 (8.7)	38 (9.6)	0.0040	0.0010
Type1 diabetes mellitus, (%)	112 (3.2)	76 (7.5)	31 (1.5)	5 (1.3)	<0.0001	<0.0001
Hypertension, (%)	749 (21.1)	156 (15.4)	496 (23.2)	97 (24.5)	<0.0001	<0.0001
Dyslipidaemia, (%)	695 (19.6)	161 (15.9)	449 (21.0)	85 (21.5)	0.0021	0.0010
Statin use, (%)	666 (18.8)	152 (15.0)	431 (20.2)	83 (21.0)	0.0010	<0.001
Ever smoked, (%)	1107 (31.2)	278 (27.4)	677 (31.7)	152 (38.4)	<0.0001	0.014
Ever smoked before end date, (%)	1555 (43.8)	429 (42.3)	930 (43.5)	196 (49.5)	0.044	0.50

Table 3.8: Baseline cardiovascular risk factors (at the diagnosis) of patients with adrenal insufficiency of any type, primary and secondary adrenal insufficiency who had linkage

Note: † P for difference between primary, secondary, and unspecified adrenal insufficiency; ‡ P for difference between primary and secondary adrenal insufficiency

3.2 Overall mortality rates and hazard ratios for all-cause mortality

All-cause mortality rates and unadjusted & adjusted hazard ratios

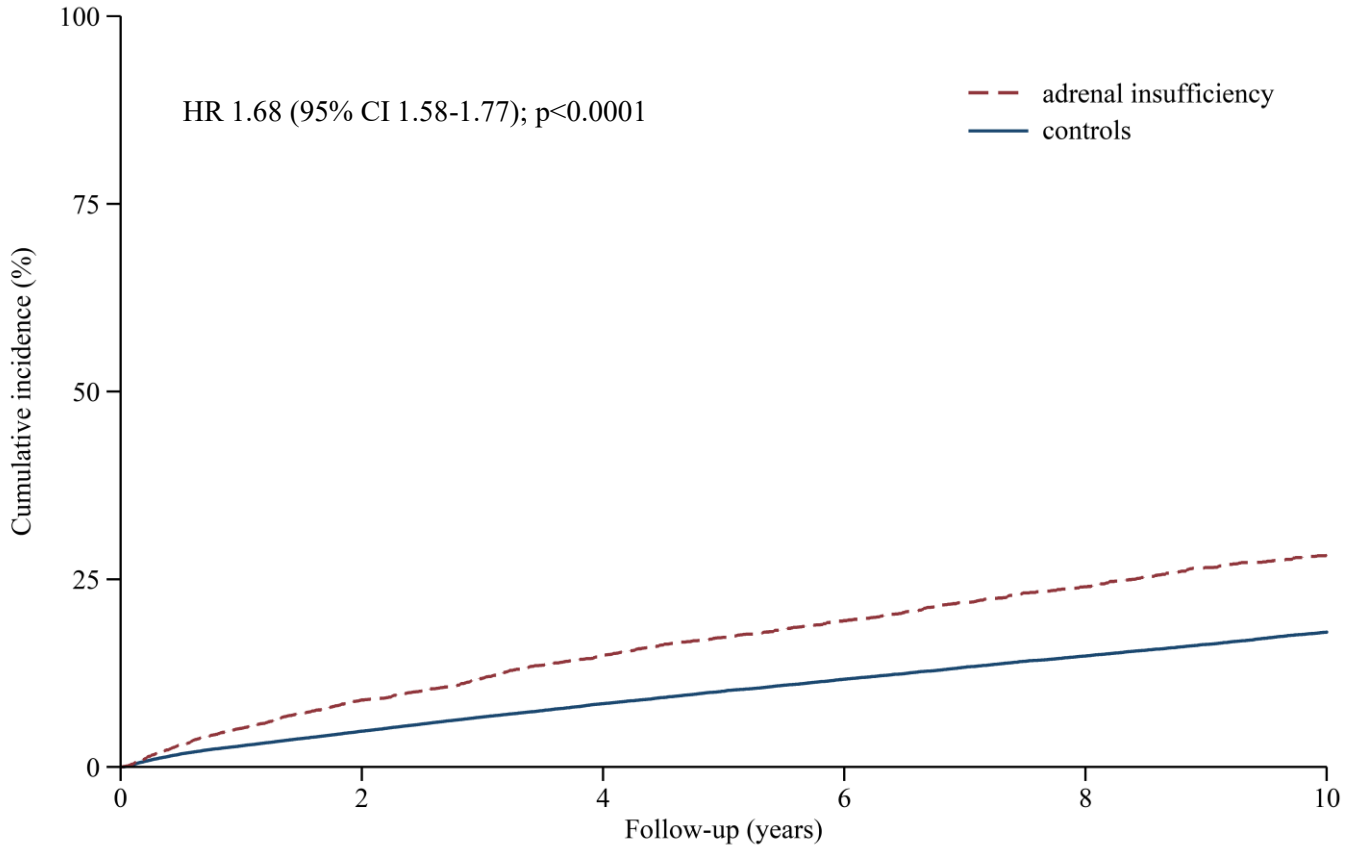
- Adrenal insufficiency of any type and matched controls

For the whole cohort of patients with adrenal insufficiency of any type and their matched controls, the follow-up periods for the 6821 patients and 67564 matched controls were 40799 and 406899 person-years, respectively. All-cause mortality rate (95% CI) of the patients was higher than that of controls (35.2 [33.4-37.0] vs 21.0 [20.6-21.5] per 1000 person-years), giving an unadjusted hazard ratio (95% CI) of 1.68 (1.58-1.77; p <0.0001; Table 3.9). After adjustment for baseline cardiovascular disease, diabetes, hypertension, dyslipidaemia and ever smoking, the hazard ratio remained significantly increased (1.48 [95% CI, 1.40-1.57], p<0.0001; Table 3.9). It is noted that the cumulative mortality profile for patients with adrenal insufficiency was readily distinguishable from that of controls almost from the beginning of the study period (Figure 3.1).

Participant cohort	Study patients				Controls				Unadjusted HR (95%CI)	P	Adjusted HR† (95%CI)	P
	No. at risk	No. death	Person-years	Mortality per 1000 person-years (95% CI)	No. at risk	No. death	Person-years	Mortality per 1000 person-years (95% CI)				
Adrenal insufficiency of any type	6821	1435	40799	35.2 (33.4-37.0)	67564	8562	406899	21.0 (20.6-21.5)	1.68 (1.58-1.77)	<0.0001	1.48 (1.40-1.57)	<0.0001
Primary adrenal insufficiency	2052	464	12961	35.8 (32.7-39.2)	20366	2567	131241	19.6 (18.8-20.3)	1.83 (1.66-2.02)	<0.0001	1.67 (1.51-1.84)	<0.0001
Secondary adrenal insufficiency	3948	745	23814	31.3 (29.1-33.6)	39134	4832	232841	20.8 (20.2-21.3)	1.52 (1.40-1.64)	<0.0001	1.34 (1.23-1.45)	<0.0001
Unspecified adrenal insufficiency	821	226	4024	56.2 (49.3-64.0)	8064	1163	42816	27.2 (25.6-28.8)	2.06 (1.79-2.38)	<0.0001	1.83 (1.57-2.12)	<0.0001

Table 3.9: All-cause mortality rates in patients with adrenal insufficiency and controls, and hazard ratios for mortality of adrenal insufficiency

Note: † adjustment for baseline cardiovascular disease, diabetes mellitus, hypertension and dyslipidaemia at the start of follow-up, and ever smoking at any time



Number at risk

adrenal insufficiency	6821	4838	3566	2677	1969	1460
controls	67564	47208	33691	25577	19482	14820

Figure 3.1: Cumulative mortality in patients with adrenal insufficiency of any type and controls

❖ Primary adrenal insufficiency and matched controls

For the sub-cohort of primary adrenal insufficiency patients and their matched controls, the follow-up periods of 2052 patients and 20366 matched controls were 12961 and 131241 person-years, respectively. Similar to the finding in the whole cohort, all-cause mortality rate of the patients was higher than that of controls (35.8 [95% CI 32.7-39.2] vs 19.6 [95% CI 18.8-20.3] per 1000 person-years), giving an unadjusted hazard ratio (95% CI) of 1.83 (1.66-2.02; p <0.0001; Table 3.9). After adjustment, the hazard ratio remained significantly increased (1.67 [95% CI, 1.51-1.84], p<0.0001; Table 3.9).

❖ Secondary adrenal insufficiency and matched controls

For the sub-cohort of secondary adrenal insufficiency patients and their matched controls, the follow-up periods of 3948 patients and 39134 matched controls were 23814 and 232841 person-years, respectively. Similar to the finding in the whole cohort, all-cause mortality rate of the patients was higher than that of controls (31.3 [95% CI 29.1-33.6] vs 20.8 [95% CI 20.2-21.3] per 1000 person-years), giving an unadjusted hazard ratio (95% CI) of 1.52 (1.40-1.64; p <0.0001; Table 3.9). After adjustment, the hazard ratio remained significantly increased (1.34 [95% CI, 1.23-1.45], p<0.0001; Table 3.9).

❖ Unspecified adrenal insufficiency and matched controls

For the sub-cohort of unspecified adrenal insufficiency patients and their matched controls, the follow-up periods of 821 patients and 8064 matched controls were 4024 and 42816 person-years, respectively. Even in unspecified adrenal insufficiency, the all-cause mortality rate of the patients was significantly higher than that of controls (56.2 [95% CI 49.3-64.0] vs 27.2 [95% CI 25.6-28.8] per 1000 person-years). Although this sub-cohort had a smaller number of participants and a shorter follow-up period, the unadjusted hazard ratio (95% CI) remained

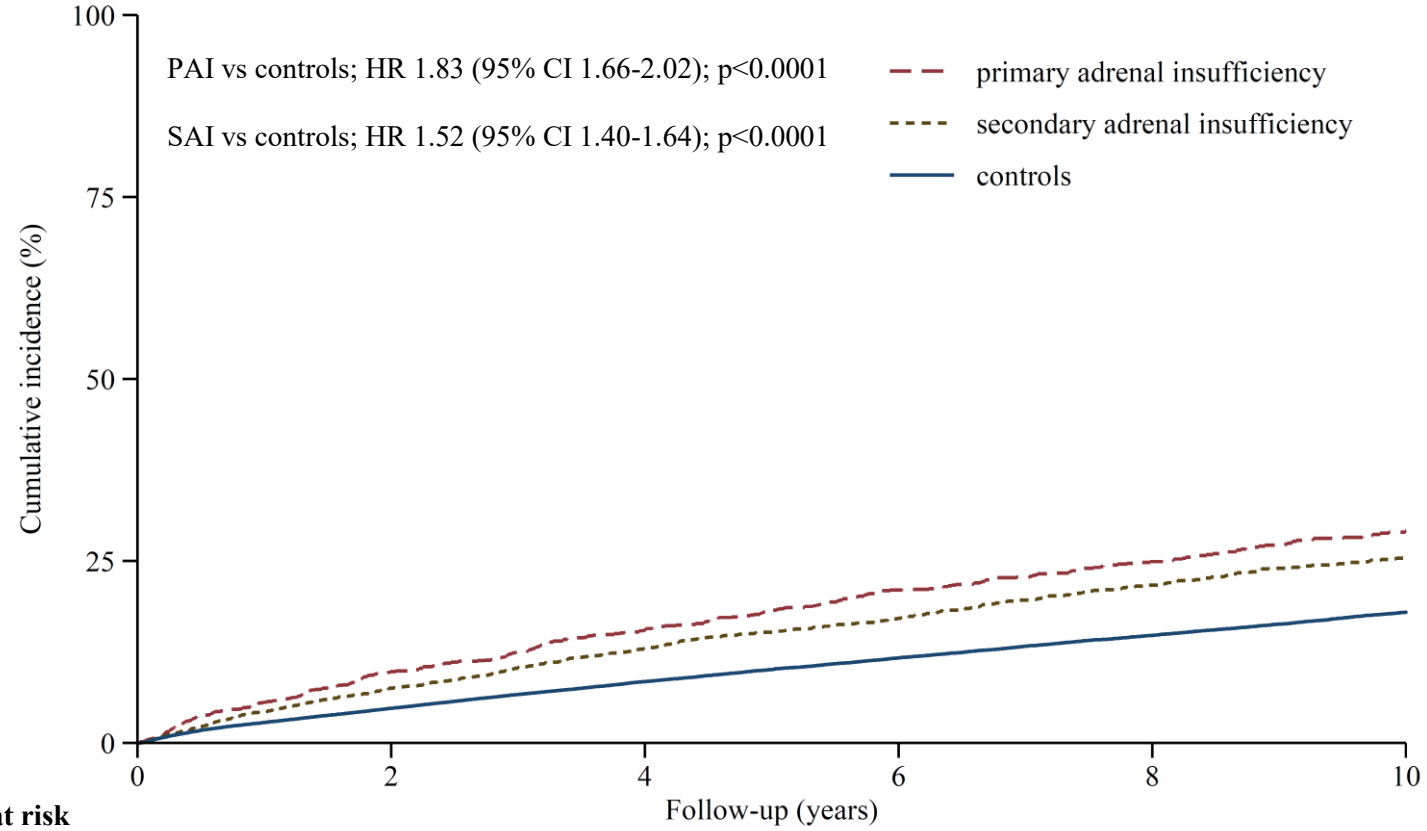
significantly increased (2.06 [1.79-2.38]; p <0.0001; Table 3.9). After adjustment, the hazard ratio was also significantly increased (1.83 [95% CI, 1.57-2.12]; p<0.0001; Table 3.9).

- Primary adrenal insufficiency compared with secondary adrenal insufficiency

In a comparison with secondary adrenal insufficiency, the unadjusted hazard ratio of primary adrenal insufficiency was significantly increased (1.16 [95% CI, 1.03-1.30]; p=0.013). After adjustment for sex and age of adrenal insufficiency, the hazard ratio was further increased (1.27 [95% CI, 1.13-1.43]; p<0.0001). After adjustment for previous cardiovascular disease, diabetes, hypertension and dyslipidaemia at adrenal insufficiency diagnosis, and ever smoking, the hazard ratio was also increased (1.24 [95% CI, 1.10-1.39]; p<0.0001; Table 3.10).

Models	HR	95%CI	P
Univariable analysis (Unadjusted)	1.16	1.03-1.30	0.013
Adjustment for sex, age in years at start of follow-up	1.25	1.11-1.40	<0.0001
Adjustment for sex, age in years at diagnosis	1.27	1.13-1.43	<0.0001
Adjustment for previous cardiovascular disease, diabetes, hypertension, dyslipidaemia at start of follow-up, and smoking any time	1.25	1.11-1.40	<0.0001
Adjustment for previous cardiovascular disease, diabetes, hypertension, dyslipidaemia at diagnosis, and smoking any time	1.24	1.10-1.39	<0.0001
Adjustment for sex, age at start of follow-up, previous cardiovascular disease, diabetes, hypertension, dyslipidaemia at start of follow-up, and smoking any time	1.20	1.07-1.35	0.0020
Adjustment for sex, age at diagnosis, previous cardiovascular disease, diabetes, hypertension, dyslipidaemia at diagnosis, and smoking any time	1.22	1.08-1.37	0.0010

Table 3.10: Unadjusted and adjusted HRs for all-cause mortality of primary adrenal insufficiency compared with secondary adrenal insufficiency



Number at risk

PAI patients	2052	1446	1099	843	639	487
SAI patients	3948	2877	2117	1593	1157	848
controls	67564	47208	33691	25577	19482	14819

Figure 3.2: Cumulative mortality in patients with primary and secondary adrenal insufficiency (PAI & SAI), and controls

Figure 3.2 illustrates three cumulative mortality rate profiles in 2052 patients with primary adrenal insufficiency, 3948 patients with secondary adrenal insufficiency and 67564 controls. According to these profiles, the cumulative mortality rate of patients with primary adrenal insufficiency was higher than that of secondary adrenal insufficiency. Similar to the finding in adrenal insufficiency of any kind, both profiles were distinguishable from the controls profile from the beginning of the follow-up period.

In summary, in a comparison with controls, the mortality risk of patients with adrenal insufficiency in overall and in specified types of adrenal insufficiency was increased. The mortality risk relative to controls was higher in patients with primary adrenal insufficiency than in those with secondary adrenal insufficiency. In a comparison between primary and secondary adrenal insufficiency, mortality was higher in primary disease whether or not adjusted for age, sex, or cardiovascular risk factors.

3.3 Mortality rates and hazard ratios for all-cause mortality stratified by sex, age, and comorbidities

3.3.1 Mortality rates, unadjusted and adjusted hazard ratios for all-cause mortality stratified by sex

- ❖ Adrenal insufficiency of any type and matched controls

There were 3173 male and 3648 female patients with adrenal insufficiency and 31283 male and 36281 female controls included in this analysis. For men, the all-cause mortality rates (95% CI) were 39.1 (36.4-42.1) and 24.6 (23.9-25.3) per 1000 person-years in the study patients and controls, respectively, giving an unadjusted hazard ratio (95% CI) of 1.59 (1.48-1.72; $p<0.0001$). After adjustment for baseline cardiovascular disease, diabetes, hypertension, dyslipidaemia and ever smoking, the hazard ratio remained increased (Table 3.11).

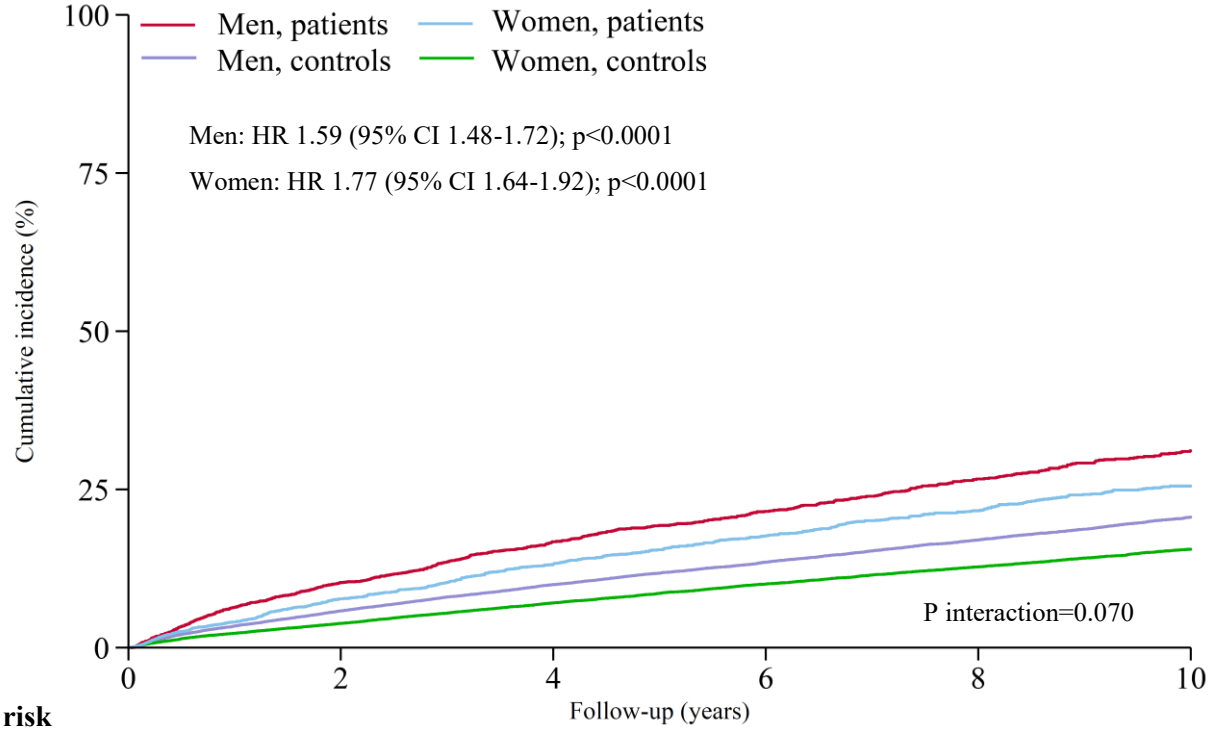
For women, the mortality rates (95% CI) were 31.7 (29.5-34.2) and 18.0 (17.5-18.6) per 1000 person-years in the study patients and controls, respectively, giving an unadjusted hazard ratio (95% CI) of 1.77 (1.64-1.92; $p<0.0001$). After adjustment, the hazard ratio was also increased (Table 3.11). The increases in unadjusted and adjusted hazard ratios for patients versus controls were not significantly different between men and women (p-for patient/sex interaction ≥ 0.05).

Figure 3.3 illustrates the four profiles for cumulative mortality in men and women with adrenal insufficiency and their matched controls. Mortality was highest in men with adrenal insufficiency followed by women with adrenal insufficiency. It is noted that all profiles were distinguishable since the early course of follow-up.

Study group	Study patients				Controls				Unadjusted HR (95%CI)	P	P for interaction	Adjusted HR† (95%CI)	P	P for interaction
	No. at risk	No. death	Person-years	Mortality per 1000 person-years (95% CI)	No. at risk	No. death	Person-years	Mortality per 1000 person-years (95% CI)						
Adrenal insufficiency of any type														
Men	3173	739	18877	39.1 (36.4-42.1)	31283	4627	188349	24.6 (23.9-25.3)	1.59 (1.48-1.72)	<0.0001	0.070	1.45 (1.34-1.57)	<0.0001	0.15
Women	3648	696	21923	31.7 (29.5-34.2)	36281	3935	218549	18.0 (17.5-18.6)	1.77 (1.64-1.92)	<0.0001		1.53 (1.41-1.67)	<0.0001	
Primary adrenal insufficiency														
Men	860	209	5480	38.1 (33.3-43.7)	8483	1183	54825	21.6 (20.4-22.8)	1.77 (1.53-2.05)	<0.0001	0.54	1.60 (1.37-1.86)	<0.0001	0.50
Women	1192	255	7481	34.1 (30.1-38.5)	11883	1384	76416	18.1 (17.2-19.1)	1.89 (1.65-2.15)	<0.0001		1.73 (1.51-1.98)	<0.0001	
Secondary adrenal insufficiency														
Men	1971	429	11859	36.2 (32.9-39.8)	19474	2924	116323	25.1 (24.2-26.1)	1.44 (1.30-1.60)	<0.0001	0.13	1.33 (1.20-1.48)	<0.0001	0.35
Women	1977	316	11954	26.4 (23.7-29.5)	19660	1908	116518	16.4 (15.7-17.1)	1.63 (1.45-1.84)	<0.0001		1.36 (1.20-1.53)	<0.0001	

Table 3.11: Mortality rates of patients with adrenal insufficiency and controls, and hazard ratios for all-cause mortality categorised by sex

Note: † adjustment for baseline cardiovascular disease, diabetes mellitus, hypertension and dyslipidaemia at the start of follow-up, and ever smoking at any time



Number at risk

Men patients	3173	2207	1632	1243	905	680
Men controls	31283	22001	15789	11959	9036	6839
Women patients	3648	2635	1935	1437	1065	781
Women controls	36281	25207	17902	13618	10448	7983

Figure 3.3: Cumulative mortality in patients with adrenal insufficiency of any type and controls categorised by sex

❖ Primary adrenal insufficiency and matched controls

There were 860 male and 1192 female patients with primary adrenal insufficiency and 8483 male and 11883 female controls included in this analysis. For men, the mortality rates (95% CI) of all-cause were 38.1 (33.3-43.7) and 21.6 (20.4-22.8) per 1000 person-years in the study patients and controls, respectively, giving an unadjusted hazard ratio (95% CI) of 1.77 (1.53-2.05; $p<0.0001$). After adjustment for baseline cardiovascular disease, diabetes, hypertension, dyslipidaemia and ever smoking, the hazard ratio remained increased (Table 3.11).

For women, the mortality rates (95% CI) were 34.1 (30.1-38.5) and 18.1 (17.2-19.1) per 1000 person-years in the study patients and controls, respectively, giving an unadjusted hazard ratio (95% CI) of 1.89 (1.65-2.15; $p<0.0001$). After adjustment, the hazard ratio was also increased (Table 3.11). The increases in unadjusted and adjusted hazard ratios between men and women were not significantly different (p-for interaction ≥ 0.05).

❖ Secondary adrenal insufficiency and matched controls

There were 1971 male and 1977 female patients with secondary adrenal insufficiency and 19474 male and 19660 female controls including in this analysis. For men, rates of mortality (95% CI) from all-cause were 36.2 (32.9-39.8) and 25.1 (24.2-26.1) per 1000 person-years in the study patients and controls, respectively, giving an unadjusted hazard ratio (95% CI) of 1.44 (1.30-1.60; $p<0.0001$). After adjustment for baseline cardiovascular disease, diabetes, hypertension, dyslipidaemia and ever smoking, the hazard ratio remained increased (Table 3.11).

For women, the mortality rates (95% CI) were 26.4 (23.7-29.5) and 16.4 (15.7-17.1) per 1000 person-years in the study patients and controls, respectively, giving an unadjusted hazard ratio (95% CI) of 1.63 (1.45-1.84; $p<0.0001$). After adjustment, the hazard ratio was also increased

(Table 3.11). Similar to primary adrenal insufficiency, the increases in unadjusted and adjusted hazard ratios between men and women were not statistically significant different (p-for interaction ≥ 0.05). Interestingly, the mortality rate of females with secondary adrenal insufficiency was similar to that of male controls.

- ❖ Primary adrenal insufficiency compared with secondary adrenal insufficiency

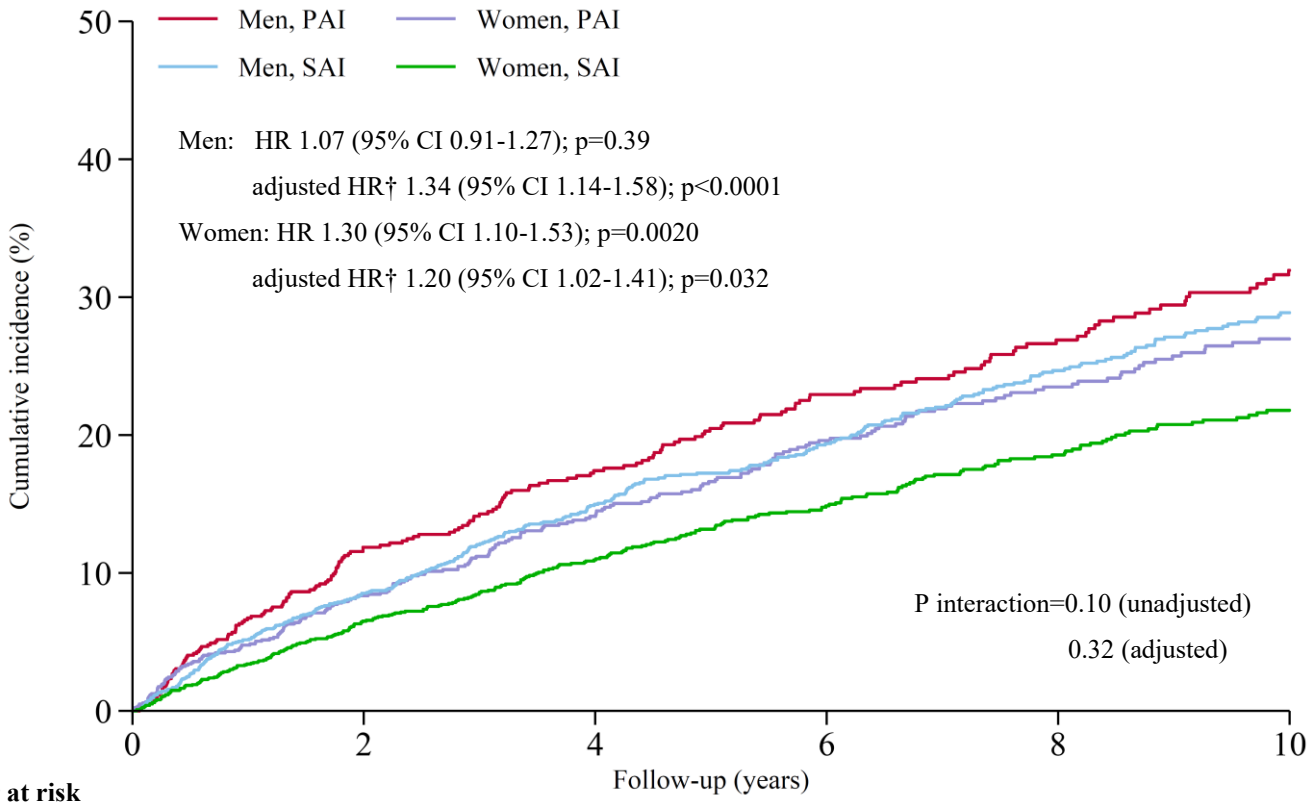
This analysis compared the mortality risk between primary and secondary adrenal insufficiency patients with the same sex. The male cohort included 860 and 1971 patients with primary and secondary adrenal insufficiency and for women the equivalent figures were 1192 and 1977, respectively (Figure 3.4).

In men, the unadjusted hazard ratio (95% CI) of primary relative to secondary adrenal insufficiency was 1.07 (0.91-1.27; p=0.39). The age of diagnosis was not initially matched between primary and secondary adrenal insufficiency. Median age of diagnosis in men with primary adrenal insufficiency was significantly lower than that in men with secondary adrenal insufficiency (48 [IQR, 33-66] vs 56 [IQR, 40-69]; p<0.0001). Adjustment for age of diagnosis was therefore performed and the hazard ratio (95% CI) of male primary adrenal insufficiency was increased to 1.34 (1.14-1.58; p<0.0001).

In women, the unadjusted hazard ratio (95%) of primary relative to secondary adrenal insufficiency was 1.30 (1.10-1.53; p=0.002). Median age of diagnosis in women with primary adrenal insufficiency was not different from that in women with secondary adrenal insufficiency (50 [IQR, 37-65] vs 49 [IQR, 35-64]; p=0.097). After adjustment for age of diagnosis, the hazard ratio (95% CI) was 1.20 (1.02-1.41); p=0.032), which was not different from the unadjusted hazard ratio.

After adjustment for age of diagnosis, the hazard ratio of patients with primary adrenal insufficiency was increased regardless of sex (p for interaction = 0.32). Interestingly, the cumulative mortality profile for women with primary adrenal insufficiency was virtually identical to that of men with secondary adrenal insufficiency (Figure 3.4).

In summary, in a comparison with controls, the mortality risk of patients with adrenal insufficiency of any kind including primary and secondary adrenal insufficiency was increased to a similar extent in men and women. In a comparison between patients with primary and secondary adrenal insufficiency, the mortality risk of primary disease, after adjustment for age at diagnosis, was also increased in a similar extent in both sexes.



Number at risk

Men, PAI	860	584	455	360	273	211
Men, SAI	1971	1421	1050	795	571	421
Women, PAI	1192	862	645	484	367	277
Women, SAI	1977	1457	1068	800	587	428

Figure 3.4: Cumulative mortality in patients with primary and secondary adrenal insufficiency categorised by sex

Note: †adjustment for age at diagnosis, PAI: Primary adrenal insufficiency, SAI: Secondary adrenal insufficiency

3.3.2 Mortality rates, unadjusted and adjusted hazard ratios for all-cause mortality stratified by age

In the analysis comparing the study patients with controls, age at the start of follow-up was stratified in two groups: less than 50 (younger group) vs 50 or more (older group). In the analysis comparing primary with secondary adrenal insufficiency, age at diagnosis was stratified as less than 50 (younger group) vs 50 or more (older group).

- ❖ Adrenal insufficiency of any type and matched controls

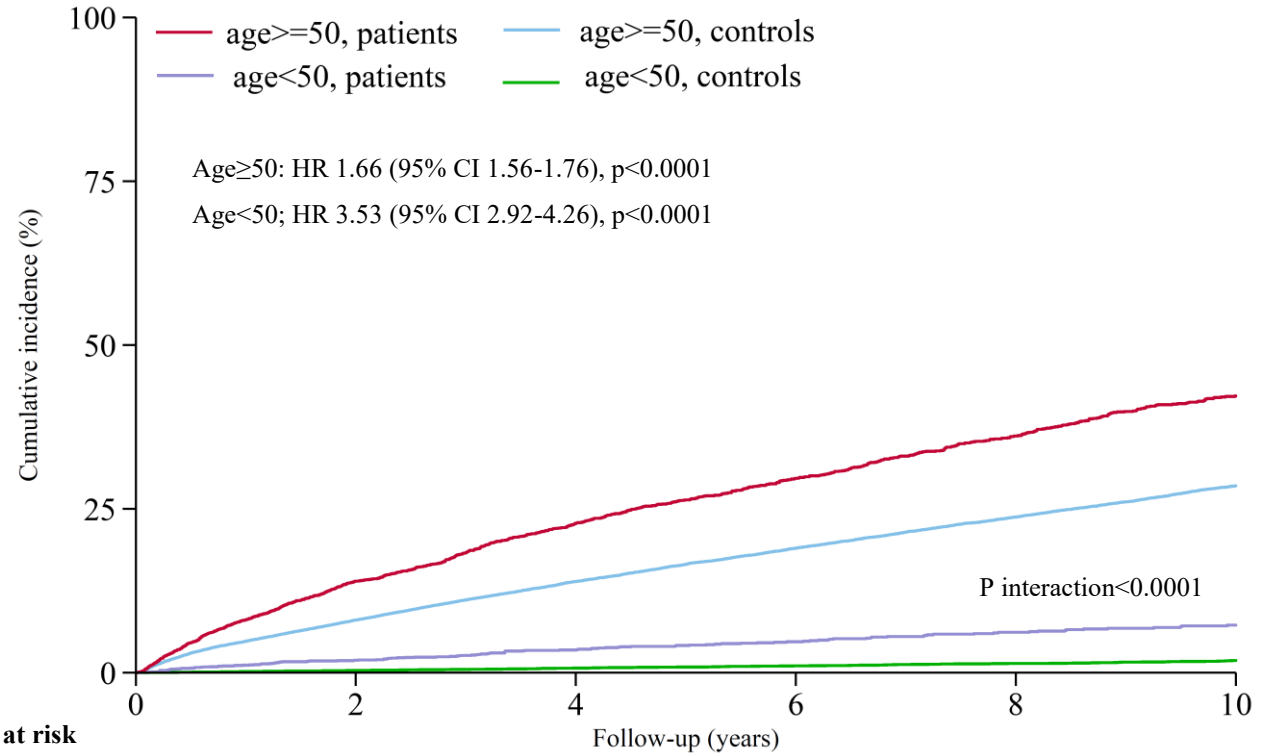
There were 2930 younger and 3891 older patients with adrenal insufficiency and 29407 younger and 38157 older controls including in this analysis. For the younger group, the mortality rates (95% CI) of all-cause were 7.7 (6.5-9.0) and 2.2 (2.0-2.4) per 1000 person-years in the study patients and controls, respectively, giving an unadjusted hazard ratio (95% CI) of 3.53 (2.92-4.26; $p<0.0001$). After adjustment for baseline cardiovascular disease, diabetes, hypertension, dyslipidaemia and ever smoking, the hazard ratio remained increased (Table 3.12).

For the older group, the mortality rates (95% CI) were 59.7 (56.6-63.1) and 36.1 (35.3-36.9) per 1000 person-years in the study patients and controls, respectively, which were markedly higher than those in the younger group, whether or not the participants had adrenal insufficiency. However, the unadjusted hazard ratio of adrenal insufficiency relative to controls remained increased in the older group (1.66 [95% CI, 1.56-1.76]; $p<0.0001$). After adjustment, the hazard ratio remained increased (Table 3.12). The increase in unadjusted and adjusted hazard ratios in the older group was significantly lower than that in the younger group (p-for patient/age interaction < 0.05).

Study group	Study patients				Controls				Unadjusted HR (95%CI)	P	P for interaction	Adjusted HR† (95%CI)	P	P for interaction
	No. at risk	No. death	Person-years	Mortality per 1000 person-years (95% CI)	No. at risk	No. death	Person-years	Mortality per 1000 person-years (95% CI)						
Adrenal insufficiency of any type														
Age start <50	2930	148	19256	7.7 (6.5-9.0)	29407	398	180732	2.2 (2.0-2.4)	3.53 (2.92-4.26)	<0.0001	<0.0001	2.97 (2.44-3.62)	<0.0001	<0.0001
Age start ≥50	3891	1287	21544	59.7 (56.6-63.1)	38157	8164	226166	36.1 (35.3-36.9)	1.66 (1.56-1.76)	<0.0001		1.56 (1.47-1.65)	<0.0001	
Primary adrenal insufficiency														
Age start <50	960	46	6742	6.8 (5.1-9.1)	9602	145	63067	2.3 (2.0-2.7)	2.99 (2.15-4.17)	<0.0001	0.010	2.61 (1.83-3.72)	<0.0001	0.0080
Age start ≥50	1092	418	6219	67.2 (61.1-74.0)	10764	2422	68174	35.5 (34.1-37.0)	1.89 (1.70-2.09)	<0.0001		1.77 (1.59-1.97)	<0.0001	
Secondary adrenal insufficiency														
Age start <50	1673	87	10927	8.0 (6.5-9.8)	16833	224	101832	2.2 (1.9-2.5)	3.67 (2.86-4.70)	<0.0001	<0.0001	3.15 (2.44-4.07)	<0.0001	<0.0001
Age start ≥50	2275	658	12886	51.1 (47.3-55.1)	22301	4608	131009	35.2 (34.2-36.2)	1.46 (1.35-1.59)	<0.0001		1.38 (1.27-1.50)	<0.0001	

Table 3.12: Mortality rates of patients with adrenal insufficiency and controls, and hazard ratios for all-cause mortality categorised by age at start of follow-up

Note: † adjustment for baseline cardiovascular disease, diabetes mellitus, hypertension and dyslipidaemia at the start of follow-up, and ever smoking at any time



Number at risk						
Age≥50, patients	3891	2696	1946	1430	1011	713
Age≥50, controls	38157	26866	19225	14505	10948	8150
Age<50, patients	2930	2144	1621	1247	959	748
Age<50, controls	29407	20342	14466	11072	8535	6672

Figure 3.5: Cumulative mortality in patients with adrenal insufficiency of any type and controls categorised by age at the start of follow-up

Figure 3.5 illustrates the four profiles for cumulative mortality in patients with adrenal insufficiency and controls, categorised by age at the start of follow-up. The cumulative mortality profile among the older group was considerably higher than that of the younger group and the highest profile was for patients with adrenal insufficiency in the older group. In younger patients with adrenal insufficiency, the profile was lower than those in the older group. However, in younger controls, any increase in the profile was minimal across the follow-up period. Therefore, the very low younger control denominator for the mortality risk of adrenal insufficiency in younger patients resulted in the hazard ratio being considerably increased.

- Primary adrenal insufficiency and matched controls

There were 960 younger and 1092 older patients with primary adrenal insufficiency and 9602 younger and 10764 older controls included in this analysis. For the younger group, the mortality rates (95% CI) of all-cause were 6.8 (5.1-9.1) and 2.3 (2.0-2.7) per 1000 person-years in the study patients and controls, respectively, giving an unadjusted hazard ratio (95% CI) of 2.99 (2.15-4.17; $p<0.0001$). After adjustment for baseline cardiovascular disease, hypertension, dyslipidaemia and ever smoking, the hazard ratio remained increased (Table 3.12).

For the older group, the mortality rates (95% CI) were 67.2 (61.1-74.0) and 35.5 (34.1-37.0) per 1000 person-years in the study patients and controls, respectively, giving an unadjusted hazard ratio (95% CI) of 1.89 (1.70-2.09; $p<0.0001$). After adjustment, the hazard ratio also remained increased (Table 3.12). The unadjusted and adjusted hazard ratios in the older group were significantly lower than those in the younger group (p-for interaction < 0.05).

- Secondary adrenal insufficiency and matched controls

There were 1673 younger and 2275 older patients with secondary adrenal insufficiency and 16833 younger and 22301 older controls including in this analysis. For the younger group, the

mortality rates (95% CI) of all-cause were 8.0 (6.5-9.8) and 2.2 (1.9-2.5) per 1000 person-years in the study patients and controls, respectively, giving an unadjusted hazard ratio (95% CI) of 3.67 (2.86-4.70; p<0.0001). After adjustment for baseline cardiovascular disease, diabetes, hypertension, dyslipidaemia and ever smoking, the hazard ratio remained increased (Table 3.12).

For the older group, the mortality rates (95% CI) were 51.1 (47.3-55.1) and 35.2 (34.2-36.2) per 1000 person-years in the study patients and controls, respectively, giving an unadjusted hazard ratio (95% CI) of 1.46 (1.35-1.59; p<0.0001). After adjustment, the hazard ratio was also increased (Table 3.12). Similar to primary adrenal insufficiency, the unadjusted and adjusted hazard ratios in the older group were significantly lower than those in the younger group (p-for interaction < 0.05).

- ❖ Primary adrenal insufficiency compared with secondary adrenal insufficiency

This analysis compared the mortality risk between primary and secondary adrenal insufficiency patients according to age of diagnosis. The younger group included 1022 and 1742 patients with primary and secondary adrenal insufficiency and the equivalent figures for the older group were 1030 and 2206, respectively (Figure 3.6).

In the younger group, the unadjusted hazard ratio of primary relative to secondary adrenal insufficiency was not increased (HR, 0.90 [95% CI, 0.65-1.25; p=0.54). The percentage of men was similar between younger primary and secondary adrenal insufficiency (56% vs 57%; p=0.65). After adjustment for sex, the hazard ratio (95% CI) was unchanged (HR, 0.90 [95% CI, 0.65-1.25; p=0.51).

In the older group, the unadjusted hazard ratio (95%) of primary relative to secondary adrenal insufficiency was 1.35 (1.19-1.53; p<0.0001). In the older group, the percentage of men in the

primary adrenal insufficiency group was higher than that in the secondary adrenal insufficiency group (60% vs 44%; p<0.0001). However, after adjustment for sex, the hazard ratio (95% CI) remained increased at 1.38 (1.22-1.56; p=0.011) (Figure 3.6).

In summary, in a comparison with controls, the increased mortality risk of patients with adrenal insufficiency of any kind including primary and secondary adrenal insufficiency was higher in those with younger age at diagnosis than older individuals. In a comparison between patients with primary and secondary adrenal insufficiency, the mortality risk of primary disease was increased only in older individuals. In younger patients, the mortality of primary adrenal insufficiency was similar to secondary adrenal insufficiency.

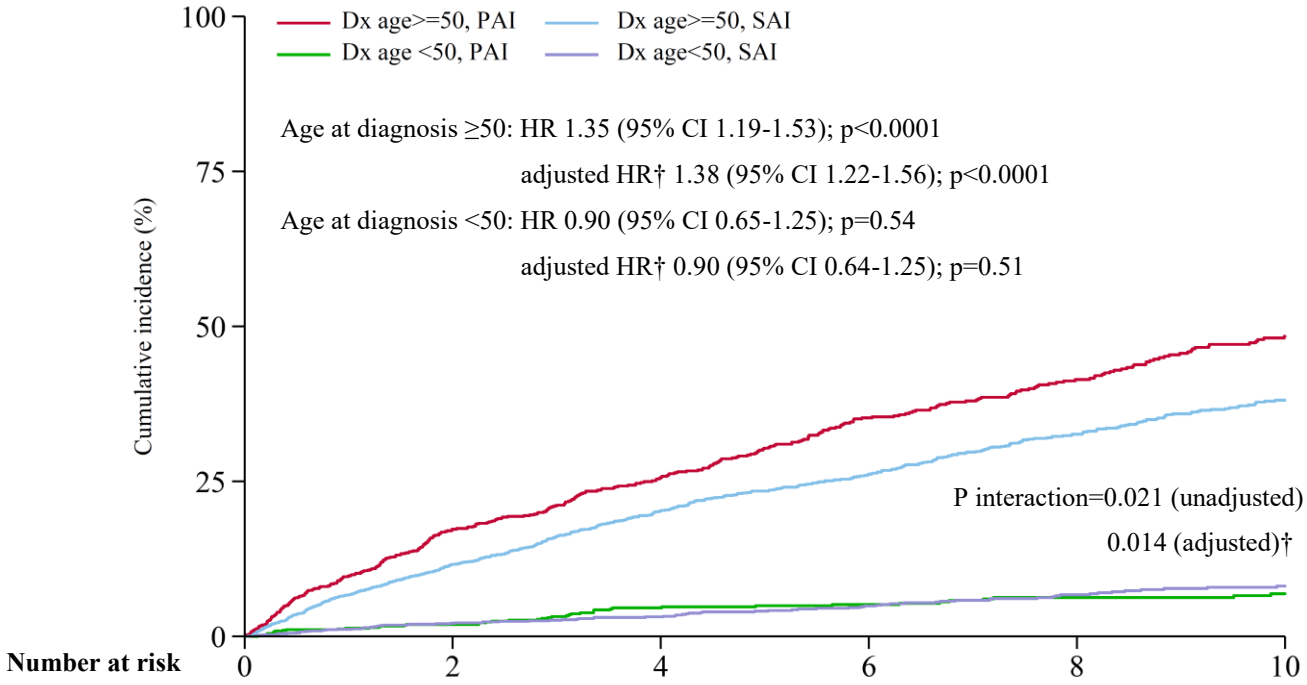


Figure 3.6: Cumulative mortality in patients with primary and secondary adrenal insufficiency categorised by age at diagnosis

Note: †adjustment for sex, PAI: Primary adrenal insufficiency, SAI: Secondary adrenal insufficiency

3.3.3 Hazard ratios for all-cause mortality stratified by age and sex

In this analysis, study patients and controls were divided into ten groups according to sex and five age groups: 0-34, 35-47, 48-59, 60-71, and 72 or more. In each group, the unadjusted hazard ratio of patients with adrenal insufficiency, relative to controls was evaluated. For adrenal insufficiency of any type, the unadjusted hazard ratios in both sexes were highest in age 0-34 (women; HR, 11.13 [95% CI, 5.97-20.79]; p<0.0001 vs men; HR, 6.43 [3.97-10.39]; p<0.0001) and decreasing when the age of the start of follow-up was increased. However, even in the oldest age group (72 or more), the hazard ratio remained significantly increased in both men and women (women; HR, 1.49 [95% CI, 1.33-1.67]; p<0.0001 vs men; HR, 1.38 [95% CI, 1.23-1.54]; p<0.0001; Figure 3.7). Primary and secondary adrenal insufficiency behaved similarly, except that in the oldest age group, men but not women with secondary adrenal insufficiency had a borderline significantly increased hazard ratio (HR, 1.15 [95% CI, 0.99-1.34], p=0.059; Figure 3.8).

In summary, the mortality risk of adrenal insufficiency of any type, including primary and secondary adrenal insufficiency showed a continuous decrease according to increasing age group in both sexes.

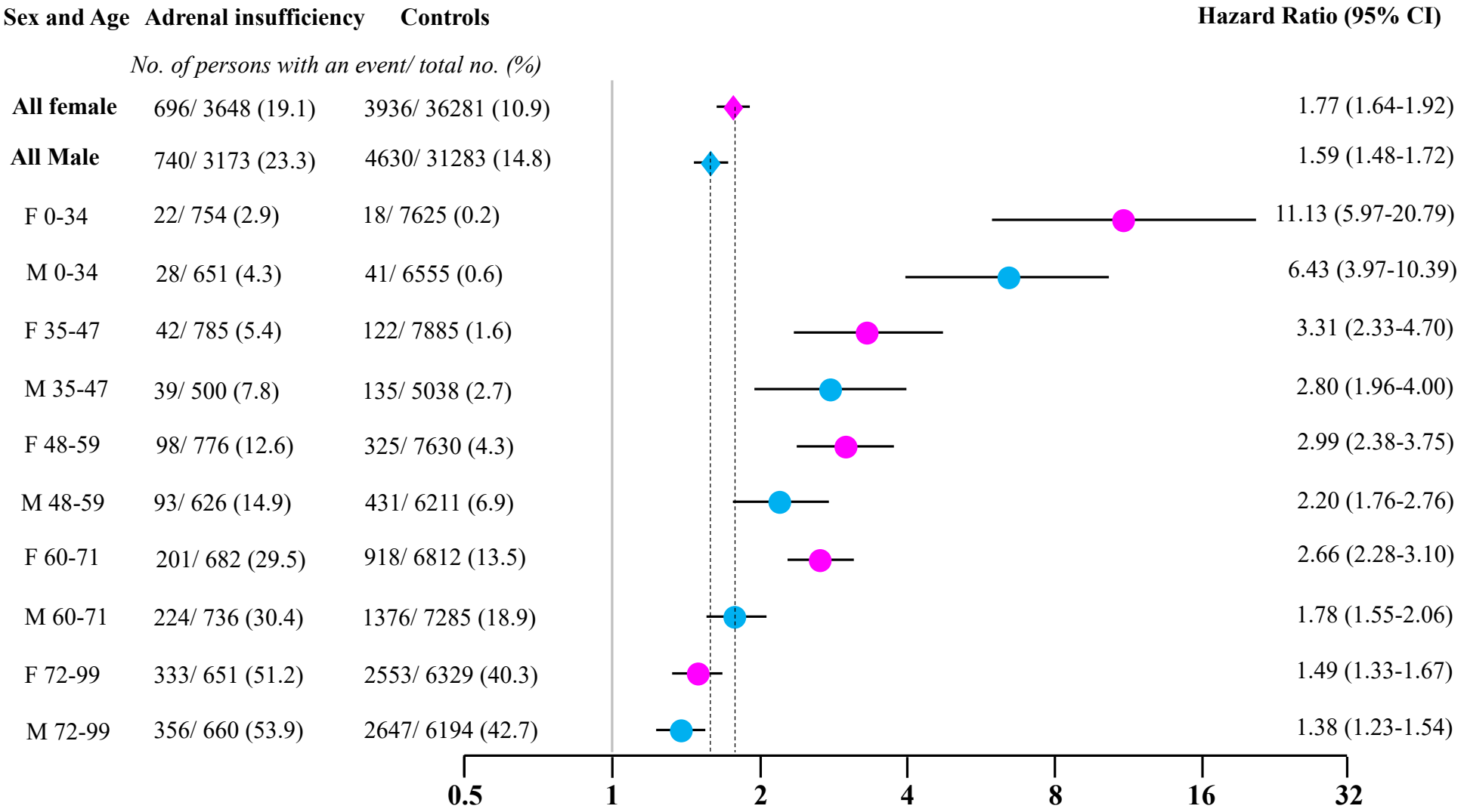


Figure 3.7: Unadjusted hazard ratios of adrenal insufficiency of any type categorised by age at the start of follow-up and sex

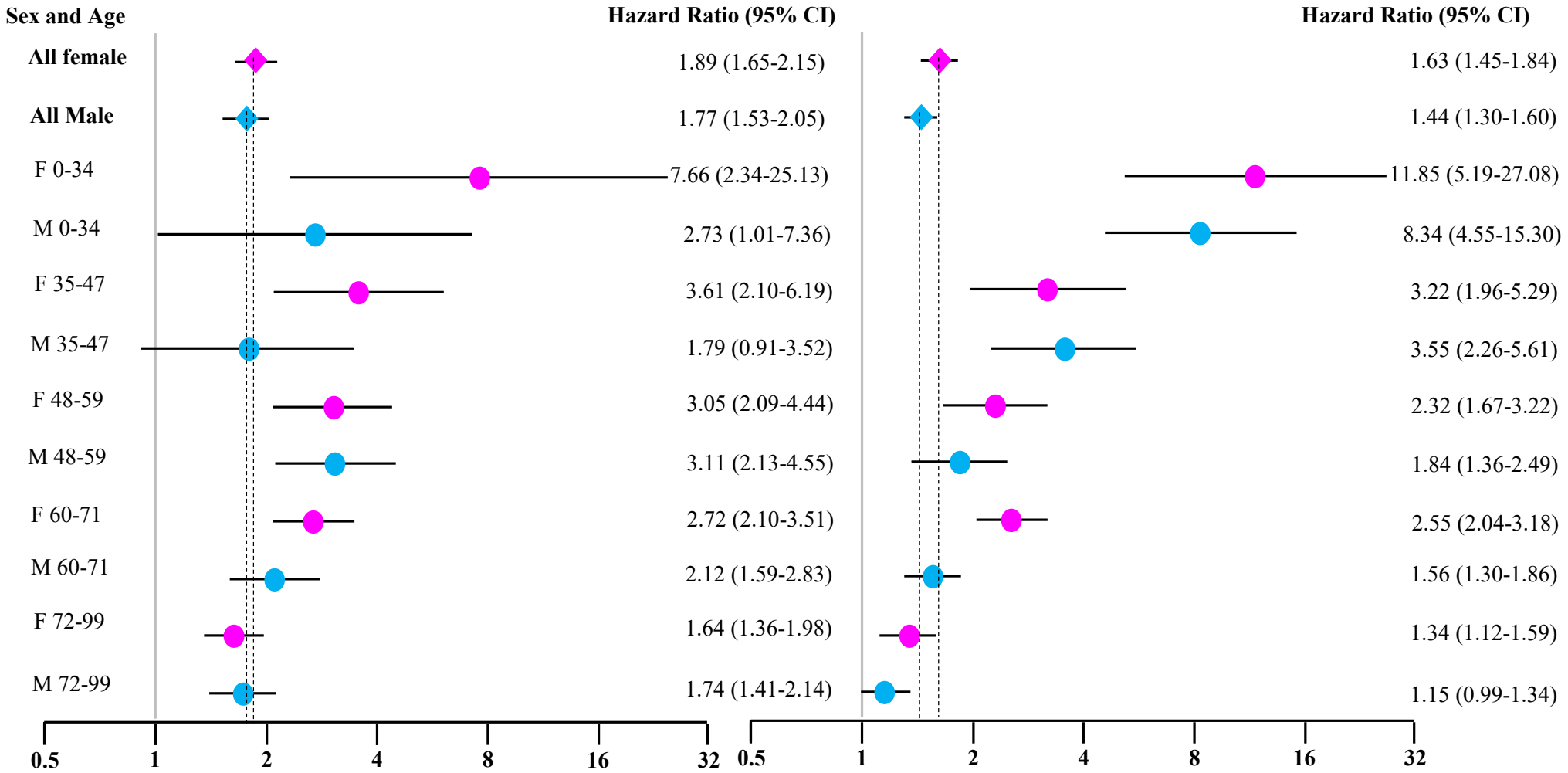


Figure 3.8: Unadjusted hazard ratios of primary (left) and secondary (right) adrenal insufficiency categorised by age at the start of follow-up and sex

3.3.4 Mortality rates, unadjusted and adjusted hazard ratios for all-cause mortality stratified by co-morbid diabetes mellitus

In this analysis, participants were divided into two groups according to the status of diabetes mellitus at any time until the end of follow-up.

- ❖ Adrenal insufficiency of any type and matched controls

In patients with adrenal insufficiency of any type, 1064 had a diagnosis of diabetes and 5757 did not whereas in controls, diabetes was present among 5725 and 61839 were diabetes-free. As diabetes is known to be common among the elderly and increased age was a major contributor to mortality, median age at the start of follow-up of the study patients and controls who had the same diabetes status was evaluated. In those without diabetes, median age of the study patients was not different from that of controls (52 [IQR, 36-67] vs 52 [IQR, 36-67]; p=0.068). However, in those with diabetes, median age of the study patients was significantly lower than that of controls (60 [IQR, 46-70] vs 66 [56-74]; p<0.0001). Since sex might have also contributed to increased mortality, the proportion of men was also examined. In those without diabetes, the proportion of men was similar between the study patients and controls (46% vs 45%; p=0.54). In those with diabetes, the proportion of men was higher in controls (50% vs 56%; p<0.0001). Therefore, age at the start of follow-up and sex difference were taken into accounted in the analysis, in addition to other cardiovascular risk factors.

In the non-diabetes group, the mortality rates (95% CI) of all-cause were 33.7 (31.8-35.7) and 19.7 (19.2-20.1) per 1000 person-years in the study patients and controls, respectively, giving an unadjusted hazard ratio (95% CI) of 1.72 (1.61-1.83; p<0.0001). After adjustment for age, sex, baseline cardiovascular disease, hypertension, dyslipidaemia and ever smoking, the hazard ratio remained increased (HR, 1.81 [95% CI, 1.69-1.92]; p<0.0001; Table 3.13).

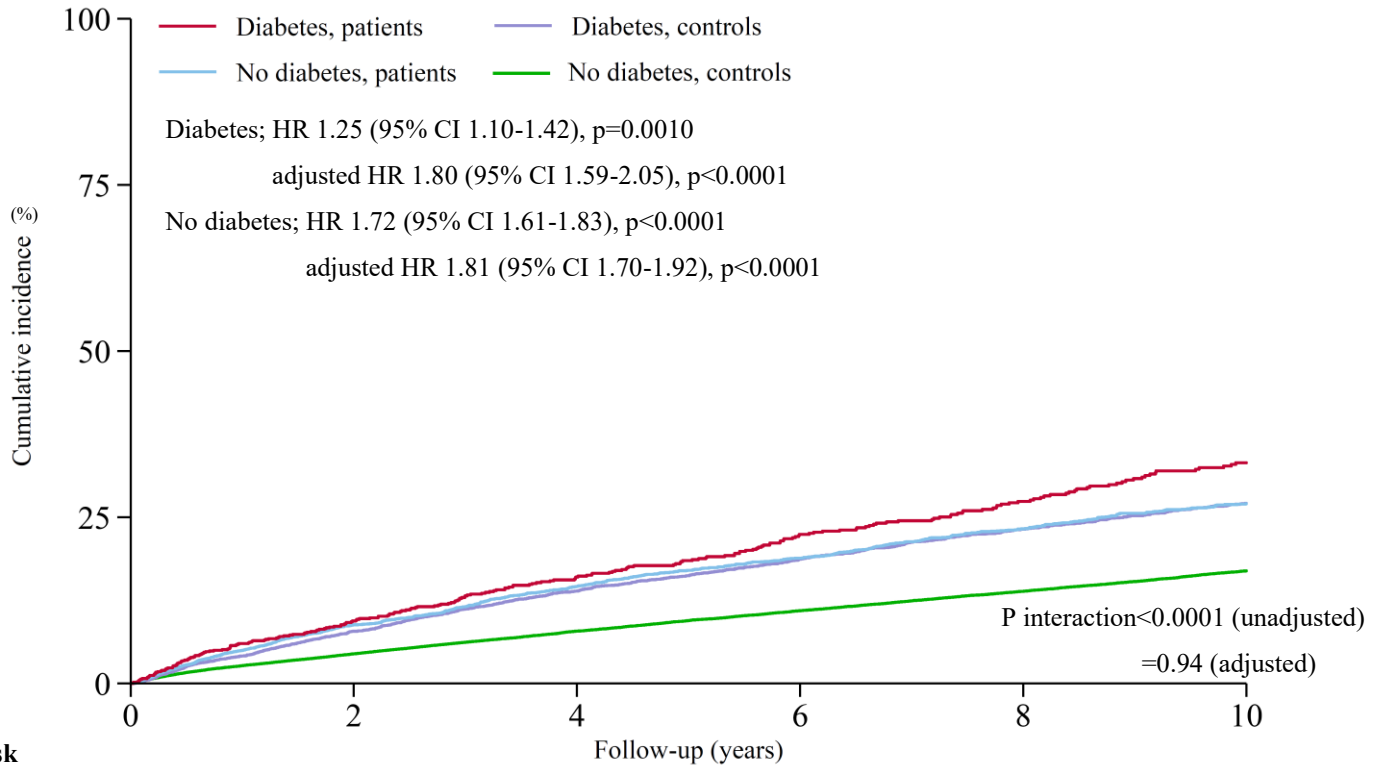
In the diabetes group, the mortality rates (95% CI) were 42.3 (37.7-47.4) and 34.0 (32.2-35.8) per 1000 person-years in the study patients and controls, respectively, giving an unadjusted hazard ratio (95% CI) of 1.25 (1.10-1.42; p=0.001). After adjustment for age, sex, baseline cardiovascular disease, hypertension, dyslipidaemia and ever smoking, the hazard ratio was considerably increased (HR, 1.79 [95% CI, 1.56-2.04]; p<0.0001). This increase meant that the adjusted hazard ratio in the diabetes group was as high as that in the non-diabetes group (p-for interaction=0.78; Table 3.13).

The mortality rate in adrenal insufficiency patients with diabetes was higher than in those without diabetes, as expected. However, before adjustment for age and sex, the mortality risk for adrenal insufficiency relative to controls in those with diabetes was lower than in those free of diabetes. Among those with diabetes, the median age of controls was higher than for the patients with adrenal insufficiency. Older ages among controls with diabetes was then consistent with their increased mortality rate and this could have resulted in the unexpectedly low relative mortality risk for those with adrenal insufficiency in the diabetes group. In non-diabetes group, the median age of controls was not different from the study patients; therefore, the relative mortality risk might have not been affected by the difference in age between study patients and controls. After adjustment, the relative mortality risk in the diabetes group was increased and no longer different from the diabetes group and this did not confirm the additive or synergistic effects of having diabetes on top of adrenal insufficiency. However, as this study did not primarily design to investigate the mortality risk difference between adrenal insufficiency with and without diabetes, parameters affecting mortality such as age, sex, time and place of clinical care did not match between the study patients and controls who were classified in the same diabetes status. Also, the number of participants in the diabetes group was low. Therefore, caution should be taken in the interpretation and extrapolation of the result.

Study group	Study patients				Controls				Unadjusted HR (95%CI)	p	P for interaction	Adjusted HR† (95% CI)	p	P for interaction	Adjusted HR‡ (95% CI)	p	P for interaction
	No. at risk	No. death	Person-years	rate per 1000 person-years (95% CI)	No. at risk	No. death	Person-years	rate per 1000 person-years (95% CI)									
Adrenal insufficiency of any type																	
Without DM	5757	1142	33865	33.7 (31.8-35.7)	61839	7238	367916	19.7 (19.2-20.1)	1.72 (1.61-1.83)	<0.0001	<0.0001	1.81 (1.70-1.92)	<0.0001	0.94	1.81 (1.69-1.92)	<0.0001	0.78
With DM	1064	293	6934	42.3 (37.7-47.4)	5725	1324	38982	34.0 (32.2-35.8)	1.25 (1.10-1.42)	0.0010		1.80 (1.59-2.05)	<0.0001		1.79 (1.56-2.04)	<0.0001	
Primary adrenal insufficiency																	
Without DM	1695	369	10380	35.5 (32.1-39.4)	18758	2203	119103	18.5 (17.7-19.3)	1.92 (1.72-2.14)	<0.0001	<0.0001	2.12 (1.89-2.36)	<0.0001	0.25	2.06 (1.85-2.31)	<0.0001	0.27
With DM	357	95	2581	36.8 (30.1-45.0)	1608	364	12138	30.0 (27.1-33.2)	1.23 (0.98-1.54)	0.074		1.83 (1.46-2.29)	<0.0001		1.90 (1.50-2.41)	<0.0001	
Secondary adrenal insufficiency																	
Without DM	3368	587	20121	29.2 (26.9-31.6)	35719	4038	210082	19.2 (18.6-19.8)	1.53 (1.40-1.66)	<0.0001	0.030	1.58 (1.45-1.73)	<0.0001	0.34	1.61 (1.48-1.76)	<0.0001	0.22
With DM	580	158	3693	42.8 (36.6-50.0)	3415	794	22759	34.9 (32.5-37.4)	1.23 (1.04-1.46)	0.016		1.73 (1.46-2.06)	<0.0001		1.63 (1.36-1.95)	<0.0001	

Table 3.13: Mortality rates of patients with adrenal insufficiency and controls, and hazard ratios for all-cause mortality categorised by concomitant diabetes

Note: † adjustment for sex and age at start of follow-up; ‡ adjustment for sex, age at start of follow-up, baseline cardiovascular disease, hypertension and dyslipidaemia at the start of follow-up, and ever smoking at any time



Number at risk

Diabetes, patients	1064	785	599	480	360	264
Diabetes, controls	5725	4226	3161	2500	1969	1552
No diabetes, patients	5757	4054	2968	2197	1610	1197
No diabetes, controls	61839	42982	30530	23077	17515	13269

Figure 3.9: Cumulative mortality in patients with adrenal insufficiency of any type and controls categorised by concomitant diabetes

Note: †adjustment for age at start of follow-up and sex

Figure 3.9 illustrates the four cumulative mortality profiles of patients with adrenal insufficiency and controls, categorised by comorbid diabetes mellitus. The cumulative mortality profile was highest in patients with adrenal insufficiency and concomitant diabetes. Interestingly, the cumulative mortality profile in the study patients without diabetes resembled the mortality profile in controls who had diabetes, and this was in line with the similarity of overall mortality rates in these two groups (Table 3.13). However, the near identical mortality profiles should be cautiously interpreted since controls with diabetes were older than the patients without diabetes and older age could play a significant role in the high mortality profile observed in controls with diabetes.

- ❖ Primary adrenal insufficiency and matched controls

In patients with primary adrenal insufficiency, 357 had diabetes and 1695 were diabetes-free whereas in controls, the equivalent figures were 1608 and 18758, respectively. As with the whole cohort of adrenal insufficiency of any type, median age at the start of follow-up of the study patients was compared with controls who had the same diabetes status. In those without diabetes, median age of the study patients was not different from that of controls (51 [IQR, 36-67] vs 50 [IQR, 35-66]; p=0.13). However, in those with diabetes, median age of the study patients was significantly lower than that of controls (56 [IQR, 41-70] vs 65 [54-74]; p<0.0001). As with the whole cohort, the proportion of men was also examined. In those without diabetes, the proportion of men was 41%, with no difference between the study patients and controls (p=0.80). In those with diabetes, the proportion of men was also similar between the study patients and controls (48% vs 50%; p=0.51). Age at the start of follow-up and sex difference were considered in the analysis, in addition to other cardiovascular risk factors.

In the non-diabetes group, the rates (95% CI) for all-cause mortality were 35.5 (32.1-39.4) and 18.5 (17.7-19.3) per 1000 person-years in the study patients and controls, respectively, giving an unadjusted hazard ratio (95% CI) of 1.92 (1.72-2.14; p<0.0001). After adjustment for age, sex, baseline cardiovascular disease, hypertension, dyslipidaemia and ever smoking, the hazard ratio remained increased (HR, 2.06 [95% CI, 1.85-2.31]; p<0.0001; Table 3.13).

Among those with diabetes, the mortality rates (95% CI) were 36.8 (30.1-45.0) and 30.0 (27.1-33.2) per 1000 person-years in the study patients and controls, respectively, giving an unadjusted hazard ratio (95% CI) of 1.23(0.98-1.54; p=0.074). After adjustment for age, sex, baseline cardiovascular disease, hypertension, dyslipidaemia and ever smoking, the hazard ratio was markedly increased (HR, 1.90 [95% CI, 1.50-2.41]; p<0.0001). Since there was a considerable increase in the hazard ratio after adjustment in the diabetes group, the adjusted hazard ratio of adrenal insufficiency in those with diabetes was as increased as that in non-diabetes (p-for interaction=0.27; Table 3.13).

- Secondary adrenal insufficiency and matched controls

In patients with secondary adrenal insufficiency, 580 had diabetes and 3368 were diabetes-free whereas in controls the equivalent figures were 3415 and 35719, respectively. Similar to the whole cohort of adrenal insufficiency, median age at the start of follow-up of the study patients was compared with controls who had the same diabetes status. In those without diabetes, median age of the study patients was not different from that of controls (52 [IQR, 37-67] vs 52 [IQR, 37-66]; p=0.31). However, in those with diabetes, median age of the study patients was significantly lower than that of controls (61 [IQR, 48-70] vs 65 [56-73]; p<0.0001). As with the whole cohort, the proportion of men was also examined. For those without diabetes, the proportion of men was 41%, similar between the study patients and controls (p=0.80). In those with diabetes, the proportion of men was higher in the study patients (53% vs 40%; p=0.001).

Age at the start of follow-up and sex difference were considered in the analysis, in addition to other cardiovascular risk factors.

In the non-diabetes group, the mortality rates (95% CI) of all-cause were 29.2 (26.9-31.6) and 19.2 (18.6-19.8) per 1000 person-years in the study patients and controls, respectively, giving an unadjusted hazard ratio (95% CI) of 1.53 (1.40-1.66; p<0.0001). After adjustment for age, sex, baseline cardiovascular disease, hypertension, dyslipidaemia and ever smoking, the hazard ratio remained increased (HR, 1.61 [95% CI, 1.48-1.76]; p<0.0001; Table 3.13).

In the diabetes group, the mortality rates (95% CI) were 42.8 (36.6-50.0) and 34.9 (32.5-37.4) per 1000 person-years in the study patients and controls, respectively, giving an unadjusted hazard ratio (95% CI) of 1.23(1.04-1.46; p=0.016). After adjustment for age, sex, baseline cardiovascular disease, hypertension, dyslipidaemia and ever smoking, the hazard ratio was increased (HR, 1.63 [95% CI, 1.36-1.95]; p<0.0001) and this resulted to the non-significant difference in the adjusted hazard ratios between diabetes and non-diabetes groups (p-for interaction=0.22; Table 3.13).

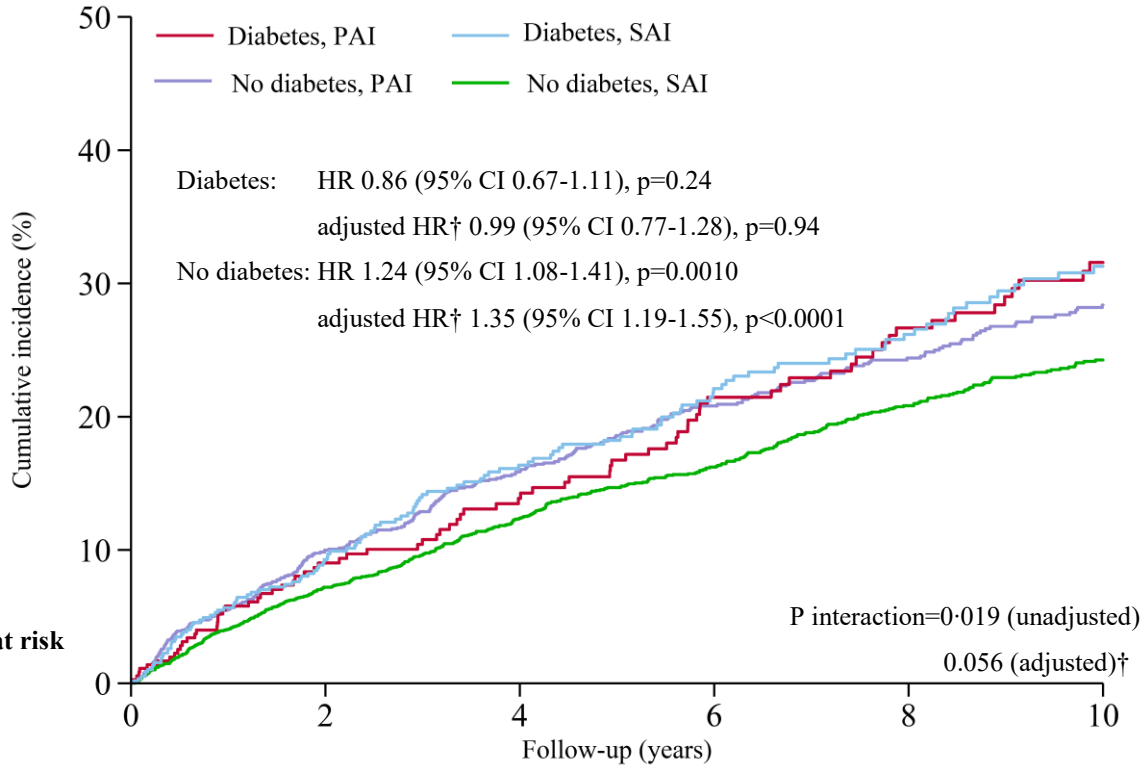
- ❖ Primary adrenal insufficiency compared with secondary adrenal insufficiency

This analysis compared the mortality risk between primary and secondary adrenal insufficiency patients with or without comorbid diabetes. The non-diabetes group included 1695 and 3368 patients with primary and secondary adrenal insufficiency and the diabetes group included 357 and 580 patients with primary and secondary adrenal insufficiency, respectively (Figure 3.10). Since age at diagnosis and sex were not initially matched between patients with primary and secondary adrenal insufficiency, the difference in these parameters was considered in a multivariable analysis.

In the non-diabetes group, median age of diagnosis in patients with primary adrenal insufficiency was not significantly different from that with secondary adrenal insufficiency (49 [IQR, 35-65] vs 51 [IQR, 35-66]; p=0.16) but the proportion of men was lower in primary adrenal insufficiency (41% vs 49%; p<0.0001). The unadjusted hazard ratio of primary relative to secondary adrenal insufficiency was increased (HR, 1.24 [95% CI, 1.08-1.41; p=0.001). After adjustment for sex and age at diagnosis, the hazard ratio (95% CI) remained increased (HR, 1.35 [95% CI, 1.19-1.55; p<0.0001).

In the diabetes group, median age of diagnosis in patients with primary adrenal insufficiency was lower than in those with secondary adrenal insufficiency (53 [IQR, 40-69] vs 59 [IQR, 47-69]; p=0.0001) but the proportion of men was not significantly different (48% vs 53%; p=0.12). The unadjusted hazard ratio of primary relative to secondary adrenal insufficiency was not increased (HR, 0.86 [95% CI, 0.67-1.11; p=0.24). After adjustment for sex and age at diagnosis, the hazard ratio (95% CI) remained non-significantly changed (HR, 0.99 [95% CI, 0.77-1.28; p=0.94). The mortality risk of primary relative to secondary adrenal insufficiency was lower among those with diabetes than those without at borderline significance (p for interaction=0.056). This was illustrated by the cumulative mortality profiles: the three highest profiles were among those with primary adrenal insufficiency regardless of comorbid diabetes, and among those with secondary adrenal insufficiency with diabetes (Figure 3.10).

In summary, in a comparison with controls, the mortality risk of patients with adrenal insufficiency of any kind including primary and secondary adrenal insufficiency, after adjustment for age and sex, was increased to a similar extent whether or not diabetes was comorbid. In a comparison between patients with primary and secondary adrenal insufficiency, the mortality risk of primary disease appeared to be increased among patients without diabetes. In those with diabetes, mortality in primary adrenal insufficiency was similar to that in secondary adrenal insufficiency.



Number at risk

Diabetes, PAI	357	272	216	182	134	104
Diabetes, SAI	580	434	326	254	195	139
No diabetes, PAI	1695	1175	884	662	506	384
No diabetes, SAI	3368	2444	1792	1339	963	710

Figure 3.10: Cumulative mortality in patients with primary and secondary adrenal insufficiency categorised by concomitant diabetes

Note: †adjustment for age at diagnosis and sex, PAI: Primary adrenal insufficiency, SAI: Secondary adrenal insufficiency

3.3.5 Mortality rates, unadjusted and adjusted hazard ratios for all-cause mortality stratified by co-morbid cardiovascular disease

In this analysis, participants (the study patients and controls) were divided into two groups according to whether or not they had a record of cardiovascular disease at any time until the end of follow-up.

- ❖ Adrenal insufficiency of any type and matched controls

In adrenal insufficiency of any type, 1830 and 4991 patients with and without cardiovascular disease, along with 13109 and 54455 controls with and without cardiovascular disease were included in the analysis. As with diabetes, cardiovascular disease is known to be common among the elderly and increased age was a major contributor of mortality; median age at the start of follow-up of the study patients and controls who had the same status of cardiovascular disease was therefore considered in the analysis. In those without cardiovascular disease, median age of the study patients was slightly lower than that of controls (47 [IQR, 33-61] vs 48 [IQR, 34-62]; p=0.001). In those with cardiovascular disease, median age of the study patients was also lower than that of controls (69 [IQR, 59-78] vs 71 [62-78]; p<0.0001). Since sex might have also contributed to increased mortality, the proportion of men was also considered. In those without cardiovascular disease, the proportion of men was similar between the study patients and controls (44% vs 44%; p=0.81). In those with cardiovascular disease, the proportion of men was higher in controls (54% vs 58%; p=0.003). Age at the start of follow-up and sex difference were taken into accounted, in addition to other cardiovascular risk factors, in the multivariable analysis.

In those without cardiovascular disease, the mortality rates (95% CI) of all-cause were 20.9 (19.3-22.6) and 12.4 (12.0-12.8) per 1000 person-years in the study patients and controls, respectively, giving an unadjusted hazard ratio (95% CI) of 1.70 (1.56-1.85; p<0.0001). After

adjustment for age, sex, baseline diabetes, hypertension, dyslipidaemia and ever smoking, the hazard ratio of adrenal insufficiency remained increased (HR, 1.95 [95% CI, 1.79-2.12]; p<0.0001; Table 3.14).

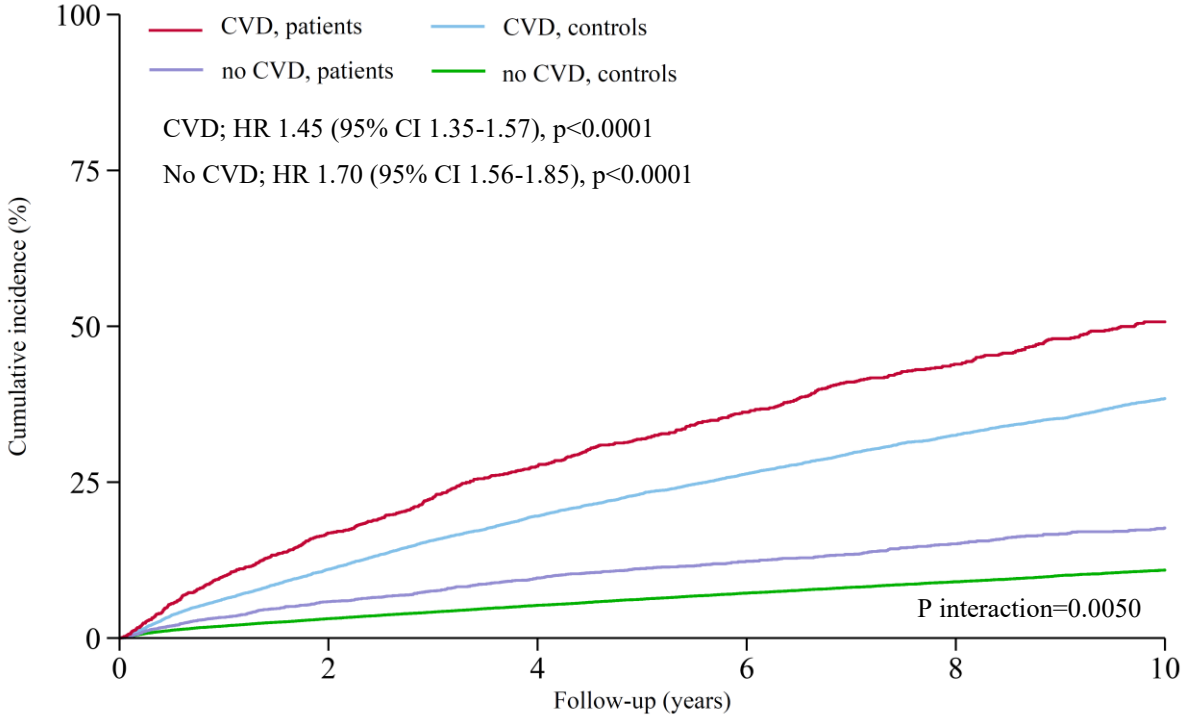
In those with cardiovascular disease, the mortality rates (95% CI) were 74.5 (69.5-79.8) and 51.0 (49.6-52.5) per 1000 person-years in the study patients and controls, respectively, giving an unadjusted hazard ratio (95% CI) of 1.45 (1.35-1.57; p<0.0001). After adjustment for age, sex, baseline diabetes, hypertension, dyslipidaemia and ever smoking, the hazard ratio of adrenal insufficiency was increased (HR, 1.72 [95% CI, 1.59-1.85]; p<0.0001). Because of this increase, the adjusted hazard ratio of adrenal insufficiency in those with cardiovascular disease was as high as those without (p-for interaction=0.063; Table 3.14).

Figure 3.11 illustrates the four profiles for cumulative mortality of patients with adrenal insufficiency and controls, categorised by comorbid cardiovascular disease. All four mortality profiles were clearly separated. As expected, the profile was higher in those with cardiovascular disease and highest in the patient group. The highest mortality among those with cardiovascular disease was partly attributed to older ages.

Study group	Study patients				Controls				Unadjusted HR (95%CI)	p	P for interaction	Adjusted HR (95% CI) †	p	P for interaction	Adjusted HR (95% CI) ‡	p	P for interaction
	No. at risk	No. death	Person-years	rate per 1000 person-years (95% CI)	No. at risk	No. death	Person-years	rate per 1000 person-years (95% CI)									
Adrenal insufficiency of any type																	
Without CVD	4991	626	29941	20.9 (19.3-22.6)	54455	3910	315718	12.4 (12.0-12.8)	1.70 (1.56-1.85)	<0.001	0.0050	1.90 (1.74-2.07)	<0.001	0.041	1.95 (1.79-2.12)	<0.001	0.063
With CVD	1830	809	10859	74.5 (69.5-79.8)	13109	4652	91181	51.0 (49.6-52.5)	1.45 (1.35-1.57)	<0.001		1.73 (1.61-1.87)	<0.001		1.72 (1.59-1.85)	<0.001	
Primary adrenal insufficiency																	
Without CVD	1550	202	9988	20.2 (17.6-23.2)	16642	1235	103244	12.0 (11.3-12.6)	1.70 (1.47-1.97)	<0.001	0.50	1.96 (1.69-2.28)	<0.001	0.41	1.94 (1.67-2.26)	<0.001	0.46
With CVD	502	262	2973	88.1 (78.1-99.5)	3724	1332	27996	47.6 (45.1-50.2)	1.84 (1.61-2.10)	<0.001		2.21 (1.93-2.52)	<0.001		2.11 (1.84-2.42)	<0.001	
Secondary adrenal insufficiency																	
Without CVD	2881	333	17112	19.5 (17.5-21.7)	31510	2196	180119	12.2 (11.7-12.7)	1.61 (1.43-1.80)	<0.001	0.0010	1.78 (1.58-1.99)	<0.001	0.0070	1.86 (1.65-2.09)	<0.001	0.013
With CVD	1067	412	6701	61.5 (55.8-67.7)	7624	2636	52722	50.0 (48.1-51.9)	1.23 (1.11-1.37)	<0.001		1.47 (1.33-1.63)	<0.001		1.49 (1.34-1.66)	<0.001	

Table 3.14: Mortality rates of patients with adrenal insufficiency and controls, and hazard ratios for all-cause mortality categorised by concomitant cardiovascular disease (CVD)

Note: † adjustment for sex and age at start of follow-up; ‡ adjustment for sex, age at start of follow-up, baseline diabetes, hypertension and dyslipidaemia at the start of follow-up, and ever smoking at any time



Number at risk

CVD, patients	1830	1287	957	724	518	386
CVD, controls	13109	9861	7462	5923	4678	3651
No CVD, patients	4991	3553	2610	1954	1452	1075
No CVD controls	54455	37347	26230	19655	14804	11174

Figure 3.11: Cumulative mortality in patients with adrenal insufficiency of any type and controls categorised by concomitant cardiovascular disease (CVD)

❖ Primary adrenal insufficiency and matched controls

In primary adrenal insufficiency, 502 and 1550 patients with and without cardiovascular disease, along with 3724 and 16642 controls with and without cardiovascular disease were included in the analysis. Similar to the whole cohort of adrenal insufficiency, median age at the start of follow-up of the study patients was compared with controls who had the same status of cardiovascular disease. In those without cardiovascular disease, median age of the study patients was slightly lower than that of controls (45 [IQR, 33-59] vs 46 [IQR, 34-60]; p=0.06). Also, in those with cardiovascular disease, median age of the study patients was lower than that of controls (70 [IQR, 59-78] vs 71 [62-78]; p=0.05). Similar to the whole cohort, the proportion of men was also examined. In those without cardiovascular disease, the proportion of men in the study patients and controls was 40% (p=0.90). For those with cardiovascular disease, the proportion of men was also similar between the study patients and controls (48% vs 49%; p=0.77). Age at the start of follow-up and sex difference were considered in the analysis, in addition to other cardiovascular risk factors.

In those without cardiovascular disease, the mortality rates (95% CI) of all-cause were 20.2 (17.6-23.2) and 12.0 (11.3-12.6) per 1000 person-years in the study patients and controls, respectively, giving an unadjusted hazard ratio (95% CI) of 1.70 (1.47-1.97; p<0.0001). After adjustment for age, sex, baseline diabetes, hypertension, dyslipidaemia and ever smoking, the hazard ratio remained increased (HR, 1.94 [95% CI, 1.67-2.26]; p<0.0001; Table 3.14).

In those with cardiovascular disease, the mortality rates (95% CI) were 88.1 (78.1-99.5) and 47.6 (45.1-50.2) per 1000 person-years in the study patients and controls, respectively, giving an unadjusted hazard ratio (95% CI) of 1.84 (1.61-2.10; p<0.0001). After adjustment for age, sex, baseline diabetes, hypertension, dyslipidaemia and ever smoking, the hazard ratio remained increased (HR, 2.11 [95% CI, 1.84-2.42]; p<0.0001). The increased unadjusted and

adjusted hazard ratios for primary adrenal insufficiency in those with cardiovascular disease were not different from those without cardiovascular disease (p-for interaction test in unadjusted =0.50 and adjusted =0.46; Table 3.14).

- Secondary adrenal insufficiency and matched controls

In secondary adrenal insufficiency, 1067 and 2881 patients with and without cardiovascular disease, along with 7624 and 31510 controls with and without cardiovascular disease were included in the analysis. Similar to the whole cohort, median age at the start of follow-up of the study patients was compared with controls who had the same status of cardiovascular disease. In those without cardiovascular disease, median age of the study patients was slightly lower than that of controls (48 [IQR, 34-62] vs 49 [IQR, 34-62]; p=0.02). In those with cardiovascular disease, median age of the study patients was significantly lower than that of controls (68 [IQR, 58-77] vs 70 [62-78]; p<0.0001). Similar to the whole cohort, the proportion of men was also examined. In those without cardiovascular disease, the proportion of men was similar between the study patients and controls (47% vs 46%; p=0.67). However, in those with cardiovascular disease, the proportion of men in the study patients was significantly lower (59% vs 64%; p=0.001). Age at the start of follow-up and sex difference were considered in the analysis, in addition to other cardiovascular risk factors.

In those without cardiovascular disease, the mortality rates (95% CI) were 19.5 (17.5-21.7) and 12.2 (11.7-12.7) per 1000 person-years in the study patients and controls, respectively, giving an unadjusted hazard ratio (95% CI) of 1.61 (1.43-1.80; p<0.0001). After adjustment for age, sex, baseline diabetes, hypertension, dyslipidaemia and ever smoking, the hazard ratio remained increased (HR, 1.86 [95% CI, 1.65-2.09]; p<0.0001; Table 3.14).

In those with cardiovascular disease, the mortality rates (95% CI) were 61.5 (55.8-67.7) and 50.0 (48.1-51.9) per 1000 person-years in the study patients and controls, respectively, giving

an unadjusted hazard ratio (95% CI) of 1.23 (1.11-1.37; p<0.0001). After adjustment for age, sex, baseline diabetes, hypertension, dyslipidaemia and ever smoking, the hazard ratio remained increased (HR, 1.49 [95% CI, 1.34-1.66]; p<0.0001). However, the increase in hazard ratio for secondary adrenal insufficiency in those without cardiovascular disease was greater than in those with cardiovascular disease (p for interaction=0.013; Table 3.14).

- ❖ Primary adrenal insufficiency compared with secondary adrenal insufficiency

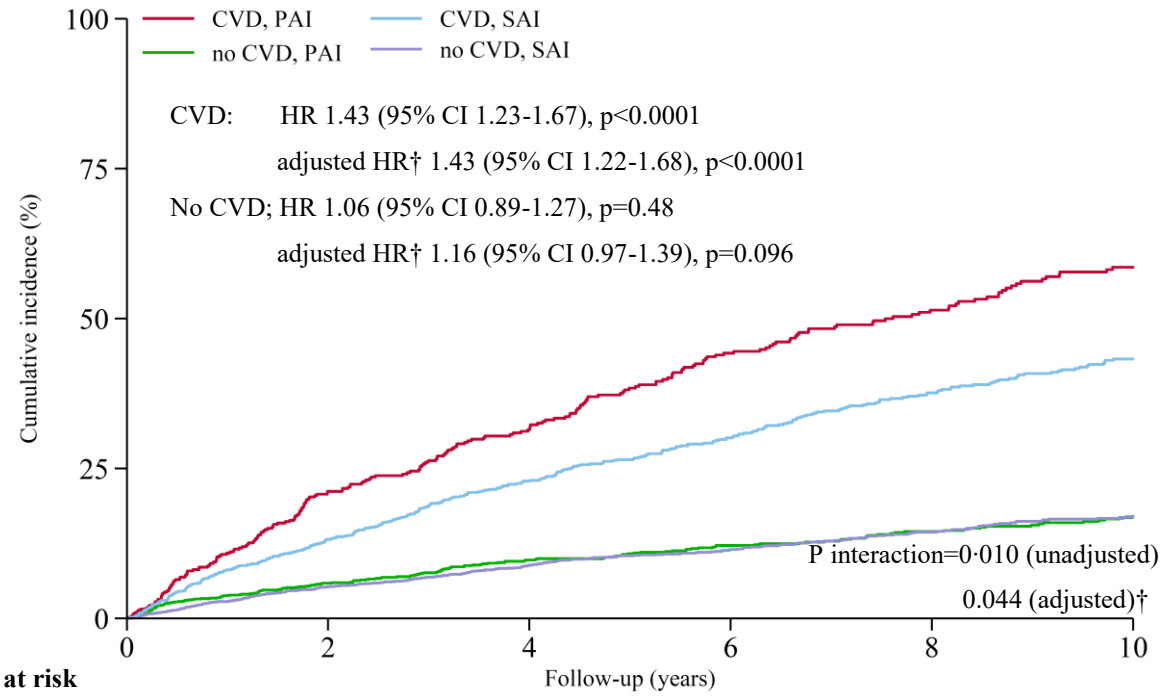
This analysis compared the mortality risk between primary and secondary adrenal insufficiency patients with or without comorbid cardiovascular disease. In non-cardiovascular disease, the analysis included 1550 and 2881 patients with primary and secondary adrenal insufficiency whereas in cardiovascular disease, it included 502 and 1067 patients with primary and secondary adrenal insufficiency, respectively (Figure 3.12). Since age at diagnosis and sex were not initially matched between patients with primary and secondary adrenal insufficiency, the difference in these parameters was considered in the multivariable analysis.

In non-cardiovascular disease, median age of diagnosis in patients with primary adrenal insufficiency was lower than that of secondary adrenal insufficiency (43 [IQR, 31-58] vs 47 [IQR, 32-61]; p=0.014) and the proportion of men was lower in primary adrenal insufficiency (40% vs 47%; p<0.0001). The unadjusted hazard ratio of primary relative to secondary adrenal insufficiency was not increased (HR, 1.06 [95% CI, 0.89-1.27; p=0.48). After adjustment for sex and age at diagnosis, the hazard ratio (95% CI) was slightly increased but not significantly (HR, 1.16 [95% CI, 0.97-1.39; p=0.096).

In cardiovascular disease, median age of diagnosis in patients with primary adrenal insufficiency was slightly higher than those with secondary adrenal insufficiency (69.5 [IQR, 57-77] vs 67 [IQR, 57-76]; p=0.087) but the proportion of men was significantly lower (48% vs 59%; p<0.0001). The unadjusted hazard ratio of primary relative to secondary adrenal

insufficiency was increased (HR, 1.43 [95% CI, 1.23-1.67]; p<0.0001). After adjustment for sex and age at diagnosis, the hazard ratio (95% CI) was unchanged (HR, 1.43 [95% CI, 1.22-1.68; p<0.0001). The mortality risk of primary relative to secondary adrenal insufficiency was higher among those with cardiovascular disease than those without (p for interaction=0.044; Figure 3.12). This is illustrated in Figure 3.12, which shows that in those with comorbid cardiovascular disease the cumulative mortality profile of primary was clearly distinguishable from the profile of secondary adrenal insufficiency whereas in those without cardiovascular disease the profile of primary was almost identical to secondary adrenal insufficiency. It was noted that these profiles (Figure 3.12) were very similar to the cumulative mortality profiles of patients with primary and secondary adrenal insufficiency stratified according to younger or older age (Figure 3.6). The similar mortality profiles suggested that the study patients with comorbid cardiovascular disease might have been the same group as those with older age and the patients without cardiovascular disease might have been the same as those with younger age.

In summary, in a comparison with controls, the mortality risk of patients with adrenal insufficiency of any kind and those with primary adrenal insufficiency was increased to a similar extent whether or not cardiovascular disease was concomitant. However, in patients with secondary adrenal insufficiency, the mortality risk relative to controls was increased to a greater extent in those without cardiovascular disease than in those with cardiovascular disease. In a comparison between patients with primary and secondary adrenal insufficiency, the mortality risk of primary disease was increased relative to secondary disease in those with comorbid cardiovascular disease. In those without cardiovascular disease, the mortality of primary adrenal insufficiency was similar to secondary adrenal insufficiency.



Number at risk						
CVD, PAI	502	340	255	188	136	105
CVD, SAI	1067	789	602	461	330	246
No CVD, PAI	1550	1106	845	656	504	383
No CVD, SAI	2881	2089	1516	1133	828	603

Figure 3.12: Cumulative mortality in patients with primary and secondary adrenal insufficiency categorised by concomitant cardiovascular disease (CVD)

Note: †adjustment for age at diagnosis and sex, PAI: Primary adrenal insufficiency, SAI: Secondary adrenal insufficiency

3.4: Mortality rates and hazard ratios for all-cause mortality according to calendar years and time

This analysis focused on (1) the difference in mortality rates and hazard ratios of adrenal insufficiency according to the period of clinical care (in calendar years) and (2) the change of mortality rates and risk according to the year of study entry and year of diagnosis (time specific for individual patients).

3.4.1 All-cause mortality rates and hazard ratios according to the calendar year of clinical care

In this analysis, the participants were divided into two equal groups according to the calendar year in which they received clinical care: previous care (before 1st July 2007) and recent care (on or after 1st July 2007).

- ❖ Adrenal insufficiency of any type and matched controls

There were 3455 study patients and 34214 controls receiving previous care whereas in recent care there were 3366 patients and 33350 controls. In previous care, the mortality rates (95% CI) were 34.5 (32.4-36.7) and 20.1 (19.6-20.6) per 1000 person-years in the study patients and controls, respectively, giving an unadjusted hazard ratio (95% CI) of 1.72 (1.61-1.84; p<0.0001). After adjustment for baseline cardiovascular disease, diabetes, hypertension, dyslipidaemia and ever smoking, the hazard ratio remained increased (HR, 1.54 [95% CI, 1.44-1.65]; p<0.0001; Table 3.15).

In recent care, the mortality rates (95% CI) were 37.1 (33.6-40.8) and 23.9 (22.9-24.8) per 1000 person-years in the study patients and controls, respectively, giving an unadjusted hazard ratio (95% CI) of 1.57 (1.41-1.74; p<0.0001). After adjustment, the hazard ratio was also increased

(HR, 1.33 [95% CI, 1.19-1.49]; p<0.0001; Table 3.15). The unadjusted and adjusted hazard ratios of adrenal insufficiency of any type remained similarly increased whether the patients received previous or recent clinical care (p-for interaction ≥ 0.05).

- ❖ Primary adrenal insufficiency and matched controls

There were 1137 study patients and 11189 controls receiving previous care whereas in recent care there were 915 patients and 9177 controls. In previous care, the mortality rates (95% CI) were 33.3 (29.9-37.1) and 18.8 (18.0-19.7) per 1000 person-years in the study patients and controls, respectively, giving an unadjusted hazard ratio (95% CI) of 1.77 (1.58-1.99; p<0.0001). After adjustment for baseline cardiovascular disease, diabetes, hypertension, dyslipidaemia and ever smoking, the hazard ratio remained increased (HR, 1.62 [95% CI, 1.44-1.82]; p<0.0001; Table 3.15).

In recent care, the mortality rates (95% CI) were 44.4 (37.4-52.9) and 22.3 (20.6-24.1) per 1000 person-years in the study patients and controls, respectively, giving an unadjusted hazard ratio (95% CI) of 2.00 (1.65-2.41; p<0.0001). After adjustment, the hazard ratio remained increased (HR, 1.80 [95% CI, 1.47-2.20]; p<0.0001; Table 3.15). The unadjusted and adjusted hazard ratios of primary adrenal insufficiency remained similarly increased whether the patients received previous or recent clinical care (p-for interaction ≥ 0.05).

Cohort	Study patients				Controls				Unadjusted hazard ratio (95% CI)	p	P for interaction	Adjusted hazard ratio (95% CI) †	P	P for interaction
	No. at risk	No. death	Person-year	Mortality per 1000 person-years	No. at risk	No. death	Person-year	Mortality per 1000 person-years						
Adrenal insufficiency of any type														
Previous	3455	1027	29788	34.5 (32.4-36.7)	34214	6088	303182	20.1 (19.6-20.6)	1.72 (1.61-1.84)	<0.0001	0.13	1.54 (1.44-1.65)	<0.0001	0.079
Recent	3366	408	11011	37.1 (33.6-40.8)	33350	2474	103717	23.9 (22.9-24.8)	1.57 (1.41-1.74)	<0.0001		1.33 (1.19-1.49)	<0.0001	
Primary adrenal insufficiency														
Previous	1137	336	10081	33.3 (29.9-37.1)	11189	1937	103000	18.8 (18.0-19.7)	1.77 (1.58-1.99)	<0.0001	0.29	1.62 (1.44-1.82)	<0.0001	0.28
Recent	915	128	2880	44.4 (37.4-52.9)	9177	630	28241	22.3 (20.6-24.1)	2.00 (1.65-2.41)	<0.0001		1.80 (1.47-2.20)	<0.0001	
Secondary adrenal insufficiency														
Previous	1962	552	16951	32.6 (30.0-35.4)	19495	3411	170066	20.1 (19.4-20.7)	1.63 (1.49-1.79)	<0.0001	0.0030	1.45 (1.33-1.59)	<0.0001	0.0020
Recent	1986	193	6862	28.1 (24.4-32.4)	19639	1421	62775	22.6 (21.5-23.8)	1.26 (1.08-1.47)	0.0030		1.06 (0.91-1.24)	0.46	

Table 3.15: Mortality rates of patients with adrenal insufficiency and controls, and hazard ratios for all-cause mortality according to the calendar year of clinical care

Note: Previous care included participants starting the care before mid-2007 and Recent care included participants starting the care after mid-2007; † adjustment for baseline cardiovascular disease, diabetes mellitus, hypertension and dyslipidaemia at the start of follow-up, and ever smoking at any time

❖ Secondary adrenal insufficiency and matched controls

There were 1962 study patients and 19495 controls receiving previous care whereas in recent care there were 1986 patients and 19639 controls. In previous care, the mortality rates (95% CI) were 32.6 (30.0-35.4) and 20.1 (19.4-20.7) per 1000 person-years in the study patients and controls, respectively, giving an unadjusted hazard ratio (95% CI) of 1.63 (1.49-1.79; p<0.0001). After adjustment for baseline cardiovascular disease, diabetes, hypertension, dyslipidaemia and ever smoking, the hazard ratio remained increased (HR, 1.45 [95% CI, 1.33-1.59]; p<0.0001; Table 3.15).

In recent care, the mortality rates (95% CI) were 28.1 (24.4-32.4) and 22.6 (21.5-23.8) per 1000 person-years in the study patients and controls, respectively, giving an unadjusted hazard ratio (95% CI) of 1.26 (1.08-1.47; p=0.003). After adjustment for baseline cardiovascular disease, diabetes, hypertension, dyslipidaemia and ever smoking, the hazard ratio was no longer increased (HR, 1.06 [95% CI, 0.91-1.24]; p=0.46; Table 3.15). Therefore, in those receiving recent care, when cardiovascular risk factors were taken into account, the hazard ratio of secondary adrenal insufficiency was not increased. The unadjusted and adjusted hazard ratios of secondary adrenal insufficiency in those receiving recent care was then significantly lower than in those receiving previous care (p for interaction <0.05).

In summary, in a comparison with controls, the mortality risk of patients with primary adrenal insufficiency was similarly increased among those receiving previous or recent clinical care. Risk was also increased in those with secondary adrenal insufficiency receiving previous care but, after adjustment for cardiovascular risk factors, was no longer increased in secondary adrenal insufficiency among those receiving recent care. It should be noted that the mortality rate in controls with recent care was unexpectedly higher than that in controls with previous care despite having a similar median age and a similar proportion of male sex (data not shown). This might have been caused by the characteristics of the CPRD dataset, in which the participant number has been increasing over the historical period. Specifically, in more recent care, participants might have expanded to include people living in more deprived areas. However, this would not have affected the risk evaluation because controls were matched to patients according to general practice and, consequently residence area.

3.4.2 All-cause mortality rates and hazard ratios according to the year of study entry and year of diagnosis

Regarding the year of study entry, the mortality rates of the study patients and controls were calculated on a yearly basis for the first five years and then every five years until 20 years from the start of follow-up for each participant. Similarly, the hazard ratios of adrenal insufficiency relative to controls were calculated according to the year of study entry, and were also adjusted for previous cardiovascular disease, diabetes mellitus, hypertension and dyslipidaemia at the start of follow-up, and ever smoking at any time.

Regarding the year of diagnosis, the mortality rates of the study patients were calculated on a yearly basis for the first five years and then every five years until 20 years after the diagnosis

of adrenal insufficiency (index date). Since the diagnosis of adrenal insufficiency was not applicable to controls, the hazard ratio in this regard was not available.

All-cause mortality rates and hazard ratios according to the year of study entry

- Adrenal insufficiency of any type and matched controls

A total of 6821 study patients and 67564 controls was included in the analysis. In the first year after study entry, the mortality rates of the study patients and controls were highest compared with the following years (53.2 [95% CI, 47.8-59.2] vs 28.9 [95% CI, 27.6-30.3] per 1000 person-years; Figure 3.13; Table 3.16). More importantly, in the first year, the mortality rate difference between the study patients and controls was also greatest (+24.3 [95% CI, 18.4-30.1] per 1000 person-years; $p<0.0001$). In the second year, the mortality rate was also high among patients with adrenal insufficiency but not controls, giving a mortality rate difference of +20.5 (95% CI, 14.9-26.1) per 1000 person-years ($p<0.0001$). In the following years, the mortality rate of the study patients declined whereas in controls it remained stable; consequently, the mortality rate difference also declined after the first two years (Figure 3.12). From year of study 15-20 onwards, the mortality rate of the patients was not different from that of controls (Figure 3.13; Table 3.16). Similar to the mortality rate difference, in the first two years, the unadjusted and adjusted hazard ratios appeared to be higher than those in the later years. During the second year, the greatest hazard ratio was observed (unadjusted HR, 2.01 [95% CI, 1.74-2.33]; $p<0.0001$; adjusted HR, 1.71 [95% CI, 1.46-1.99]; $p<0.0001$). From the year of 15-20 onwards, the hazard ratios were no longer significantly increased (Table 3.16).

Years of study	Adrenal insufficiency of any type				Controls				Mortality rate difference per 1000 person-years (95% CI)	P for mortality rate difference	Unadjusted HR (95%CI)	P	Adjusted HR (95%CI) †	P
	No. at risk	No. death	Person-years	Mortality per 1000 person-years (95% CI)	No. at risk	No. death	Person-years	Mortality per 1000 person-years (95% CI)						
0-1	6821	334	6283	53.2 (47.8-59.2)	67564	1799	62252	28.9 (27.6-30.3)	24.3 (18.4 to 30.1)	<0.0001	1.84 (1.64-2.07)	<0.00001	1.56 (1.38-1.76)	<0.0001
1-2	5718	215	5265	40.8 (35.7-46.7)	56586	1050	51723	20.3 (19.1-21.6)	20.5 (14.9 to 26.1)	<0.0001	2.01 (1.74-2.33)	<0.00001	1.71 (1.46-1.99)	<0.0001
2-3	4838	143	4472	32.0 (27.1-37.7)	47208	866	43232	20.0 (18.7-21.4)	11.9 (6.5 to 17.4)	<0.0001	1.60 (1.34-1.91)	<0.00001	1.33 (1.11-1.60)	<0.0001
3-4	4111	133	3815	34.9 (29.4-41.3)	39494	702	36483	19.2 (17.9-20.7)	15.6 (9.5 to 21.7)	<0.0001	1.81 (1.51-2.18)	<0.00001	1.66 (1.37-2.01)	<0.0001
4-5	3566	97	3308	29.3 (24.0-35.8)	33691	572	31384	18.2 (16.8-19.8)	11.1 (5.1 to 17.1)	<0.0001	1.61 (1.30-2.00)	<0.00001	1.46 (1.17-1.82)	<0.0001
5-10	3083	309	10871	28.4 (25.4-31.8)	29226	1936	106243	18.2 (17.4-19.1)	10.2 (6.9 to 13.5)	<0.0001	1.56 (1.38-1.76)	<0.00001	1.41 (1.25-1.59)	<0.0001
10-15	1460	156	4852	32.1 (27.5-37.6)	14820	1089	51946	21.0 (19.8-22.3)	11.2 (6.0 to 16.4)	<0.0001	1.54 (1.30-1.82)	<0.00001	1.49 (1.26-1.76)	<0.0001
15-20	560	40	1515	26.4 (19.4-36.0)	6471	400	18118	22.1 (20.0-24.3)	4.3 (-4.1 to 12.8)	0.14	1.20 (0.87-1.66)	0.275	1.19 (0.86-1.65)	0.30
>20	131	8	418	19.1 (9.6-38.2)	1660	148	5518	26.8 (22.8-31.5)	-7.7 (-21.6 to 6.2)	0.17	0.71 (0.35-1.45)	0.349	0.72 (0.35-1.46)	0.36
All	6821	1435	40800	35.2 (33.4-37.0)	67564	8562	406899	21.0 (20.6-21.5)	14.1 (12.3 to 16.0)	<0.0001	1.67 (1.58-1.77)	<0.00001	1.48 (1.40-1.57)	<0.0001

Table 3.16: Mortality rates of patients with adrenal insufficiency of any type and controls, and hazard ratios for all-cause mortality according to the year of study entry

Note: † adjustment for baseline cardiovascular disease, diabetes mellitus, hypertension and dyslipidaemia at the start of follow-up, and ever smoking at any time

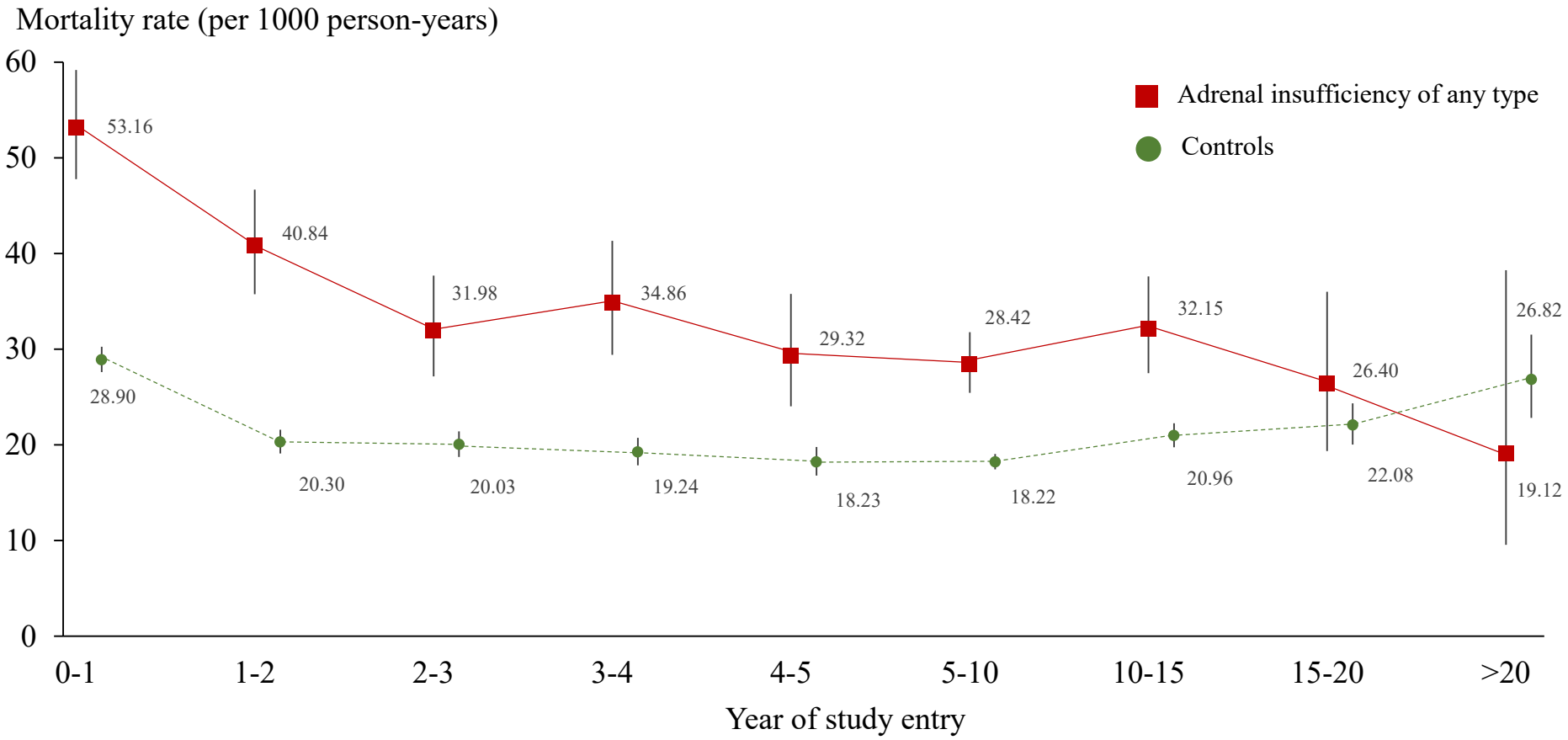


Figure 3.13: Mortality rates of patients with adrenal insufficiency of any type and controls by the year of study entry

❖ Primary adrenal insufficiency and matched controls

A total of 2052 study patients and 20366 controls was included in the analysis. In the first year after study entry, the mortality rates of the study patients and controls were highest compared with the following years (58.3 [95% CI, 48.4-70.3] vs 26.5 [95% CI, 24.3-29.0] per 1000 person-years; Figure 3.14; Table 3.17). Similar to the whole cohort of adrenal insufficiency, in the first year, the mortality rate difference between the study patients and controls was also greatest (+31.8 [95% CI, 20.6-42.9] per 1000 person-years; p<0.0001). In the following years, the mortality rate of the study patients declined whereas in controls it remained stable; consequently, the mortality rate difference also declined after the first two years (Figure 3.13). From the year of study of 15-20 onwards, the mortality rate of the patients was not different from that of controls (Figure 3.14; Table 3.17). Similar to the mortality rate difference, in the first two years, the unadjusted and adjusted hazard ratios were higher than those in the later years. During the second year, the greatest hazard ratio was observed (unadjusted HR, 2.50 [95% CI, 1.93-3.23]; p<0.00001; adjusted HR, 2.15 [95% CI, 1.65-2.81]; p<0.0001). From the year of 15-20 onwards, the hazard ratios were no longer significantly increased (Table 3.17).

❖ Secondary adrenal insufficiency and matched controls

A total of 3948 study patients and 39134 controls was included in the analysis. Similar to the whole cohort of adrenal insufficiency, in the first year, the mortality rates of the study patients and controls were highest compared with the following years (44.0 [95% CI, 37.7-51.3] vs 28.6 [95% CI, 26.9 -30.4] per 1000 person-years; Figure 3.15; Table 3.18). In the first year, the mortality rate difference between the study patients and controls was greatest (+15.4 [95% CI, 8.4-22.5] per 1000 person-years; p<0.0001), although to a lesser degree than the mortality rate difference observed in primary adrenal insufficiency. In the following years, the mortality rate in the study patients declined whereas in controls it remained stable. Consequently, the mortality rate difference also declined and from the year of study of 15-20 onwards, the

mortality rate of the patients was no longer different from that of controls (Figure 3.15; Table 3.18). However, since the mortality rates in patients with secondary adrenal insufficiency were not as high as those with primary adrenal insufficiency, in the first year the unadjusted and adjusted hazard ratios were not different from those in the later years (Table 3.18).

- ❖ All-cause mortality risks changed over time

For Cox models of all-cause mortality in patients with adrenal insufficiency of any type, primary and secondary adrenal insufficiency, relative to controls, there were significant departures from the proportional hazards assumption (PH test; p=0.0001, 0.009 and 0.044, respectively). This was consistent with the mortality risk associated with adrenal insufficiency changing during the follow-up periods in all types of adrenal insufficiency. As shown in Figure 3.13-3.15 and Table 3.16-3.18, beyond 20 years of follow-up, the mortality rates of adrenal insufficiency patients were lower than those of controls and the hazard ratio changed from greater than 1.00 to less than 1.00, confirming the risk did, indeed, change over time in all types of adrenal insufficiency. However, when the follow-up period was censored at 20 years, departures from the proportionality assumption remained significant in adrenal insufficiency of any type and in primary adrenal insufficiency (p=0.0008 and p=0.0017, respectively). This suggested that although the mortality rates of the study patients remained higher than those of controls during the follow-up period of 0-20 years, the magnitude of the increased mortality risk varied with time, as was apparent in the early, relatively high mortality risks in adrenal insufficiency of any type and in primary adrenal insufficiency. However, in secondary disease, there was no significant departure from the proportionality assumption after censoring at 20 years of follow-up (p=0.28).

Years of study	Primary adrenal insufficiency				Controls				Mortality rate difference per 1000 person-years (95% CI)	P for mortality rate difference	Unadjusted HR (95%CI)	P	Adjusted HR (95%CI) †	P
	No. at risk	No. death	Person-years	Mortality per 1000 person-years (95% CI)	No. at risk	No. death	Person-years	Mortality per 1000 person-years (95% CI)						
0-1	2052	110	1886	58.3 (48.4-70.3)	20366	500	18835	26.5 (24.3-29.0)	31.8 (20.6 to 42.9)	<0.0001	2.20 (1.79-2.70)	<0.0001	1.83 (1.48-2.27)	<0.0001
1-2	1718	72	1579	45.6 (36.2-57.5)	17141	287	15719	18.3 (16.3-20.5)	27.3 (16.6 to 38.1)	<0.0001	2.50 (1.93-3.23)	<0.0001	2.15 (1.65-2.81)	<0.0001
2-3	1446	40	1346	29.7 (21.8-40.5)	14422	251	13282	18.9 (16.7-21.4)	10.8 (1.3 to 20.3)	0.0057	1.57 (1.13-2.20)	0.008	1.29 (0.91-1.82)	0.14
3-4	1240	41	1162	35.3 (26.0-47.9)	12224	210	11384	18.4 (16.1-21.1)	16.8 (5.8 to 27.9)	0.0002	1.91 (1.37-2.67)	<0.0001	1.87 (1.33-2.63)	<0.0001
4-5	1099	34	1028	33.1 (23.6-46.3)	10580	177	9944	17.8 (15.4-20.6)	15.3 (3.8 to 26.7)	0.0010	1.86 (1.29-2.68)	0.0010	1.81 (1.24-2.63)	0.0020
5-10	962	100	3481	28.7 (23.6-34.9)	9346	607	34756	17.5 (16.1-18.9)	11.3 (5.5 to 17.1)	<0.0001	1.65 (1.33-2.03)	<0.0001	1.52 (1.22-1.88)	<0.0001
10-15	487	50	1707	29.3 (22.2-38.7)	5077	357	18369	19.4 (17.5-21.6)	9.9 (1.5 to 18.2)	0.0047	1.51 (1.12-2.03)	0.0060	1.54 (1.14-2.09)	0.0050
15-20	212	14	583	24.0 (14.2-40.6)	2361	136	6688	20.3 (17.2-24.1)	3.7 (-9.3 to 16.7)	0.26	1.19 (0.68-2.06)	0.54	1.35 (0.76-2.37)	0.30
>20	52	3	190	15.8 (5.1-49.0)	638	42	2263	18.6 (13.7-25.1)	-2.7 (-21.5 to 16.0)	0.42	0.85 (0.26-2.75)	0.78	0.77 (0.23-2.55)	0.66
All	2052	464	12961	35.8 (32.7-39.2)	20366	2567	131241	19.6 (18.8-20.3)	16.2 (12.9 to 19.6)	<0.0001	1.83 (1.66-2.02)	<0.0001	1.67 (1.51-1.84)	<0.0001

Table 3.17: Mortality rates of patients with primary adrenal insufficiency and controls, and hazard ratios for all-cause mortality according to the year of study entry

Note: † adjustment for baseline cardiovascular disease, diabetes mellitus, hypertension and dyslipidaemia at the start of follow-up, and ever smoking at any time

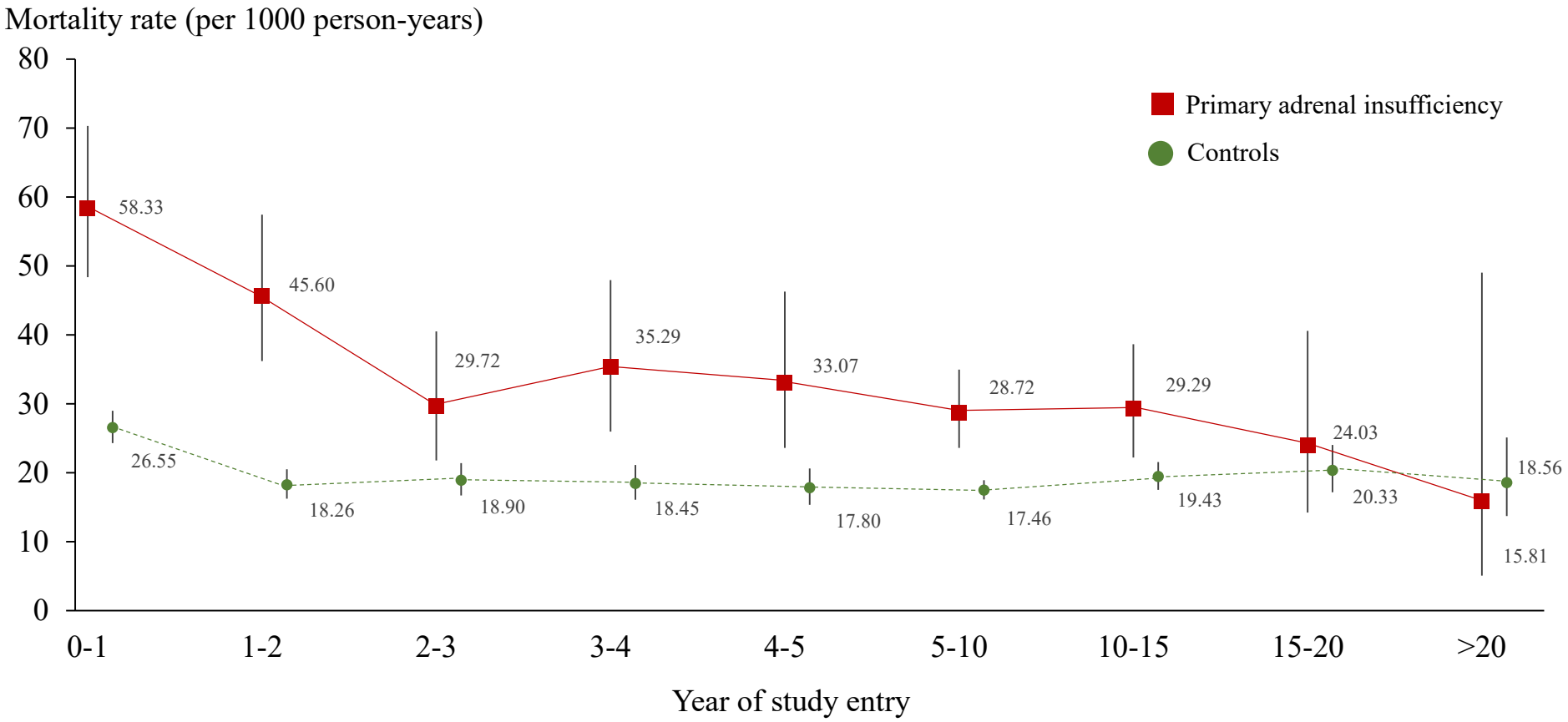


Figure 3.14: Mortality rates of patients with primary adrenal insufficiency and controls by the year of study entry

Years of study	Secondary adrenal insufficiency				Controls				Mortality rate difference per 1000 person-years (95% CI)	P for mortality rate difference	Unadjusted HR (95%CI)	P	Adjusted HR (95%CI) †	**P**
	No. at risk	No. death	Person-years	Mortality per 1000 person-years (95% CI)	No. at risk	No. death	Person-years	Mortality per 1000 person-years (95% CI)						
0-1	3948	161	3660	44.0 (37.7-51.3)	39134	1030	36068	28.6 (26.9-30.4)	15.4 (8.4 to 22.5)	<0.0001	1.54 (1.31-1.82)	<0.0001	1.31 (1.11-1.56)	0.0020
1-2	3351	107	3105	34.5 (28.5-41.6)	32836	617	30064	20.5 (19.0-22.2)	13.9 (7.2 to 20.7)	<0.0001	1.68 (1.37-2.06)	<0.0001	1.43 (1.16-1.77)	0.0010
2-3	2877	81	2653	30.5 (24.6-38.0)	27477	492	25143	19.6 (17.9-21.4)	11.0 (4.1 to 17.8)	0.0002	1.56 (1.23-1.97)	<0.0001	1.35 (1.06-1.73)	0.014
3-4	2445	68	2269	30.0 (23.6-38.0)	22933	413	21153	19.5 (17.7-21.5)	10.4 (3.1 to 17.8)	0.0009	1.54 (1.19-1.98)	0.001	1.37 (1.05-1.79)	0.019
4-5	2117	52	1959	26.5 (20.2-34.8)	19541	311	18173	17.1 (15.3-19.1)	9.4 (2.0 to 16.9)	0.0026	1.55 (1.16-2.08)	0.003	1.35 (1.00-1.84)	0.050
5-10	1835	166	6426	25.8 (22.2-30.1)	16900	1066	61058	17.5 (16.4-18.5)	8.4 (4.3 to 12.4)	<0.0001	1.48 (1.26-1.74)	<0.0001	1.32 (1.11-1.56)	0.0010
10-15	848	85	2733	31.1 (25.1-38.5)	8330	591	28732	20.6 (19.0-22.3)	10.5 (3.7 to 17.4)	0.0003	1.52 (1.21-1.90)	<0.0001	1.43 (1.14-1.80)	0.0020
15-20	307	23	809	28.4 (18.9-42.8)	3522	220	9697	22.7 (19.9-25.9)	5.8 (-6.2 to 17.8)	0.15	1.26 (0.82-1.94)	0.29	1.19 (0.77-1.84)	0.42
>20	68	2	201	10.0 (2.5-39.8)	870	92	2754	33.4 (27.2-41.0)	-23.4 (-38.8 to -8.0)	0.026	0.30 (0.07-1.20)	0.089	0.28 (0.07-1.13)	0.074
All	3948	745	23814	31.3 (29.1-33.6)	39134	4832	232842	20.8 (20.2-21.3)	10.5 (8.2 to 12.9)	<0.0001	1.52 (1.40-1.64)	<0.0001	1.34 (1.23-1.45)	<0.0001

Table 3.18: Mortality rates of patients with secondary adrenal insufficiency and controls, and hazard ratios for all-cause mortality according to the year of study entry

Note: † adjustment for baseline cardiovascular disease, diabetes mellitus, hypertension and dyslipidaemia at the start of follow-up, and ever smoking at any time

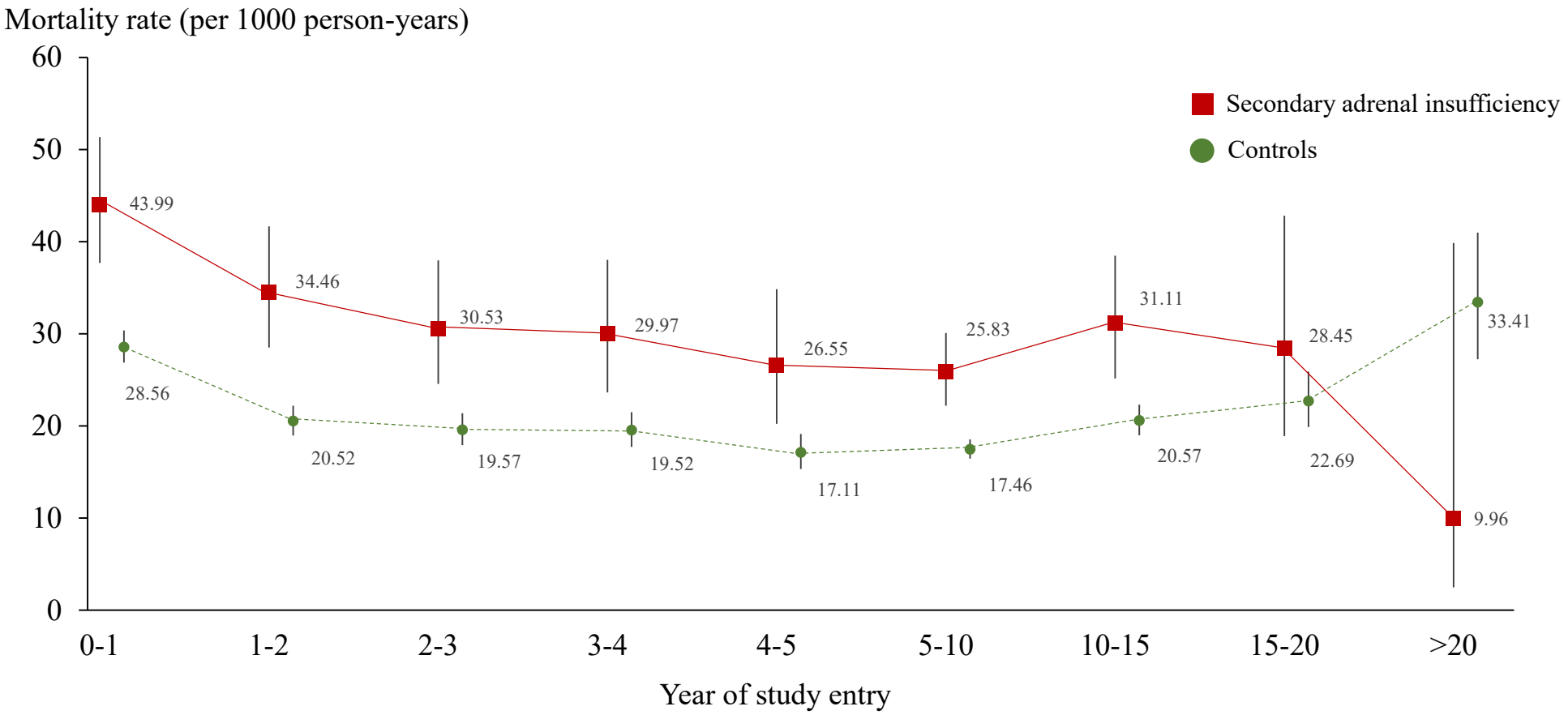


Figure 3.15: Mortality rates of patients with secondary adrenal insufficiency and controls by the year of study entry

All-cause mortality rates according to the year of diagnosis of adrenal insufficiency

A total of 6821 patients with adrenal insufficiency of any type, of whom 2052 and 3948 had primary and secondary adrenal insufficiency, was included in the analysis. In the first year after diagnosis, the mortality rate of patients with adrenal insufficiency of any type was highest (44.6 [95% CI, 39.7-50.1]; p<0.0001). Also, in the first year after the diagnosis, the mortality rates of patients with primary and secondary adrenal insufficiency were highest (for primary adrenal insufficiency, 48.5 [95% CI, 39.6-59.4]; p<0.0001; for secondary, 35.9 [95% CI, 30.3-42.5]; p<0.0001; Table 3.19). The peak mortality rates observed in the first year after the diagnosis in patients with adrenal insufficiency were consistent with the peak mortality rates observed in the first year after the start of follow-up as the median year at the diagnosis was approximately only one year before the median year at the start of follow-up (Table 3.3).

In summary, the mortality rate of patients with adrenal insufficiency of any type was greatest in the first year after diagnosis and in the first year of follow-up. In later years, the mortality rate decreased and was no longer higher than the mortality rate in controls after 15 years of follow-up. A similar trend of mortality rates was observed in patients with primary and secondary adrenal insufficiency. It is noted that in the first year the mortality rate of controls was also higher than the mortality rates in the following years. This might reflect a systematic bias where some participants (both patients and controls) in CPRD were registered to the GP practice after they had developed a serious illness from which they subsequently died. Also, among those having died in the first year, the calendar start year was later than for those having died after the first year of follow-up (data not shown), and in more recent calendar years CPRD has expanded its coverage to people living in more deprived areas in which mortality would be expected to be higher. However, in the first few years, the significantly increased mortality rate differences and mortality risks of adrenal insufficiency relative to controls appeared to be higher than later years, especially in primary disease (which accords with the significant departures from the proportional hazard assumption detected). In secondary adrenal insufficiency, the mortality rate differences and mortality risks remained similarly increased across the whole follow-up period.

Years after diagnosis	Adrenal insufficiency of any type				Primary adrenal insufficiency				Secondary adrenal insufficiency			
	No. at risk	No. death	Person-years	Mortality per 1000 person-years (95% CI)	No. at risk	No. death	Person-years	Mortality per 1000 person-years (95% CI)	No. at risk	No. death	Person-years	Mortality per 1000 person-years (95% CI)
0-1	6821	284	6372	44.6 (39.7-50.1)	2052	93	1918	48.5 (39.6-59.4)	3948	133	3707	35.9 (30.3-42.5)
1-2	5896	183	5503	33.3 (28.8-38.4)	1781	63	1661	37.9 (29.6-48.6)	3448	88	3235	27.2 (22.1-33.5)
2-3	5125	130	4785	27.2 (22.9-32.3)	1543	37	1448	25.5 (18.5-35.3)	3039	69	2837	24.3 (19.2-30.8)
3-4	4453	122	4172	29.2 (24.5-34.9)	1356	39	1280	30.5 (22.3-41.7)	2646	58	2481	23.4 (18.1-30.2)
4-5	3935	100	3695	27.1 (22.2-32.9)	1220	33	1154	28.6 (20.3-40.2)	2336	57	2188	26.1 (20.1-33.8)
5-10	3481	326	12853	25.4 (22.8-28.3)	1090	107	4136	25.9 (21.4-31.3)	2068	178	7574	23.5 (20.3-27.2)
10-15	1830	157	6569	23.9 (20.4-27.9)	613	45	2310	19.5 (14.5-26.1)	1059	90	3675	24.5 (19.9-30.1)
15-20	905	98	3103	31.6 (25.9-38.5)	337	37	1192	31.0 (22.5-42.9)	491	52	1642	31.7 (24.1-41.6)
>20	380	35	1454	24.1 (17.3-33.5)	154	10	650	15.4 (8.3-28.6)	191	20	692	28.9 (18.7-44.8)
All	6821	1435	48509	29.6 (28.1-31.2)	2052	464	15749	29.5 (26.9-32.3)	3948	745	28031	26.6 (24.7-28.6)

Table 3.19: Mortality rates of patients with adrenal insufficiency for all-cause mortality according to the year after diagnosis

3.5 Cause-specific mortality

Cause of death was available for the sub-group of patients and controls with ONS-linked information. Causes of death were assigned by ONS as the principal cause and other associated causes. The principal cause of death was examined and stratified according to ICD-10 organ systems and particular diseases. In addition, both principal and associated causes of death were examined if the cause was related to disease of the endocrine system. Participants in this analysis included those who had linked data with ONS and the start of follow-up from 1st January 1997 onwards. More details of death from disease of the circulatory system and cardiovascular disease is shown in Chapter 4 (Section 4.3-4.4).

3.5.1 Principal cause of death according to organ systems

- Adrenal insufficiency of any type and matched controls

Among 3547 patients with adrenal insufficiency of any type and 34944 controls, there were 632 and 3643 deaths during the follow-up period of 18592 and 179833 person-years, respectively (Table 3.20). All-cause mortality rate of the study patients was higher than that of controls (34.0 [95% CI, 31.4-36.7] vs 20.3 [19.6-20.9] per 1000 person-years; p<0.0001), resulting in an unadjusted hazard ratio of 1.68 [95% CI, 1.55-1.83]; p<0.0001).

The three leading causes of death of the study patients and controls were in the following descending order: disease of the circulatory system, neoplasm, and disease of the respiratory system (Table 3.20; Figure 3.16). For disease of the circulatory system, the mortality rate of the study patients was higher than that of controls (9.9 [95% CI, 8.6-11.4] vs 6.4 [6.1-6.8] per 1000 person-years), giving a mortality rate difference of 3.5 (95% CI, 2.0-4.9) per 1000 person-years (p<0.0001). For neoplasms including benign and malignant tumours, the mortality rate of the study patients was also higher than that of controls (8.1 [95% CI, 6.9-9.5] vs 5.6 [5.3-

6.0] per 1000 person-years), giving a mortality rate difference of 2.5 (95% CI, 1.1-3.8) per 1000 person-years ($p<0.0001$). For disease of the respiratory system, the mortality rate of the study patients was considerably higher than that of controls (6.6 [95% CI, 5.5-7.8] vs 2.8 [2.5-3.0] per 1000 person-years) and the mortality rate difference was 3.8 (95% CI, 2.6-5.0) per 1000 person-years ($p<0.0001$), which was the greatest among other causes. Mortality rates of the study patients were also significantly higher than those of controls in deaths from diseases of the digestive system, endocrine system, genitourinary system, infectious disease, and the musculoskeletal system. However, for mental and behavioural disorders, and the nervous system, the mortality rates of the study patients were not different from those of controls (Table 3.20; Figure 3.16).

Rather than absolute mortality rates, the mortality rate for adrenal insufficiency relative to controls was also explored. Accordingly, unadjusted hazard ratios for principal causes of death according to organ system were derived. Causes of death according to organ systems are considered here in three groups depending on the degree of increment in the hazard ratios. The first group comprised causes with the greatest hazard ratios, including disease of the endocrine system (HR, 4.85 [95% CI, 3.08-7.64]; $p<0.0001$), infectious disease (HR, 4.00 [95% CI, 2.15-7.46]; $p<0.0001$) and disease of the musculoskeletal system (HR, 3.46 [95% CI, 1.68-7.12]; $p=0.001$). The second group comprised causes for which the hazard ratio was approximately doubled, and these included diseases of the respiratory, digestive, and musculoskeletal systems. The third group comprised causes for which the hazard ratio was increased 1.5-fold and included diseases of the circulatory system and neoplasms (Table 3.20). In accord with the mortality rate difference, the hazard ratios for death from mental and behavioural disorders and disease of the nervous system were not increased.

Principal cause of death	**Adrenal insufficiency of any type**		**Controls**		Mortality rate difference per 1000 person-years (95% CI)	P for mortality rate difference	Unadjusted HR (95%CI)	P
	No. death	Mortality per 1000 person-years (95% CI)	No. death	Mortality per 1000 person-years (95% CI)				
Circulatory	184	9.9 (8.6-11.4)	1157	6.4 (6.1-6.8)	3.5 (2.0-4.9)	<0.0001	1.54 (1.32-1.80)	<0.0001
Neoplasm	151	8.1 (6.9-9.5)	1014	5.6 (5.3-6.0)	2.5 (1.1-3.8)	<0.0001	1.44 (1.22-1.71)	<0.0001
Respiratory	122	6.6 (5.5-7.8)	499	2.8 (2.5-3.0)	3.8 (2.6-5.0)	<0.0001	2.38 (1.95-2.90)	<0.0001
Digestive	43	2.3 (1.7-3.1)	174	1.0 (0.8-1.1)	1.3 (0.6 to 2.1)	<0.0001	2.39 (1.71-3.34)	<0.0001
Endocrine	28	1.5 (1.0-2.2)	56	0.3 (0.2-0.4)	1.1 (0.6 to 1.8)	<0.0001	4.85 (3.08-7.64)	<0.0001
Mental & Behavioural disorders	21	1.1 (0.7-1.7)	236	1.3 (1.2-1.5)	-0.2 (-0.7 to 0.3)	0.26	0.87 (0.55-1.35)	0.52
Nervous	15	0.8 (0.5-1.3)	203	1.1 (1.0-1.3)	-0.3 (-0.8 to 0.1)	0.10	0.72 (0.43-1.21)	0.21
Genitourinary	17	0.9 (0.6-1.5)	78	0.4 (0.3-0.5)	0.5 (0.0 to 0.9)	0.0049	2.11 (1.25-3.57)	0.0050
Infectious diseases	14	0.8 (0.5-1.3)	34	0.2 (0.1-0.3)	0.6 (0.2 to 1.0)	0.0001	4.00 (2.15-7.46)	<0.0001
Musculoskeletal	10	0.5 (0.3-1.0)	28	0.2 (0.1-0.2)	0.4 (0.0 to 0.7)	0.0013	3.46 (1.68-7.12)	0.001
Other systems	27	1.5 (1.0-2.1)	164	0.9 (0.8-1.1)	0.5 (-0.0 to 1.1)	0.016	1.60 (1.06-2.40)	0.024
All-cause	632	34.0 (31.4-36.7)	3643	20.3 (19.6-20.9)	13.7 (11.0 to 16.5)	<0.0001	1.68 (1.55-1.83)	<0.0001

Table 3.20: Mortality rates of patients with adrenal insufficiency of any type and controls, and hazard ratios for mortality according to the cause of death by organ systems

Note: N, study patients vs controls = 3547 vs 34944; period of follow-up, study patients vs controls = 18592 vs 179833 person-years

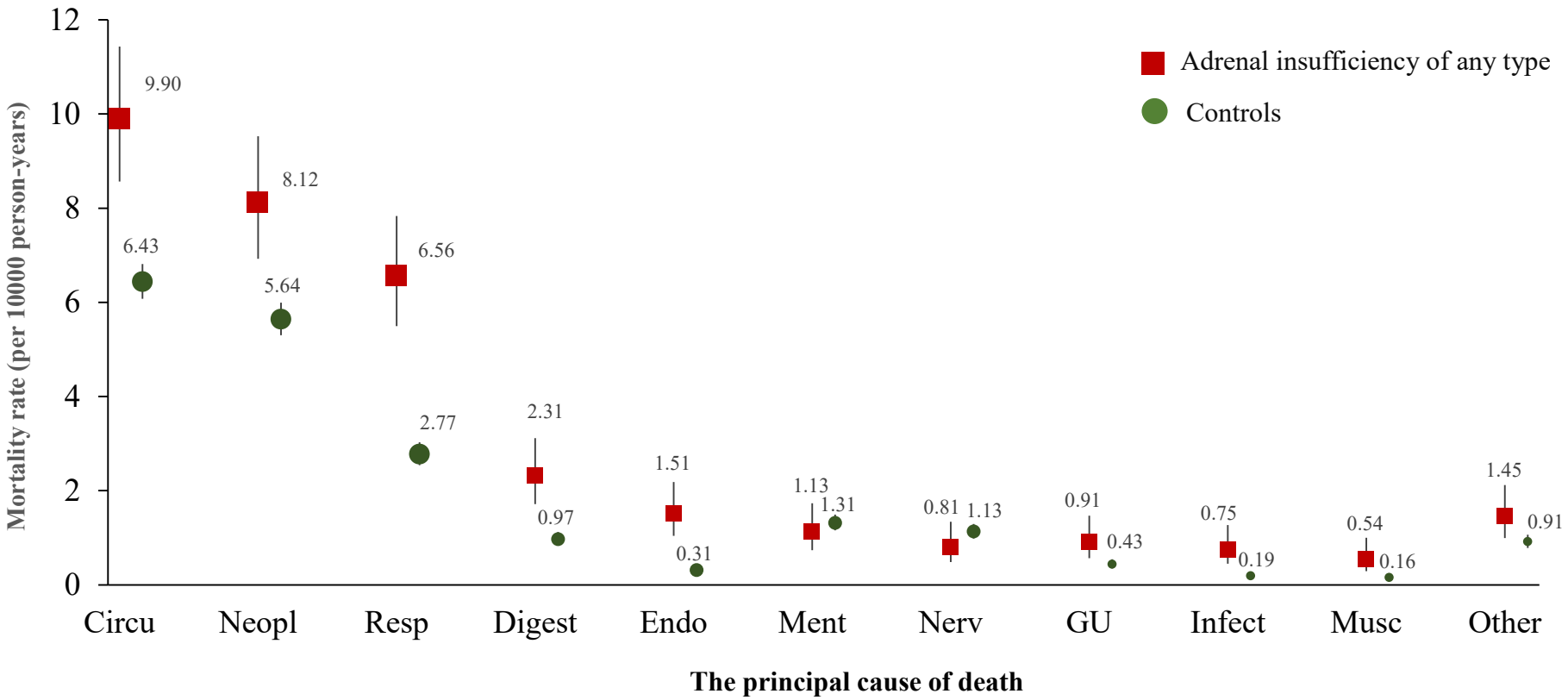


Figure 3.16: Mortality rates of patients with adrenal insufficiency of any type and controls according to the principal cause of death by organ systems

Note: Circu: Circulatory system, Neopl: Neoplasm; Resp: Respiratory system; Digest: Digestive system; Endo: Endocrine system; Ment: Mental & behavioural disorders; Nerv: Nervous system, GU: Genitourinary system, Infect: Infectious disease, Musc: Musculoskeletal; Other: Other systems

❖ Primary adrenal insufficiency and matched controls

Among 1015 patients with primary adrenal insufficiency and 10025 controls, there were 207 and 1001 deaths during the follow-up period of 5474 and 54933 person-years, respectively (Table 3.21). All-cause mortality rate of the study patients was markedly higher than that of controls (37.8 [95% CI, 33.0-43.3] vs 18.2 [17.1-19.4] per 1000 person-years; p<0.0001), resulting in an unadjusted hazard ratio of 2.07 [95% CI, 1.78-2.41]; p<0.0001).

The three leading causes of death in patients with primary adrenal insufficiency were in the following descending order: disease of the circulatory system, respiratory system, and neoplasms (Table 3.21; Figure 3.17). The order was slightly different from the leading causes of death observed in controls, which was: disease of the circulatory system, neoplasm, and disease of the respiratory system, respectively. For disease of the circulatory system, the mortality rate of the study patients was higher than that of controls (10.6 [95% CI, 8.2-13.7] vs 6.0 [5.4-6.7] per 1000 person-years), giving a mortality rate difference of 4.6 (95% CI, 1.8-7.4) per 1000 person-years (p<0.0001). For neoplasms, the mortality rate of the study patients was not different from that of controls (6.8 [95% CI, 4.9-9.3] vs 4.9 [4.3-5.5] per 1000 person-years), as shown by the borderline significant difference in the mortality rates (1.9 [95% CI, -0.4 to 4.1] per 1000 person-years; p=0.037). For disease of the respiratory system, the mortality rate of the study patients was considerably higher than that of controls (9.7 [95% CI, 7.4-12.7] vs 2.6 [2.2-3.0] per 1000 person-years) and the mortality rate difference was greatest (7.1 [95% CI, 4.5-9.8] per 1000 person-years; p<0.0001), as also observed in the whole cohort of adrenal insufficiency of any type. In causes of death involving other organ systems, the mortality rate of the study patients was higher than that of controls in disease of the digestive and endocrine system but was not significantly increased in disease of the musculoskeletal system and infectious disease (Table 3.21; Figure 3.17). Similar to the whole cohort of adrenal

insufficiency of any type, the mortality rate was not different between the study patients and controls in disease of mental and behavioural disorders, the nervous, and genitourinary system (Table 3.21; Figure 3.17).

The mortality of primary adrenal insufficiency relative to controls, specific for the principal cause of death in organ systems, was investigated using the unadjusted hazard ratios. Causes of death are considered here in three groups according to the degree of the increment in hazard ratios. First, the greatest hazard ratios – those with more than a four-fold increase - were observed in death from disease of the endocrine system (HR, 9.93 [95% CI, 4.85-20.30]; p<0.0001), disease of the musculoskeletal system (HR, 5.93 [95% CI, 2.15-16.31]; p=0.001), and infectious diseases (HR, 4.06 [95% CI, 1.27-12.95]; p=0.018). Second, hazard ratios of between a three- and four-fold increase were observed in disease of the respiratory system (HR, 3.77 [95% CI, 2.75-5.17]; p<0.0001) and digestive system (HR, 3.59 [95% CI, 1.99-6.48]; p<0.0001). Third, a hazard ratio of close to a two-fold increase was observed for disease of the circulatory system (HR, 1.76 [95% CI, 1.33-2.33]; p<0.0001; Table 3.21). In accord with the mortality rate difference, the hazard ratios for death from neoplasms and disease of the genitourinary system were not significantly increased. Also, in deaths from mental and behavioural disorders, and disease of the nervous system the hazard ratios were less than one but non-significant (Table 3.21).

Principal cause of death	Primary adrenal insufficiency		Controls		Mortality rate difference per 1000 person-years (95% CI)	P for mortality rate difference	Unadjusted HR (95%CI)	P
	No. death	Mortality per 1000 person-years (95% CI)	No. death	Mortality per 1000 person-years (95% CI)				
Circulatory	58	10.6 (8.2-13.7)	331	6.0 (5.4-6.7)	4.6 (1.8-7.4)	0.0001	1.76 (1.33-2.33)	<0.0001
Neoplasm	37	6.8 (4.9-9.3)	269	4.9 (4.3-5.5)	1.9 (-0.4 to 4.1)	0.037	1.38 (0.98-1.95)	0.065
Respiratory	53	9.7 (7.4-12.7)	141	2.6 (2.2-3.0)	7.1 (4.5 to 9.8)	<0.0001	3.77 (2.75-5.17)	<0.0001
Digestive	15	2.7 (1.7-4.5)	42	0.8 (0.6-1.0)	2.0 (0.6 to 3.4)	0.0001	3.59 (1.99-6.48)	<0.0001
Endocrine	15	2.7 (1.7-4.5)	15	0.3 (0.2-0.5)	2.5 (1.1 to 3.9)	<0.0001	9.93 (4.85-20.30)	<0.0001
Mental & Behavioural disorders	5	0.9 (0.4-2.2)	63	1.1 (0.9-1.5)	-0.2 (-1.1 to 0.6)	0.33	0.80 (0.32-1.99)	0.62
Nervous	4	0.7 (0.3-1.9)	57	1.0 (0.8-1.3)	-0.3 (-1.1 to 0.5)	0.26	0.70 (0.25-1.92)	0.48
Genitourinary	3	0.5 (0.2-1.7)	22	0.4 (0.3-0.6)	0.1 (-0.5 to 0.8)	0.29	1.35 (0.41-4.53)	0.62
Infectious diseases	4	0.7 (0.3-1.9)	10	0.2 (0.1-0.3)	0.5 (-0.2 to 1.3)	0.019	4.06 (1.27-12.95)	0.018
Musculoskeletal	6	1.1 (0.5-2.4)	10	0.2 (0.1-0.3)	0.9 (0.0 to 1.8)	0.0011	5.93 (2.15-16.31)	0.0010
Other systems	7	1.3 (0.6-2.7)	41	0.7 (0.5-1.0)	0.5 (-0.0 to 1.5)	0.10	1.69 (0.76-3.78)	0.19
All-cause	207	37.8 (33.0-43.3)	1001	18.2 (17.1-19.4)	19.6 (14.3 to 24.9)	<0.0001	2.07 (1.78-2.41)	<0.0001

Table 3.21: Mortality rates of patients with primary adrenal insufficiency and controls, and hazard ratios for mortality according to the cause of death by organ systems

Note: N, study patients vs controls = 1015 vs 10025; period of follow-up, study patients vs controls = 5474 vs 54933 person-years

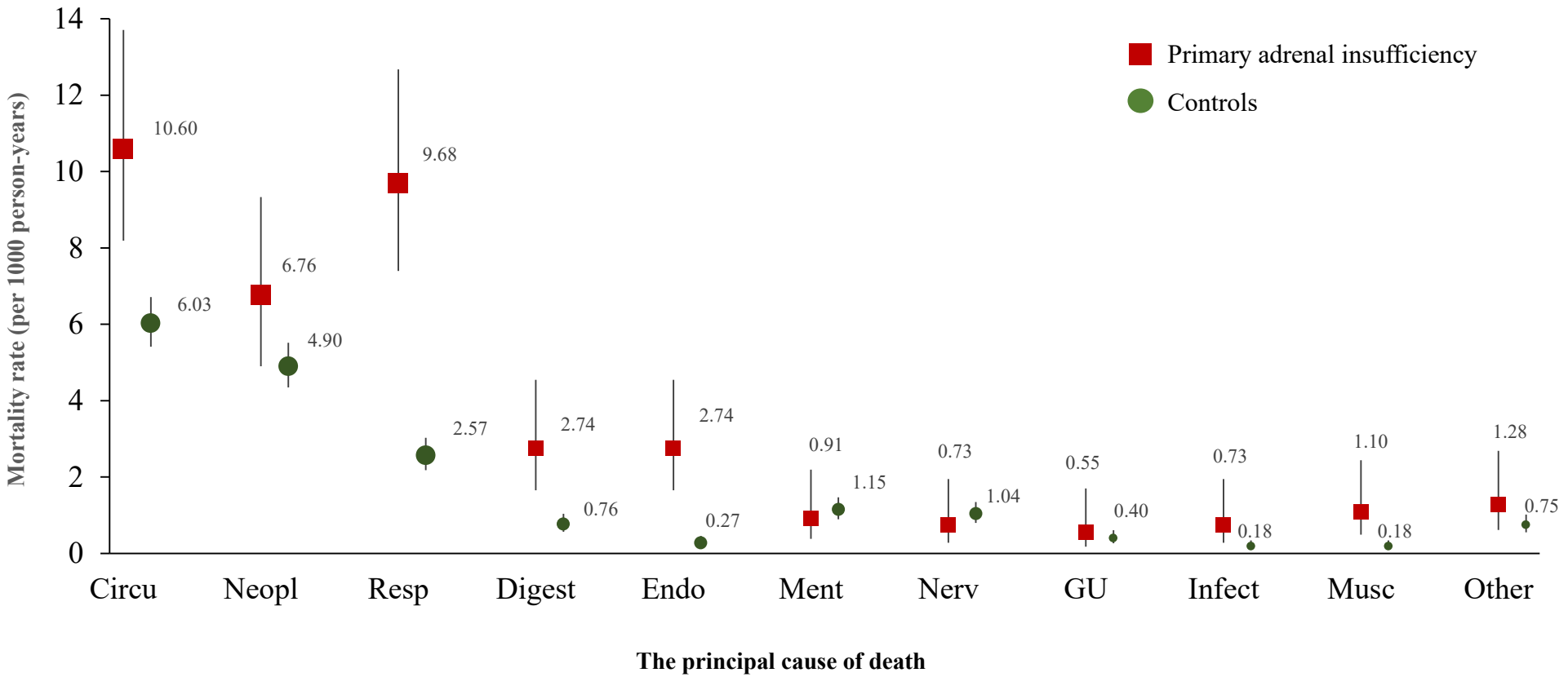


Figure 3.17: Mortality rates of patients with primary adrenal insufficiency and controls according to the principal cause of death by organ systems

Note: Circu: Circulatory system, Neopl: Neoplasm; Resp: Respiratory system; Digest: Digestive system; Endo: Endocrine system; Ment: Mental & behavioural disorders; Nerv: Nervous system, GU: Genitourinary system, Infect: Infectious disease, Musc: Musculoskeletal; Other: Other systems

❖ Secondary adrenal insufficiency and matched controls

Among 2136 patients with secondary adrenal insufficiency and 20991 controls, there were 340 and 2186 deaths during the follow-up period of 11377 and 106850 person-years, respectively (Table 3.22). All-cause mortality rate of the study patients was higher than that of controls (29.9 [95% CI, 26.9-33.2] vs 20.5 [19.6-21.3] per 1000 person-years; p<0.0001), resulting in an unadjusted hazard ratio of 1.47 [95% CI, 1.31-1.65]; p<0.0001).

Similar to controls and patients with adrenal insufficiency of any type, three leading causes of death of patients with secondary adrenal insufficiency were disease of the circulatory system, neoplasm, and disease of the respiratory system, respectively (Table 3.22; Figure 3.18). For disease of the circulatory system, the mortality rate of the study patients was higher than that of controls (9.7 [95% CI, 8.0-11.7] vs 6.4 [6.0-6.9] per 1000 person-years), giving a mortality rate difference of 3.2 (95% CI, 1.4-5.1) per 1000 person-years (p=0.0001). For neoplasms, the mortality rate of the study patients was also higher than that of controls (8.8 [95% CI, 7.2-10.7] vs 5.9 [5.5-6.4] per 1000 person-years), giving a mortality rate difference of 2.9 (95% CI, 1.1-4.7) per 1000 person-years; p=0.0002). For disease of the respiratory system, the mortality rate of the study patients was slightly higher than that of controls (4.0 [95% CI, 3.0-5.4] vs 2.8 [2.5-3.1] per 1000 person-years), resulting in a small mortality rate difference (1.3 [95% CI, 0.1-2.5] per 1000 person-years; p<0.0001). In causes of death involving other organ systems, the mortality rate was not different between the study patients and controls in the nervous, genitourinary, and musculoskeletal systems, as expected. Interestingly, for disease of the endocrine system and infectious disease, the mortality rates were also not different and this might have resulted from a lower mortality rate in both the study patients and controls (Table 3.22; Figure 3.18). In causes associated with mental and behavioural disorders, the mortality

rate of patients with secondary adrenal insufficiency was lower than that of controls (Table 3.22; Figure 3.18).

The mortality of secondary adrenal insufficiency relative to controls, specific for the principal cause of death in organ systems, was investigated using the unadjusted hazard ratios. Causes of death are considered here in three groups according to the degree of the increment in hazard ratios. First, the greatest hazard ratio, with more than a three-fold increase, was observed in death from infectious disease (HR, 3.14 [95% CI, 1.33-7.38]; p=0.009). Second, hazard ratios increased by two- to three-fold were observed for disease of the endocrine system (HR, 2.22 [95% CI, 1.03-4.80]; p=0.042), genitourinary system (HR, 2.21 [95% CI, 1.11-4.39]; p=0.024), and digestive system (HR, 2.13 [95% CI, 1.38-3.29]; p=0.001). Third, a 1.5-fold increase in hazard ratio was observed for disease of the circulatory system (HR, 1.51 [95% CI, 1.23-1.85]; p<0.0001), neoplasms (HR, 1.50 [95% CI, 1.21-1.85]; p<0.0001), and disease of the respiratory system (HR, 1.48 [95% CI, 1.08-2.02]; p=0.014). In accord with the mortality rate difference, the hazard ratios for death from disease of the nervous and musculoskeletal system were not significantly increased. Also, in deaths from mental and behavioural disorders, the hazard ratio of secondary adrenal insufficiency was decreased (Table 3.22).

Principal cause of death	**Secondary adrenal insufficiency**		**Controls**		Mortality rate difference per 1000 person-years (95% CI)	P for mortality rate difference	Unadjusted HR (95%CI)	P
	No. death	Mortality per 1000 person-years (95% CI)	No. death	Mortality per 1000 person-years (95% CI)				
Circulatory	110	9.7 (8.0-11.7)	686	6.4 (6.0-6.9)	3.2 (1.4 to 5.1)	0.0001	1.51 (1.23-1.85)	<0.0001
Neoplasm	100	8.8 (7.2-10.7)	630	5.9 (5.5-6.4)	2.9 (1.1 to 4.7)	0.0002	1.50 (1.21-1.85)	<0.0001
Respiratory	46	4.0 (3.0-5.4)	294	2.8 (2.5-3.1)	1.3 (0.1 to 2.5)	0.0099	1.48 (1.08-2.02)	0.014
Digestive	25	2.2 (1.5-3.3)	110	1.0 (0.9-1.2)	1.2 (0.3 to 2.1)	0.0008	2.13 (1.38-3.29)	0.0010
Endocrine	8	0.7 (0.4-1.4)	34	0.3 (0.2-0.4)	0.4 (-0.1 to 0.9)	0.030	2.22 (1.03-4.80)	0.042
Mental & Behavioural disorders	6	0.5 (0.2-1.2)	145	1.4 (1.2-1.6)	-0.8 (-1.3 to -0.4)	0.0053	0.39 (0.17-0.89)	0.025
Nervous	10	0.9 (0.5-1.6)	116	1.1 (0.9-1.3)	-0.2 (-0.8 to 0.4)	0.27	0.82 (0.43-1.56)	0.54
Genitourinary	10	0.9 (0.5-1.6)	43	0.4 (0.3-0.5)	0.5 (-0.1 to 1.0)	0.019	2.21 (1.11-4.39)	0.024
Infectious disease	7	0.6 (0.3-1.3)	21	0.2 (0.1-0.3)	0.4 (-0.0 to 0.9)	0.0093	3.14 (1.33-7.38)	0.0090
Musculoskeletal	2	0.2 (0.0-0.7)	13	0.1 (0.1-0.2)	0.1 (-0.1 to 0.3)	0.30	1.46 (0.33-6.46)	0.61
Other systems	16	1.4 (0.9-2.3)	94	0.9 (0.7-1.1)	0.5 (-0.2 to 1.2)	0.048	1.61 (0.95-2.73)	0.079
All-cause	340	29.9 (26.9-33.2)	2186	20.5 (19.6-21.3)	9.4 (6.1 to 12.7)	<0.0001	1.47 (1.31-1.65)	<0.0001

Table 3.22: Mortality rates of patients with secondary adrenal insufficiency and controls, and hazard ratios for mortality according to the cause of death by organ systems

Note: N, study patients vs controls = 2136 vs 20991; period of follow-up, study patients vs controls = 11377 vs 106850 person-years

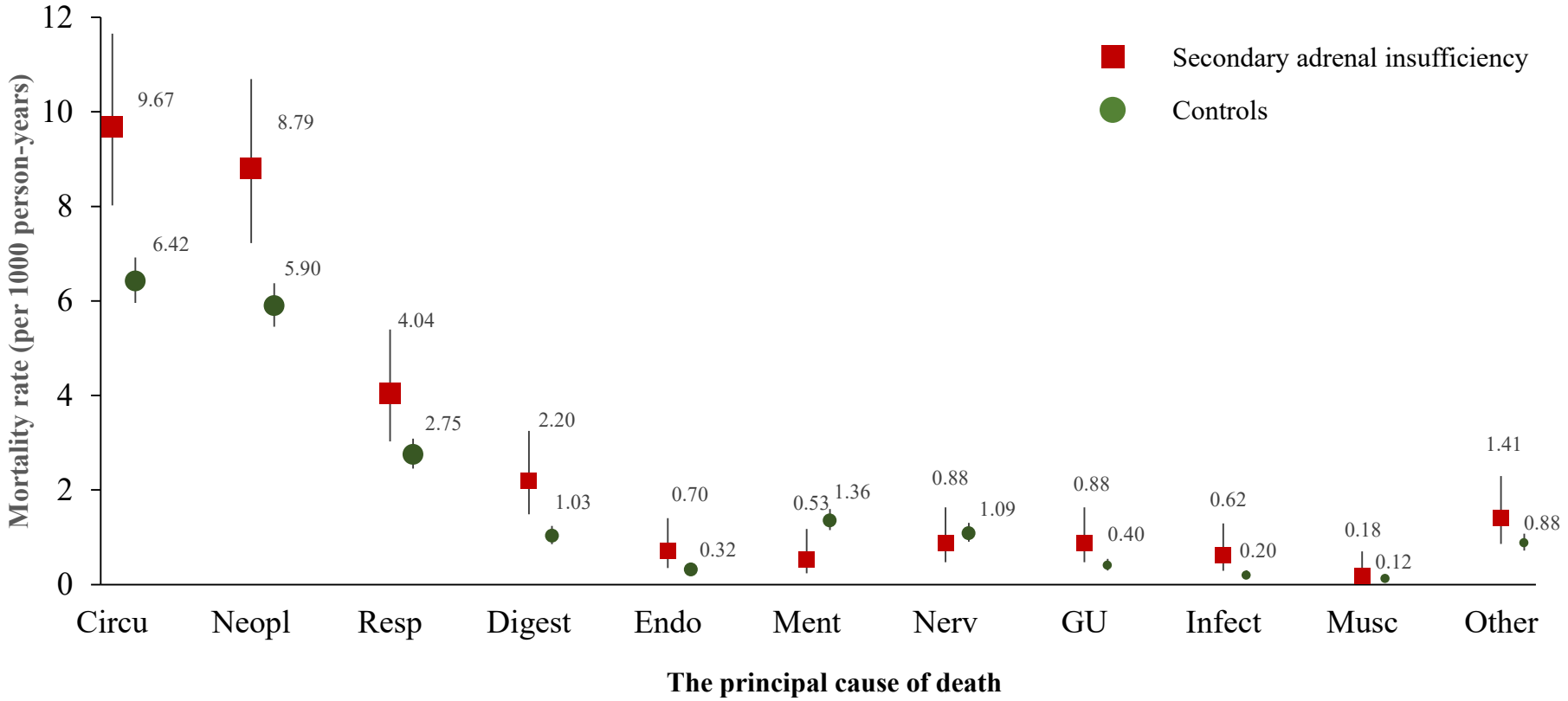


Figure 3.18: Mortality rates of patients with secondary adrenal insufficiency and controls according to the principal cause of death by organ systems

Note: Circu: Circulatory system, Neopl: Neoplasm; Resp: Respiratory system; Digest: Digestive system; Endo: Endocrine system; Ment: Mental & behavioural disorders; Nerv: Nervous system, GU: Genitourinary system, Infect: Infectious disease, Musc: Musculoskeletal; Other: Other systems

3.5.2 Principal cause of death according to particular diseases

The study patients appeared to have increased risk of death from diseases in the circulatory system, neoplasm, respiratory system, digestive system, endocrine system, genitourinary system, infectious diseases, and musculoskeletal system. Specific diseases that were the leading cause of death involving these organ systems in the study patients were, in descending order, malignant neoplasms, ischaemic heart disease, lower respiratory tract infection, disorders of the pituitary or adrenal glands, urinary tract infection, and connective tissue disease and rheumatoid arthritis (Table 3.23). Deaths recorded from infectious diseases were assigned only when an infective organism had been identified whereas the leading causes of death in the respiratory and genitourinary system were recorded as respiratory tract and urinary tract infections, respectively. Deaths from these causes were, therefore, combined with deaths from infectious disease (combined infections) and evaluated as a further specific disease category.

Organ systems †	Disease responsible for the leading cause of death in the organ system	
	Patients with adrenal insufficiency	**Controls**
Circulatory system	Ischaemic heart disease	Ischaemic heart disease
Neoplasms	Malignancy ‡	Malignancy ‡
Respiratory system	Pneumonia and lower respiratory tract infection	Pneumonia and lower respiratory tract infection
Digestive system	Alcoholic liver disease	Alcoholic liver disease
Endocrine system	Disease of the pituitary and adrenal glands	Diabetes mellitus
Genitourinary system	Urinary tract infection	Urinary tract infection
Infectious diseases	Based on identifiable organisms	Based on identifiable organisms
Musculoskeletal system	Connective tissue disease and rheumatoid arthritis	Osteoporosis

Table 3.23: Disease responsible for the leading cause of death in each organ system in patients with adrenal insufficiency and controls

Note: † Listed in descending order of death rates according to organ systems, ‡ Mortality rate of malignancy was higher than that of ischaemic heart disease

❖ Adrenal insufficiency of any type and matched controls

Patients with adrenal insufficiency had increased mortality caused by ischaemic heart disease, malignancy, respiratory tract infection, and combined infections, compared with controls (Table 3.24). For ischaemic heart disease, the mortality rate (95% CI) of the study patients and controls was 4.9 (4.0-6.1) and 2.7 (2.5-3.0) per 1000 person-years, respectively, giving a mortality rate difference of 2.2 (1.2-3.3) per 1000 person-years ($p<0.0001$) and an unadjusted hazard ratio (95% CI) of 1.83 (1.46-2.28; $p<0.0001$). For malignancy, the mortality rate (95% CI) of the study patients and controls was 6.8 (5.7-8.1) and 5.5 (5.2-5.8) per 1000 person-years, respectively, giving a mortality rate difference of 1.3 (0.1-2.5) per 1000 person-years ($p=0.014$) and an unadjusted hazard ratio (95% CI) of 1.24 (1.03-1.49; $p=0.024$). For lower respiratory tract infection including pneumonia, the mortality rate (95% CI) of the study patients and controls was 3.9 (3.1-4.9) and 1.3 (1.2-1.5) per 1000 person-years, respectively, giving a mortality rate difference of 2.5 (1.6-3.4) per 1000 person-years ($p<0.0001$) and an unadjusted hazard ratio (95% CI) of 2.89 (2.22-3.76; $p<0.0001$). For combined infections, the mortality rate of the study patients was considerably higher than that of controls (5.1 [95% CI, 4.1-6.2] vs 1.8 [95% CI, 1.6-2.0]), resulting a high mortality rate difference (3.3 [95% CI, 2.2-4.3] per 1000 person-years; $p<0.0001$) and an unadjusted hazard ratio of 2.86 (95% CI, 2.27-3.60; $p<0.0001$).

The mortality rates of the study patients and controls were low in deaths from urinary tract infection, and connective tissue disease and rheumatoid arthritis, and alcoholic liver disease. In these diseases, the mortality rates of adrenal insufficiency and controls were not different and the hazard ratios were not significantly increased (Table 3.24).

Principal cause of death	**Adrenal insufficiency of any type**		**Controls**		Mortality rate difference per 1000 person-years (95% CI)	P for mortality rate difference	Unadjusted HR (95%CI)	P
	No. death	Mortality per 1000 person-years (95% CI)	No. death	Mortality per 1000 person-years (95% CI)				
Ischaemic heart disease	92	4.9 (4.0-6.1)	487	2.7 (2.5-3.0)	2.2 (1.2 to 3.3)	<0.0001	1.83 (1.46-2.28)	<0.0001
Malignancy	126	6.8 (5.7-8.1)	987	5.5 (5.2-5.8)	1.3 (0.1 to 2.5)	0.014	1.24 (1.03-1.49)	0.024
Lower respiratory infection	72	3.9 (3.1-4.9)	242	1.3 (1.2-1.5)	2.5 (1.6 to 3.4)	<0.0001	2.89 (2.22-3.76)	<0.0001
Combined infections	94	5.1 (4.1-6.2)	319	1.8 (1.6-2.0)	3.3 (2.2 to 4.3)	<0.0001	2.86 (2.27-3.60)	<0.0001
Alcoholic liver disease	4	0.2 (0.1-0.6)	28	0.2 (0.1-0.2)	0.1 (-0.2 to 0.3)	0.26	1.37 (0.48-3.92)	0.55
Urinary tract infection	8	0.4 (0.2-0.9)	43	0.2 (0.2-0.3)	0.2 (-0.1 to 0.5)	0.073	1.80 (0.85-3.83)	0.12
Connective tissue disease & Rheumatoid arthritis	3	0.2 (0.1-0.5)	8	0.0 (0.0-0.1)	0.1 (-0.1 to 0.3)	0.045	3.61 (0.96-13.62	0.058
All-cause	632	34.0 (31.4-36.7)	3643	20.3 (19.6-20.9)	13.7 (11.0 to 16.5)	<0.0001	1.68 (1.55-1.83)	<0.0001

Table 3.24: Mortality rates of patients with adrenal insufficiency of any type and controls, and hazard ratios for mortality according to the cause of death in specific disease

Note: Combined infections: deaths from infectious disease, lower respiratory tract infection, and urinary tract infection

N, study patients vs controls = 3547 vs 34944; period of follow-up, study patients vs controls = 18592 vs 179833 person-years

❖ Primary adrenal insufficiency and matched controls

Compared with controls, patients with primary adrenal insufficiency had increased mortality caused by ischaemic heart disease, respiratory tract infection, and combined infections; however, mortality from malignancy was not increased (Table 3.25). For ischaemic heart disease, the mortality rate (95% CI) of the study patients and controls was 5.7 (4.0-8.1) and 2.6 (2.2-3.1) per 1000 person-years, respectively, giving a mortality rate difference of 3.0 (1.0-5.1) per 1000 person-years ($p<0.0001$) and an unadjusted hazard ratio (95% CI) of 2.17 (1.47-3.19; $p<0.0001$). For lower respiratory tract infection including pneumonia, the mortality rate of the study patients was markedly higher than that of controls (5.3 [95% CI, 3.7-7.6] vs 1.1 [95% CI, 0.8-1.4] per 1000 person-years), giving a mortality rate difference of 4.2 (2.3-6.2) per 1000 person-years ($p<0.0001$) and an unadjusted hazard ratio (95% CI) of 4.91 (3.15-7.65; $p<0.0001$). For combined infections, the mortality rate of the study patients was also markedly higher than that of controls (6.2 [95% CI, 4.4-8.7] vs 1.5 [95% CI, 1.2-1.9]), resulting a high mortality rate difference (4.7 [95% CI, 2.6-6.8] per 1000 person-years; $p<0.0001$) and an unadjusted hazard ratio of 4.14 (95% CI, 2.78-6.18; $p<0.0001$). For malignancy, the mortality rate (95% CI) of the study patients was non-significantly higher than that of controls (6.6 [95% CI, 4.7-9.1] vs 4.7 [2.6-6.8] per 1000 person-years) with a mortality rate difference of 1.9 (95% CI, -0.3 to 4.1) per 1000 person-years ($p=0.032$) and an unadjusted hazard ratio of 1.41 (95% CI, 0.99-2.00; $p=0.054$).

In deaths from urinary tract infection and alcoholic liver disease, the mortality rates of primary adrenal insufficiency and controls were not different, and the hazard ratios were not increased, in line with the findings in the whole cohort of adrenal insufficiency of any type. In deaths from connective tissue disease and rheumatoid arthritis, an increased hazard ratio was

observed, although it was not significant probably because of the small number of deaths in both study patients and controls (Table 3.25).

Principal cause of death	**Primary adrenal insufficiency**		**Controls**		Mortality rate difference per 1000 person-years (95% CI)	P for mortality rate difference	Unadjusted HR (95%CI)	P
	No. death	Mortality per 1000 person-years (95% CI)	No. death	Mortality per 1000 person-years (95% CI)				
Ischaemic heart disease	31	5.7 (4.0-8.1)	144	2.6 (2.2-3.1)	3.0 (1.0 to 5.1)	0.0002	2.17 (1.47-3.19)	<0.0001
Malignancy	36	6.6 (4.7-9.1)	257	4.7 (4.1-5.3)	1.9 (-0.3 to 4.1)	0.032	1.41 (0.99-2.00)	0.054
Lower respiratory tract infection	29	5.3 (3.7-7.6)	59	1.1 (0.8-1.4)	4.2 (2.3 to 6.2)	<0.0001	4.91 (3.15-7.65)	<0.0001
Combined infection	34	6.2 (4.4-8.7)	82	1.5 (1.2-1.9)	4.7 (2.6 to 6.8)	<0.0001	4.14 (2.78-6.18)	<0.0001
Alcoholic liver disease	1	0.2 (0.0-1.3)	7	0.1 (0.1-0.3)	0.1 (-0.3 to 0.4)	0.34	1.42 (0.17-11.54)	0.74
Urinary tract infection	1	0.2 (0.0-1.3)	13	0.2 (0.1-0.4)	-0.1 (-0.4 to 0.3)	0.44	0.76 (0.10-5.82)	0.79
Connective tissue disease & Rheumatoid arthritis	1	0.2 (0.0-1.3)	1	0.0 (0.0-0.1)	0.2 (-0.2 to 0.5)	0.090	9.84 (0.62-157.40)	0.10
All	207	37.8 (33.0-43.3)	1001	18.2 (17.1-19.4)	19.6 (14.3 to 24.9)	<0.0001	2.07 (1.78-2.41)	<0.0001

Table 3.25: Mortality rates of patients with primary adrenal insufficiency and controls, and hazard ratios for mortality according to the cause of death in specific disease

Note: N, study patients vs controls = 1015 vs 10025; period of follow-up, study patients vs controls = 5474 vs 54933 person-years

❖ Secondary adrenal insufficiency and matched controls

Similar to the findings in primary adrenal insufficiency, patients with secondary adrenal insufficiency had increased mortality caused by ischaemic heart disease, respiratory tract infection, and combined infections but no increase in mortality from malignancy (Table 3.26). For ischaemic heart disease, the mortality rate (95% CI) of the study patients and controls was 4.7 (3.6-6.1) and 2.6 (2.4-3.0) per 1000 person-years, respectively, giving a mortality rate difference of 2.0 (0.7-3.3) per 1000 person-years (p=0.0002) and an unadjusted hazard ratio (95% CI) of 1.76 (1.31-2.36; p<0.0001). For lower respiratory tract infection including pneumonia, the mortality rate of the study patients was higher than that of controls (2.9 [95% CI, 2.1-4.1] vs 1.4 [95% CI, 1.2-1.6] per 1000 person-years), giving a mortality rate difference of 1.5 (0.5-2.5) per 1000 person-years (p=0.0002) and an unadjusted hazard ratio (95% CI) of 2.10 (1.44-3.06; p<0.0001). For combined infections, the mortality rate of the study patients was also higher than that of controls (4.0 [95% CI, 3.0-5.4] vs 1.8 [95% CI, 1.6-2.1]), resulting a high mortality rate difference (2.2 [95% CI, 1.0-3.4] per 1000 person-years; p<0.0001) and an unadjusted hazard ratio of 2.25 (95% CI, 1.63-3.10; p<0.0001). For malignancy, the mortality rate (95% CI) of the study patients was non-significantly higher than that of controls (6.7 [95% CI, 5.3-8.4] vs 5.8 [5.4-6.3] per 1000 person-years) with a mortality rate difference of 0.9 (-0.7 to 2.4) per 1000 person-years (p=0.12) and an unadjusted hazard ratio (95% CI) of 1.16 (0.91-1.47; p=0.22).

In deaths from alcoholic liver disease, the mortality rates for secondary adrenal insufficiency and controls were not different and the hazard ratio was not increased. In deaths from urinary tract infection, the hazard ratio was not significantly increased and numbers of deaths were small in both study patients and controls. Also, no death from connective tissue disease and

rheumatoid arthritis was observed in patients with secondary adrenal insufficiency (Table 3.26).

Principal cause of death	**Secondary adrenal insufficiency**		**Controls**		Mortality rate difference per 1000 person-years (95% CI)	P for mortality rate difference	Unadjusted HR (95%CI)	P
	No. death	Mortality per 1000 person-years (95% CI)	No. death	Mortality per 1000 person-years (95% CI)				
Ischaemic heart disease	53	4.7 (3.6-6.1)	283	2.6 (2.4-3.0)	2.0 (0.7 to 3.3)	0.0002	1.76 (1.31-2.36)	<0.0001
Malignancy	76	6.7 (5.3-8.4)	620	5.8 (5.4-6.3)	0.9 (-0.7 to 2.4)	0.12	1.16 (0.91-1.47)	0.22
Lower respiratory tract infection	33	2.9 (2.1-4.1)	149	1.4 (1.2-1.6)	1.5 (0.5 to 2.5)	0.0002	2.10 (1.44-3.06)	<0.0001
Combined infection	46	4.0 (3.0-5.4)	194	1.8 (1.6-2.1)	2.2 (1.0 to 3.4)	<0.0001	2.25 (1.63-3.10)	<0.0001
Alcoholic liver disease	2	0.2 (0.0-0.7)	20	0.2 (0.1-0.3)	-0.0 (-0.2 to 0.2)	0.50	0.93 (0.22-3.99)	0.92
Urinary tract infection	6	0.5 (0.2-1.2)	24	0.2 (0.2-0.3)	0.3 (-0.0 to 0.7)	0.042	2.38 (0.97-5.82)	0.058
Connective tissue disease & Rheumatoid arthritis	0	0	4	0.0 (0.0-0.1)	NA	..	NA	..
All	340	29.9 (26.9-33.2)	2186	20.5 (19.6-21.3)	9.4 (6.1 to 12.7)	<0.0001	1.47 (1.31-1.65)	<0.0001

Table 3.26: Mortality rates of patients with secondary adrenal insufficiency and controls, and hazard ratios for mortality according to the cause of death in specific disease

Note: N, study patients vs controls = 2136 vs 20991; period of follow-up, study patients vs controls = 11377 vs 106850 person-years

3.5.3 Principal cause of death in patients with primary adrenal insufficiency compared with secondary adrenal insufficiency

Figure 3.19 illustrates the pattern of cause of death according to the organ systems and their specific diseases in patients with primary and secondary adrenal insufficiency. The rates of death from disease in the respiratory and musculoskeletal system were higher in patients with primary adrenal insufficiency, in line with higher mortality rates observed in lower respiratory tract infection and connective tissue disease and rheumatoid arthritis, which were the leading causes in these systems. Death from lower respiratory tract infections was also the major contributor to death from combined infections in both primary and secondary adrenal insufficiency and the mortality rate from combined infections was higher in primary adrenal insufficiency. In addition, patients with primary adrenal insufficiency had a higher mortality rate from disease of the endocrine system (See below section: Principal and associated causes of death from disease of the endocrine system).

Although the all-cause mortality rate was higher in patients with primary adrenal insufficiency than secondary adrenal insufficiency, the mortality caused by neoplasms appeared to be higher in secondary adrenal insufficiency. However, the rate of death from malignancy, which is the leading causes of death in the category of neoplasms, was not different between primary and secondary adrenal insufficiency. In deaths from disease in the circulatory system including ischaemic heart disease, digestive, and nervous system, mental and behavioural disorders, the mortality rates in patients with primary adrenal insufficiency were not different from those in secondary adrenal insufficiency (Figure 3.18).

In summary, the leading causes of death according to organ systems were similar between patients with adrenal insufficiency of any type, primary and secondary adrenal insufficiency, and controls, comprising diseases of the circulatory system, neoplasm, and respiratory system. However, the mortality rates of patients with adrenal insufficiency from these organ systems appeared to be higher than those of controls. Regarding the mortality risk relative to controls, the hazard ratio was greatest in death from infectious disease, which was observed in both primary and secondary adrenal insufficiency, although more obviously in primary adrenal insufficiency. When death from infectious disease was combined with causes of death from infection in respiratory and urinary systems, the mortality rate was further increased, was among the leading causes of death and was associated with a substantially increased hazard ratio.

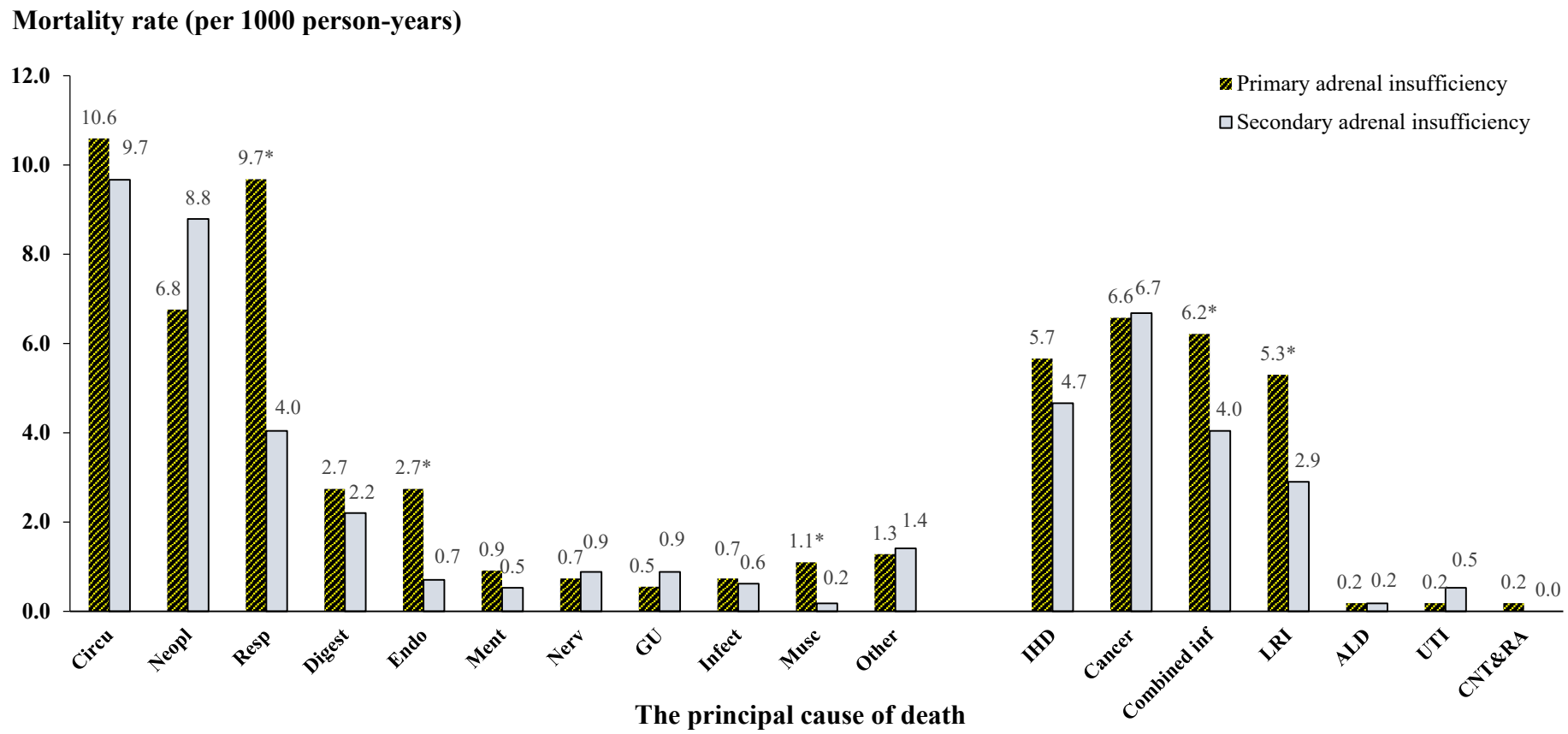


Figure 3.19: A comparisons of mortality rates between primary and secondary adrenal insufficiency according to the principal cause of death

Note: * p for mortality rate difference <0.05; Circu: Circulatory system, Neopl: Neoplasm; Resp: Respiratory system; Digest: Digestive system; Endo: Endocrine system; Ment: Mental & behavioural disorders; Musc: Musculoskeletal; Other: Other systems; IHD: Ischaemic heart disease; Combined inf: infectious disease & LRI & UTI; LRI: lower respiratory tract infection; ALD: Alcoholic liver disease; UTI: Urinary tract infection; CNT&RA: Connective tissue disease and rheumatoid arthritis

3.5.4 Principal and associated causes of death from disease of the endocrine system

Death from disease of the endocrine system included death from diabetes mellitus and diseases involving other endocrine glands. This analysis evaluated the causes of death from disease of the endocrine system, focusing on the causes from disorders of the pituitary gland including pituitary adenoma, and adrenal insufficiency, assigned as the principal and associated causes of death. The analysis included 3547 patients with adrenal insufficiency of any type (1015 with primary, 2136 with secondary, and 396 for unspecified adrenal insufficiency) with a follow-up period of 18592 person-years for all patients (5474 for primary, 11377 for secondary, and 1741 for unspecified adrenal insufficiency), and 34944 controls with a follow period of 179833 person-years.

- ❖ Deaths from disease of the endocrine system

Disease of the endocrine system accounted for the principal cause of death in 28 of a total of 632 deaths (4.4%) in patients with adrenal insufficiency of any type, 15 of 207 (7.2%) in primary, 8 of 340 (2.4%) in secondary and 5 of 85 (5.9%) in unspecified adrenal insufficiency, and 56 of 3643 (1.5%) in controls. The mortality rate of patients with adrenal insufficiency of any type was higher than that of controls (1.5 [95% CI, 1.0-2.2] vs 0.3 [95% CI, 0.2-0.4] per 1000 person-years), giving a mortality rate difference of 1.1 (95% CI, 0.6-1.80) per 1000 person-years ($p<0.0001$) and an unadjusted hazard ratio of 4.85 (95% CI, 3.08-7.64; $p<0.0001$; Table 3.20). In patients with primary adrenal insufficiency, the mortality rate of death from endocrine disease was also higher than controls (2.7 [95% CI, 1.7-4.5] vs 0.3 [0.2-0.5] per 1000 person-years; $p<0.0001$; Table 3.21). In patients with secondary adrenal insufficiency, the mortality rate was slightly higher than controls (0.7 [95% CI, 0.4-1.4] vs 0.3 [0.2-0.4] per 1000 person-years; $p=0.030$; Table 3.22). In 396 patients with unspecified adrenal insufficiency, the mortality rate of death from endocrine disease was 2.9 (95% CI, 1.2-6.9). In a comparison of

primary with secondary adrenal insufficiency, the mortality rate difference was 2.0 (95% CI, 0.6-3.5) per 1000 person-years (p=0.0008) and the unadjusted hazard ratio was 3.93 (95% CI, 1.67-9.27; p=0.002; Table 3.27). As expected, the specific disease responsible for the leading cause of death in the study patients was disorders related to the pituitary or adrenal glands whereas in controls, it was diabetes.

Causes of death	**Adrenal insufficiency of any type** N = 3547		**Primary adrenal insufficiency** N = 1015		**Secondary adrenal insufficiency** N = 2136		Mortality rate difference per 1000 person-years (95% CI) †	P	Unadjusted HR (95% CI) †	P
	No. death	Mortality rate per 1000 person-years (95% CI)	No. death	Mortality rate per 1000 person-years (95% CI)	No. death	Mortality rate per 1000 person-years (95% CI)				
Disease of the Endocrine system										
Principal cause	28	1.5 (1.0-2.2)	15	2.7 (1.7-4.5)	8	0.7 (0.4-1.4)	2.0 (0.6-3.5)	0.0008	3.93 (1.67-9.27)	0.0020
Pituitary disorders										
Principal cause	7	0.4 (0.1-0.8)	0	0.0	6	0.5 (0.2-1.2)	-0.5 (-0.9 to -0.1)	0.047	NA	NA
Principal or Associated causes	59	3.2 (2.5-4.1)	0	0.0	55	4.8 (3.7-6.3)	-4.8 (-6.1 to -3.6)	<0.0001	NA	NA
Adrenal insufficiency										
Principal cause	9	0.5 (0.3-0.9)	9	1.6 (0.9-3.2)	0	0.0	1.6 (0.6 to 2.7)	<0.0001	NA	NA
Principal or Associated causes	74	4.0 (3.2-5.0)	63	11.5 (9.0-14.7)	5	0.4 (0.2-1.1)	11.1 (8.2 to 13.9)	<0.0001	26.2 (10.5-65.10)	<0.0001
Adrenal crisis										
Principal cause	0	0.0	0	0.0	0	0.0	NA	NA	NA	NA
Principal or Associated causes	66	3.5 (2.8-4.5)	61	11.1 (6.7-14.3)	3	0.3 (0.1-0.8)	10.9 (8.1 to 13.7)	<0.0001	42.27 (13.26-134.71)	<0.0001

Table 3.27: The principal and associated causes of death from disease of the endocrine system in the study patients

Note: † A comparison between patients with primary and secondary adrenal insufficiency

❖ Deaths from disorders of the pituitary gland and pituitary adenoma

Pituitary disorders accounted for the principal cause of death in 7 of a total of 632 deaths (1.1%) in the study patients, including 6 of 340 (1.8%) and 1 of 85 (1.2%) deaths in patients with secondary and unspecified adrenal insufficiency, respectively. When the associated cause of death was included (inclusive cause of death), pituitary disorders accounted for 59 deaths (9.3% of total deaths) in all patients, including 55 (16.2%) in secondary and 4 (4.7%) in unspecified adrenal insufficiency. As expected, no death from pituitary disorders was recorded among patients with primary adrenal insufficiency. In those with secondary adrenal insufficiency, the mortality rate regarding the principal and inclusive causes was 0.5 (95% CI, 0.3-0.9) and 4.8 (3.7-6.3) per 1000 person-years, respectively (Table 3.27).

❖ Deaths from adrenal insufficiency

Adrenal insufficiency accounted for the principal cause of death in 9 of 632 deaths (1.4%) in all patients, and all these deaths were recorded only in primary adrenal insufficiency, corresponding to 4.3% (9 of 207 deaths). When the associated cause of death was included (inclusive cause of death), adrenal insufficiency accounted for 74 deaths of a total of 632 deaths (11.7%) in the study patients, including 63 of 207 (30.4%) deaths in primary and 5 of 340 (1.5%) in secondary adrenal insufficiency. In patients with primary adrenal insufficiency, the mortality rate regarding the principal and inclusive causes was 1.6 (95% CI, 0.9-3.2) and 11.5 (9.0-14.7) per 1000 person-years, respectively. In those with secondary adrenal insufficiency, the rate of deaths from adrenal insufficiency as an associated cause was 0.4 (0.2-1.1) per 1000 person-years (Table 3.27).

❖ Deaths from adrenal crisis

No death from adrenal crisis was assigned as the principal cause of death in this study. However, it was assigned as an associated cause of death in 66 patients with adrenal insufficiency of any kind, corresponding to 10.4% of total deaths and a mortality rate of 3.5 (95% CI, 2.8-4.5) per 1000 patient-years (Table 3.27). Among these, 61 were patients with primary adrenal insufficiency, corresponding to 29.5% of total deaths and a mortality rate of 11.1 (95% CI, 6.7-14.3) per 1000 patient-years. In patients with secondary adrenal insufficiency, 3 deaths (0.9% of total deaths) were associated with adrenal crisis, giving a mortality rate of 0.3 (95% CI, 0.1-0.8) per 1000 patient-years. In a comparison between type of adrenal insufficiency, the mortality rate was higher in primary disease, with a mortality rate difference of 10.9 (95% CI, 8.1-13.7) per 1000 patient-years ($p<0.0001$; Table 3.27).

Mortality from adrenal crisis appeared to differ between the sexes. In patients with adrenal insufficiency of any kind, 24 deaths were in men whereas 42 were in women, giving a mortality rate of 2.8 (95% CI, 1.9-4.2) and 4.2 (3.1-5.7) per 1000 patient-years, respectively, but this was not statistically different ($p=0.057$). In patients with primary adrenal insufficiency, 20 and 41 deaths were in men and women, respectively. Men also had a non-significantly lower mortality rate than women (8.9 [95% CI, 5.8-13.9] vs 12.7 [9.3-17.2] per 1000 patient-years; $p=0.10$). In patients with secondary adrenal insufficiency, 3 deaths were observed in men with a mortality rate of 0.5 (95%CI, 0.2-1.7) per 1000 patient-years, but there were no deaths in women.

Among the 66 patients having adrenal crisis as an associated cause of deaths, the leading principal causes of death were disease of the circulatory system, neoplasms, and respiratory systems, corresponding to 29%, 18%, and 17%, respectively. This was consistent with the principal cause of death in the whole cohort of adrenal insufficiency of any type and controls.

In summary, the mortality rate for cause of death recorded as disease of the endocrine system was higher in patients with adrenal insufficiency than that of controls. The leading cause of death in diseases of the endocrine system was adrenal or pituitary disorders for the patients but diabetes mellitus for controls. Adrenal crisis was recorded as an associated cause of death in 10%, 30%, and 1% of total deaths in patients with adrenal insufficiency of any type, primary, and secondary adrenal insufficiency, respectively.

3.6 In-hospital outcomes

Among those with HES data linkage, in-hospital outcomes consisted of hospital admissions for any reason and adrenal crisis noted in the admission record. Hospital admissions for any reason in the study patients were compared with those in controls. Adrenal crisis in the hospital admission record was evaluated in patients with adrenal insufficiency of any type and in primary and secondary adrenal insufficiency.

3.6.1 Hospital admissions for any reason

This analysis included 3547 patients with adrenal insufficiency of any type (1015 primary, 2136 secondary adrenal insufficiency) and 34944 controls (10025 and 20991 matched with patients with primary and secondary adrenal insufficiency, respectively). The analysis included: the proportion of patients admitted to hospital, including emergency admissions; the average number of admission episodes; and the length of stay of the study patients and controls.

The proportion of study patients admitted to hospital was higher than that in controls. In adrenal insufficiency of any type, 2674 study patients and 15962 controls were admitted to hospital, corresponding to 75% and 46%, respectively ($p< 0.0001$; Table 3.28) with an unadjusted odds ratio of 3.64 (95% CI, 3.37-3.94; $p<0.0001$). In primary adrenal insufficiency, 75% of patients and 46% of controls were admitted to hospital ($p<0.0001$), giving an odds ratio of 3.48 (95% CI, 3.00-4.03; $p<0.0001$). Similarly, patients with secondary adrenal insufficiency had a higher proportion of hospital admissions, compared with controls (75% vs 46%; $p<0.0001$), giving an odds ratio of 3.60 (95% CI, 3.25-3.99; $p<0.0001$). In a comparison between patients with primary and secondary adrenal insufficiency, the proportion of hospitalised patients was not different ($p=0.94$) with an odds ratio of 0.99 (95% CI, 0.84-1.18; $p=0.94$). Since sex and age at diagnosis were not intentionally matched between primary and secondary adrenal

insufficiency, the adjusted odds ratio for age and sex was evaluated and it was in line with the unadjusted odds ratio (adjusted OR, 1.00 [95% CI, 0.84-1.19]; p=0.96).

The average number of admission episodes per follow-up year was also higher in the study patients, compared with controls. In adrenal insufficiency of any type, the average number of admissions (median [IQR]) was 0.98 (0.44-2.09) and 0.49 (0.23-1.10) per follow-up year in the study patients and controls, respectively (p<0.0001). In primary adrenal insufficiency, the number of admission episodes was higher in the study patients (0.98 [0.39-2.29] vs 0.46 [0.22-1.04] per follow-up year; p<0.0001). In secondary adrenal insufficiency, the number was also higher in the study patients (0.92 [0.43-1.86] vs 0.50 [0.23-1.11] per follow-up year; p<0.0001). In a comparison between patients with primary and secondary adrenal insufficiency, the average number of admission episodes was not significantly different (p=0.22; Table 3.28).

The proportion of patients experiencing emergency admissions was higher in the study patients, compared with controls. In adrenal insufficiency of any type, there were 1849 patients and 9629 controls who were admitted to hospital with an emergency reason, corresponding to 52% and 28%, respectively (Table 3.28) with an odds ratio of 2.86 (95% CI, 2.67-3.07; p<0.0001). In primary adrenal insufficiency, the proportion of emergency hospital admissions was higher in the study patients than that in controls (57% vs 27%; p<0.0001), giving an odds ratio of 3.47 (95% CI, 3.04-3.96; p<0.0001). In secondary adrenal insufficiency, the proportion was also higher in the study patients compared with controls (49% vs 28%; p<0.0001), giving an odds ratio of 2.55 (95% CI, 2.33-2.79; p<0.0001). In a comparison between patients with primary and secondary adrenal insufficiency, the proportion of emergency admissions was higher in patients with primary disease than in secondary disease, resulting in an unadjusted odds ratio of 1.35 (95% CI, 1.17-1.57; p<0.0001). After adjustment for sex and age at diagnosis, the odds ratio remained significantly increased (adjusted OR, 1.40 [95% CI, 1.20-1.63]; p<0.0001).

The average length of stay in the study patients appeared to be higher than in controls. In adrenal insufficiency of any type, the average length of stay (median [IQR]) in days was 4.25 (2.00-9.14) and 4.00 (2.00-9.00) days per patient-year for the study patients and controls, respectively (p=0.0017). In primary adrenal insufficiency, the average length of stay in the study patients was not different from that in controls (4.00 [2.00-8.57] vs 4.00 [2.00-8.60] days per patient-year, p=0.88). However, in secondary adrenal insufficiency, the average length of stay was higher in the study patients, compared with controls (4.50 [2.00-9.00] vs 4.00 [2.00-9.00] days per patient-year; p=0.0009). In a comparison between patients with primary and secondary adrenal insufficiency, the average length of stay was 0.5 days per patient-year higher in secondary than that in primary disease (p=0.019; Table 3.28).

	All adrenal insufficiency			Primary adrenal insufficiency			Secondary adrenal insufficiency			P‡
	Patients N = 3547	Controls N = 34944	P	Patients N = 1015	Controls N = 10025	P	Patients N = 2136	Controls N = 20991	P	
Number of patients with hospital admissions from any reason (%)	2674 (75.4)	15962 (45.7)	<0.0001	760 (74.9)	4624 (46.1)	<0.0001	1602 (75.0)	9541 (45.5)	<0.0001	0.94
Average number of admission episodes per year of FUP for each patient, median (IQR)*	0.98 (0.44-2.09)	0.49 (0.23-1.10)	<0.0001	0.98 (0.39-2.29)	0.46 (0.22-1.04)	<0.0001	0.92 (0.43-1.86)	0.50 (0.23-1.11)	<0.0001	0.22
Number of patients with emergency admission (%)	1849 (52.1)	9629 (27.6)	<0.0001	575 (56.7)	2744 (27.4)	<0.0001	1049 (49.1)	5767 (27.5)	<0.0001	<0.0001
Average length of stay; days per patient-years, median (IQR)†	4.25 (2.00-9.14)	4.00 (2.00-9.00)	0.0017	4.00 (2.00-8.57)	4.00 (2.00-8.60)	0.88	4.50 (2.00-9.00)	4.00 (2.00-9.00)	0.0009	0.019

Table 3.28: In-hospital outcomes of patients with adrenal insufficiency and controls

Note: *data analysed in those ever admitted to hospital; †data analysed in those ever admitted to hospital and excluded a day case or those with missing duration of admission (start 1997 onwards); ‡ a comparison between patients with primary and secondary adrenal insufficiency

3.6.2 Adrenal crisis in hospital

Adrenal crisis in hospital included a record of adrenal crisis as a primary reason for hospital admission and adrenal crisis occurring later in hospitalisation. The analysis included the proportion of patients having adrenal crisis; the rate of the first event of adrenal crisis in hospital overall and on a yearly basis after the diagnosis of adrenal insufficiency; and the rate of all events of adrenal crisis in hospital, covering the period between the date of diagnosis of adrenal insufficiency recorded by general practitioners (index date) to the end of study. In addition, the association between adrenal crisis in hospital and all-cause mortality was evaluated. In 3547 patients with adrenal insufficiency of any type, 223 patients (6.3%) had at least one episode of adrenal crisis in hospital and 33% of these patients had recurrent episodes of adrenal crisis. In 1015 patients with primary adrenal insufficiency, there was a total of 364 episodes of adrenal crisis in hospital during the follow-up period, recorded in 150 patients (15%) and 38% of these patients had recurrent episodes. In 2136 patients with secondary adrenal insufficiency, there were 47 episodes of adrenal crisis, recorded in 37 patients (2%) and only 14% of these patients had recurrent episodes. In a comparison between patients with primary and secondary adrenal insufficiency, the proportions of patients having adrenal crisis in hospital and recurrent adrenal crisis were significantly higher in those with primary disease (Table 3.29). The maximum number of episodes of adrenal crisis was also different: 12 and 5 in primary and secondary adrenal insufficiency, respectively. It is noted that six patients (2.7% of those with adrenal crisis) had adrenal crisis in hospital on the date of diagnosis of adrenal insufficiency (index date) and another four patients (1.8%) had adrenal crisis within 7 days after index date.

	Adrenal insufficiency of any type (N = 3547)	Primary adrenal insufficiency (N = 1015)	Secondary adrenal insufficiency (N = 2136)	P (primary vs secondary)
Number of total episodes of adrenal crisis	364	265	47	NA
Number of patients having at least one adrenal crisis	223† (6.3%)	150 (14.8%)	37 (1.7%)	<0.0001
Number of patients having recurrent adrenal crisis (% of those with ever adrenal crisis in hospital)	73 (32.7%)	57 (38.0%)	5 (13.5%)	0.0050

Table 3.29: Adrenal crisis in hospital after the diagnosis of adrenal insufficiency

Note: † Six patients had adrenal crisis in hospital on the same date as the date recorded diagnosis of adrenal insufficiency. Further four patients had adrenal crisis in hospital within 7 days after the diagnosis of adrenal insufficiency.

The incidence rate of first adrenal crisis in hospital was 9.9 (95% CI, 8.7-11.3) per 1000 patient-years in patients with adrenal insufficiency of any kind during a follow-up time of 21881 patient-years. In a comparison between patients with primary and secondary adrenal insufficiency, the rate of first adrenal crisis was considerably higher in primary disease (23.7 [95% CI, 20.2-27.8] vs 2.7 [2.0-3.8] per 1000 patient-years; $p<0.0001$). When the incidence rate was categorised by year, the highest rate was observed in the first year after the diagnosis of adrenal insufficiency, 38.9 (95% CI, 28.0-53.9) in primary and 5.5 (3.1-10.0) per 1000 patient-years in secondary adrenal insufficiency (Table 3.30).

Since there were recurrent episodes of adrenal crisis, the incidence rate of all events of adrenal crisis in hospital was considered. In patients with adrenal insufficiency of any kind, the rate of all episodes of adrenal crisis was 16.0 (95% CI, 14.4-17.7) per 1000 patient-years. In a comparison between patients with primary and secondary adrenal insufficiency, the incidence rate of all episodes was also considerably higher in primary disease (38.3 [95% CI, 34.0-43.3] vs 3.4 [2.6-4.6] per 1000 patient-years; $p<0.0001$; Table 3.30).

Years from diagnosis	All adrenal insufficiency patients				Primary adrenal insufficiency				Secondary adrenal insufficiency			
	No. at risk	No. 1st crisis	Person-years	Incidence per 1000 patient-year (95% CI)	No. at risk	No. 1st crisis	Person-years	Incidence per 1000 patient-year (95% CI)	No. at risk	No. 1st crisis	Person-years	Incidence per 1000 patient-year (95% CI)
0-1	3547	58	3257	17.8 (13.8-23.0)	1015	36	927	38.9 (28.0-53.9)	2136	11	1988	5.5 (3.1-10.0)
1-2	2957	30	2725	11.0 (7.7-15.7)	845	20	766	26.1 (16.8-40.4)	1821	5	1697	2.9 (1.2-7.1)
2-3	2511	16	2319	6.9 (4.2-11.3)	701	11	653	16.9 (9.3-30.4)	1576	2	1454	1.4 (0.3-5.5)
3-4	2156	18	2008	9.0 (5.6-14.2)	610	14	568	24.7 (14.6-41.6)	1353	4	1259	3.2 (1.2-8.5)
4-5	1877	12	1748	6.9 (3.9-12.1)	531	9	495	18.2 (9.5-34.9)	1176	1	1096	0.9 (0.1-6.5)
5-10	1636	43	5797	7.4 (5.5-10.0)	463	29	1651	17.6 (12.2-25.3)	1032	8	3645	2.2 (1.1-4.4)
10-15	780	25	2595	9.6 (6.5-14.3)	226	20	778	25.7 (16.6-39.8)	488	3	1569	1.9 (0.6-5.9)
15-20	329	11	1026	10.7 (5.9-19.4)	97	9	314	28.6 (14.9-55.0)	199	2	595	3.4 (0.8-13.4)
>20	114	4	407	9.8 (3.7-26.2)	38	1	144	6.9 (1.0-49.1)	60	1	213	4.7 (0.7-33.4)
All	3547	217*	21881	9.9 (8.7-11.3)	1015	149	6297	23.7 (20.2-27.8) †	2136	37	13517	2.7 (2.0-3.8) †
All multiple‡	3547	364	22768	16.0 (14.4-17.7)	1015	265	6911	38.3 (34.0-43.3) †	2136	47†	13661	3.4 (2.6-4.6) †

Table 3.30: Incidence rate of record of adrenal crisis in hospital according to year of after diagnosis of adrenal insufficiency

Note: † $p<0.0001$ in a comparison between primary and secondary adrenal insufficiency; ‡ recurrent adrenal crises in a given patient were included in the analysis; *6 patients (1 primary, 5 unspecified adrenal insufficiency) had the first adrenal crisis on index date and were excluded from the survival analysis

All-cause mortality was compared between patients with a history of adrenal crisis in hospital and those without adrenal crisis. There were 49 deaths (22%) of 223 patients with a history of adrenal crisis in hospital whereas 583 deaths (18%) were observed in 3324 patients without adrenal crisis (p=0.094). In addition, the proportion of deaths caused by adrenal crisis was compared between those with a history of adrenal crisis in hospital and those without. The proportion of patients who died with adrenal crisis was higher in those with a history of in-hospital adrenal crisis (7.2% vs 1.5%; p<0.0001), giving an odds ratio of 5.06 (95% CI, 2.83-9.04; p<0.0001).

In summary, patients with adrenal insufficiency of any type including primary and secondary adrenal insufficiency had higher proportions of hospital admissions and emergency admissions than controls. The average length of stay was slightly higher among the patients. In a comparison between primary and secondary adrenal insufficiency, the proportion of hospital admissions for any reason was not different but emergency admissions were higher in patients with primary adrenal insufficiency. The overall incidence rate of adrenal crisis in hospital in patients with primary was higher than those with secondary adrenal insufficiency. The incidence of adrenal crisis was maximum during the first year after diagnosis in both primary and secondary adrenal insufficiency.

CHAPTER 4: CARDIOVASCULAR DISEASE

MAIN FINDINGS

- The risk for cardiovascular events of any kind relative to controls was increased in patients with adrenal insufficiency (Unadjusted HR, 1.28 [95% CI, 1.20-1.36]; p<0.0001) but after pre-existing cardiovascular disease was considered, the risk was just marginally increased (Adjusted HR, 1.07 [95% CI, 1.01-1.14]; p=0.032).
- The risk for ischaemic heart disease were increased in patients with adrenal insufficiency (Unadjusted HR, 1.16 [95% CI, 1.06-1.28]; p= 0.0020) but after confounding from pre-existing cardiovascular risk factors was considered, the risk for ischaemic heart disease events was no longer increased (Adjusted HR, 0.95 [95% CI, 0.86-1.04]; p= 0.27). However, the risk for cerebrovascular events remained significantly increased independent of cardiovascular risk factors, only in patients with secondary adrenal insufficiency (Adjusted HR, 1.53 [95% CI, 1.34-1.74]; p<0.0001).
- The risks for cardiovascular events of any kind relative to controls were unchanged in patients receiving recent clinical care, compared with previous care in patients with adrenal insufficiency of any type including primary and secondary disease.
- No sex differences in the risks for cardiovascular events of any kind in patients with primary adrenal insufficiency. In adrenal insufficiency of any type and secondary adrenal insufficiency, the risks for composite cardiovascular events appeared to be higher in women but the risks for a specific disease: ischaemic heart and cerebrovascular disease, were not different between sexes.
- No age differences in the risks for cardiovascular events of any kind in patients with primary adrenal insufficiency. In adrenal insufficiency of any type and secondary adrenal insufficiency, the risks for composite cardiovascular and cerebrovascular

events were higher among younger patients but the risk for ischaemic heart disease was similar between age groups.

- The risks for cardiovascular events of any kind were not different according to pre-existing diabetes status in patients with adrenal insufficiency of any type, including primary and secondary disease.
- In primary adrenal insufficiency, the risks for cardiovascular events of any kind were similar whether or not the patients had pre-existing cardiovascular disease. In adrenal insufficiency of any type and secondary adrenal insufficiency, the risks for events of composite cardiovascular and cerebrovascular disease were higher in those without pre-existing cardiovascular disease but the risk for ischaemic heart disease was not different according to the existence of previous cardiovascular disease.
- The risks of adrenal insufficiency on cardiovascular events of any kind were not different whether or not the patients had previously use of statins.
- Mortality from disease of the circulatory system and ischaemic heart disease was increased across all types of adrenal insufficiency even after pre-existing cardiovascular risk factors were taking into account (adjusted HR for death from disease of the circulatory system, 1.31 [95% CI, 1.12-1.54]; p= 0.0010 and from ischemic heart disease, 1.49 [95% CI, 1.18-1.88]; p= 0.0010). Cerebrovascular mortality was not increased either before or after adjustment for cardiovascular risk factors (adjusted HR, 1.03 [95% CI, 1.12-1.54]; p=0.0010).
- The mortality risk for any cardiovascular disease was not different according to sex in adrenal insufficiency of any type, including primary and secondary disease.
- In adrenal insufficiency of any type and secondary adrenal insufficiency, younger patients carried a higher mortality risk from disease of the circulatory system and cerebrovascular disease but for ischaemic heart disease, the mortality risk was not

different between age groups. In primary adrenal insufficiency, mortality risk from cardiovascular disease of any kind was similar across different age groups.

- The risk for hospitalisation due to disease of the circulatory system but not ischaemic heart disease was increased in patients with adrenal insufficiency of any kind, including primary and secondary disease. The risk for hospitalisation from cerebrovascular disease was increased only in patients with adrenal insufficiency of any kind and secondary adrenal insufficiency.
- In a comparison between type of adrenal insufficiency, risk for cerebrovascular events but mortality was higher in those with secondary disease. However, the risk for the morbidity and mortality of ischaemic heart disease was not different between type of adrenal insufficiency.
- Adrenal insufficiency patients ever having composite cardiovascular events carried a higher risk for death associated with adrenal crisis, compared with those without cardiovascular events.
- Secondary adrenal insufficiency patients ever treated with radiotherapy had a higher risk for cerebrovascular disease than those never treated.

CHAPTER 4: CARDIOVASCULAR DISEASE

This chapter presents cardiovascular events as primary outcome, and, as secondary outcomes, cardiovascular mortality and hospital admissions from cardiovascular disease. As the data were analysed statistically using the similar methods as in chapter 3, results in this chapter for sections 4.2, 4.4, and 4.6 are presented in abbreviated form for ease of reading and clarity. Full data are available in the supplementary tables in the appendix.

Participants evaluated in this chapter included those with and without previous cardiovascular disease at baseline as this study did not aim to evaluate the risk for primary prevention of cardiovascular disease. Also, inclusion of those with pre-existing cardiovascular disease can ensure the generalisability of the analysis, as in real-life practice there are patients both with and without underlying cardiovascular disease. Nevertheless, the sub-analysis of participants without baseline cardiovascular disease is reported in sections 4.2.4 and 4.4.4.

4.1 Overall cardiovascular events and cardiovascular events according to calendar years

Cardiovascular events consisted of incident fatal or non-fatal events differentiated according to composite cardiovascular disease, ischaemic heart disease, and cerebrovascular disease. Events were defined when the first event for a given participant was recorded during the follow-up period. Cardiovascular events were evaluated in all participants overall and were also compared between participants receiving care in different calendar years.

4.1.1 Incidence rates and hazard ratios for risk of composite cardiovascular, ischaemic heart disease and cerebrovascular events associated with adrenal insufficiency

The incidence rate for each kind of cardiovascular events in the study patients and controls was compared and analysed as the incidence rate difference. The unadjusted hazard ratio for each kind of cardiovascular events was analysed and then was adjusted for ‘cardiovascular risk

factors', consisting of: previous cardiovascular disease, baseline diabetes mellitus, hypertension and dyslipidaemia at the start of follow-up, and ever smoking at any time. In addition, a similar analysis was performed to compare cardiovascular events between patients with primary and secondary adrenal insufficiency.

In Cox modelling of composite cardiovascular events, the test for proportional hazard assumption (PH test) showed no statistical significance, with p-values of 0.49, 0.22 and 0.86 for patients with adrenal insufficiency of any types, primary and secondary adrenal insufficiency, respectively. Neither were there significant departures from the proportionality assumption for ischaemic heart disease events (p= 0.15, 0.22 and 0.65, respectively) or cerebrovascular events (p= 0.15, 0.07 and 0.53, respectively). This was consistent with risks of cardiovascular events remaining constant over the period of follow-up across all types of adrenal insufficiency.

- Adrenal insufficiency of any type and controls

This analysis included 6821 patients with adrenal insufficiency of any type and 67564 controls. For composite cardiovascular disease, the incidence rates for the study patients and controls were 31.4 (95% CI, 29.6-33.3) and 24.4 (23.9-24.9) per 1000 person-years with follow-up periods of 36492 and 366711 person-years, respectively (Table 4.1). The incidence rate difference was significant (7.0 [95% CI, 5.1-8.9] per 1000 person-years, p<0.0001) and the unadjusted hazard ratio was 1.28 (95% CI, 1.20-1.36; p<0.0001). After adjustment for cardiovascular risk factors, the hazard ratio was only marginally increased (adjusted HR 1.07, [95% CI, 1.01-1.14]; p=0.032; Figure 4.1).

For ischaemic heart disease, the incidence rate in the study patients was also higher than that in controls (12.3 [95% CI, 11.2-13.4] vs 10.5 [10.2-10.8] per 1000 person-years), giving an incidence rate difference of 1.7 (95% CI, 0.6-2.9; p=0.001; Table 4.1) and an unadjusted hazard

ratio of 1.16 (95% CI, 1.06-1.28; p=0.002). However, after adjustment for cardiovascular risk factors, the hazard ratio was no longer increased (adjusted HR, 0.95 [95% CI, 0.86-1.04]; p=0.27; Figure 4.1).

For cerebrovascular disease, the incidence rates for the study patients and controls were 10.4 (95% CI, 9.5-11.5) and 7.2 (7.0-7.5) per 1000 person-years, respectively. Although the incidence rate of cerebrovascular disease was lower than that of ischaemic heart disease, the incidence rate difference between the study patients and controls was higher (3.2 [95% CI, 2.2-4.2]; p<0.0001; Table 4.1), in line with the unadjusted hazard ratio of 1.44 (95% CI, 1.30-1.60; p<0.0001). After adjustment for cardiovascular risk factors, the hazard ratio remained significantly increased (adjusted HR, 1.27 [95% CI, 1.15-1.42]; p<0.0001; Figure 4.1).

Outcome	Study patients			Controls			Incidence rate difference per 1000 person-years (95% CI)	P
	No. 1st event	Person-years	Incidence per 1000 person-years (95% CI)	No. 1st event	Person-years	Incidence per 1000 person-years (95% CI)		
Adrenal insufficiency of any type (N= 6821 vs 67564)								
Composite cardiovascular disease	1146	36492	31.4 (29.6-33.3)	8953	366711	24.4 (23.9-24.9)	7.0 (5.1 to 8.9)	<0.0001
Ischaemic heart disease	475	38767	12.3 (11.2-13.4)	4058	386021	10.5 (10.2-10.8)	1.7 (0.6 to 2.9)	0.0010
Cerebrovascular disease	412	39470	10.4 (9.5-11.5)	2868	396533	7.2 (7.0-7.5)	3.2 (2.2 to 4.2)	<0.0001
Primary adrenal insufficiency (N= 2052 vs 20366)								
Composite cardiovascular disease	314	11738	26.8 (24.0-29.9)	2627	118657	22.1 (21.3-23.0)	4.6 (1.5 to 7.7)	0.0010
Ischaemic heart disease	141	12337	11.4 (9.7-13.5)	1233	124485	9.9 (9.4-10.5)	1.5 (-0.4 to 3.5)	0.055
Cerebrovascular disease	91	12691	7.2 (5.8-8.8)	854	128019	6.7 (6.2-7.1)	0.5 (-1.0 to 2.0)	0.25
Secondary adrenal insufficiency (N= 3948 vs 39134)								
Composite cardiovascular disease	693	21148	32.8 (30.4-35.3)	5176	209714	24.7 (24.0-25.4)	8.1 (5.6 to 10.6)	<0.0001
Ischaemic heart disease	271	22608	12.0 (10.6-13.5)	2352	220792	10.7 (10.2-11.1)	1.3 (-0.2 to 2.8)	0.034
Cerebrovascular disease	281	22851	12.3 (10.9-13.8)	1609	226977	7.1 (6.8-7.4)	5.2 (3.7 to 6.7)	<0.0001

Table 4.1: Incidence rates and hazard ratios of cardiovascular events in patients with adrenal insufficiency

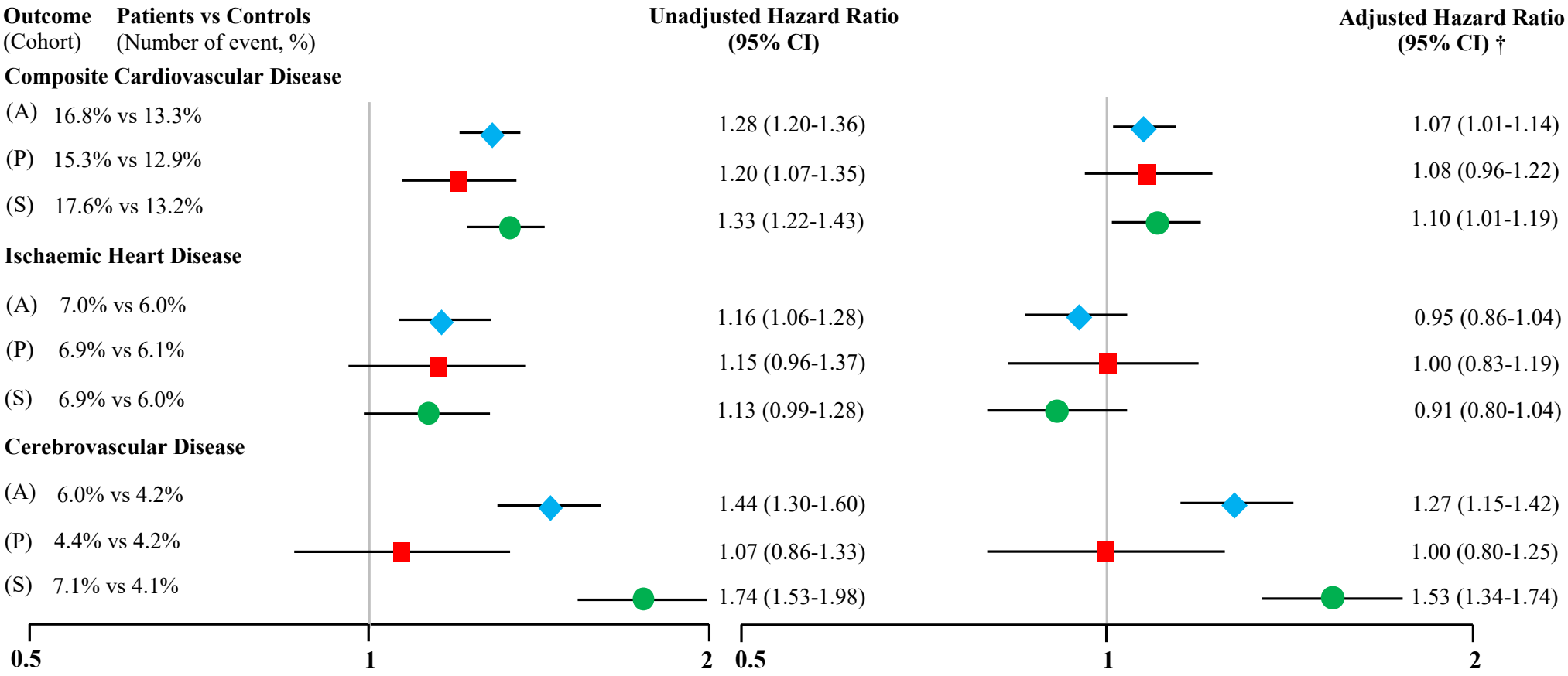


Figure 4.1: Unadjusted and adjusted hazard ratios of cardiovascular events in patients with adrenal insufficiency

Note: † Adjustment for previous cardiovascular disease, baseline diabetes mellitus, hypertension and dyslipidaemia, and smoking any time; (A)-Adrenal insufficiency of any type (N= 6821 vs 67564); (P)-Primary adrenal insufficiency (N= 2052 vs 20366); (S)-Secondary adrenal insufficiency (N= 3948 vs 39134)

❖ Primary adrenal insufficiency and controls

This analysis included 2052 patients with primary adrenal insufficiency and 20366 controls. For composite cardiovascular disease, the incidence rates for the study patients and controls were 26.8 (95% CI, 24.0-29.9) and 22.1 (21.3-23.0) per 1000 person-years with the follow-up period of 11738 and 118657 person-years, respectively (Table 4.1). Compared with the whole cohort of adrenal insufficiency of any type, the incidence rate difference was lower but remained significant (4.6 [95% CI, 1.5-7.7] per 1000 person-years, p=0.0010) and the unadjusted hazard ratio was 1.20 (95% CI, 1.07-1.35; p=0.0020). However, after adjustment for cardiovascular risk factors, the hazard ratio was no longer increased (adjusted HR 1.08, [95% CI, 0.96-1.22]; p=0.20; Figure 4.1).

For ischaemic heart disease, the incidence rate for the study patients was non-significantly higher than that in controls (11.4 [95% CI, 9.7-13.5] vs 9.9 [9.4-10.5 per 1000 person-years), giving an incidence rate difference of 1.5 (95% CI, -0.4 to 3.5 per 1000 person-years; p=0.055; Table 4.1) and a non-significant increase of the unadjusted hazard ratio (HR, 1.15 [95% CI, 0.96-1.37; p=0.12). After adjustment for cardiovascular risk factors, the hazard ratio was also not increased (adjusted HR, 1.00 [95% CI, 0.83-1.19]; p=0.96; Figure 4.1).

For cerebrovascular disease, the incidence rate for the study patients was similar to controls (7.2 [95% CI, 5.8-8.8] vs 6.7 [6.2-7.1] per 1000 person-years), giving an incidence rate difference of 0.5 (-1.0 to 2.0 per 1000 person-years; p=0.25; Table 4.1) and an unadjusted hazard ratio of 1.07 (95% CI, 0.86-1.33; p=0.52). After adjustment for cardiovascular risk factors, the hazard ratio remained non-significantly increased (adjusted HR, 1.00 [95% CI, 0.80-1.25]; p=0.99; Figure 4.1).

❖ Secondary adrenal insufficiency and controls

This analysis included 2052 patients with secondary adrenal insufficiency and 20366 controls. For composite cardiovascular disease, the incidence rate for the study patients was higher than that of controls (32.8 [95% CI, 30.4-35.3] vs 24.7 [24.0-25.4] per 1000 person-years), with follow-up periods of 21148 and 209714 person-years, respectively. Compared with primary adrenal insufficiency, the incidence rate difference was higher (8.1 [95% CI, 5.6-10.6] per 1000 person-years, p<0.0001; Table 4.1) and the unadjusted hazard ratio was 1.33 (95% CI, 1.22-1.43; p<0.0001). After adjustment for cardiovascular risk factors, the hazard ratio remained increased although only to a marginal extent (adjusted HR 1.10, [95% CI, 1.01-1.19]; p=0.025; Figure 4.1).

For ischaemic heart disease, similar to the finding in primary adrenal insufficiency, the incidence rate in the study patients was non-significantly higher than that in controls (12.0 [95% CI, 10.6-13.5] vs 10.7 [10.2-11.1] per 1000 person-years), giving an incidence rate difference of 1.3 (95% CI, -0.2 to 2.8 per 1000 person-years; p=0.034; Table 4.1) and a non-significant increase of the unadjusted hazard ratio (HR, 1.13 [95% CI, 0.99-1.28]; p=0.066). After adjustment for cardiovascular risk factors, the hazard ratio was also not increased (adjusted HR, 0.91 [95% CI, 0.80-1.04]; p=0.16; Figure 4.1).

For cerebrovascular disease, in contrast to the finding in primary adrenal insufficiency, the incidence rate for the study patients was significantly higher than that for controls (12.3 [95% CI, 10.9-13.8] vs 7.1 [6.8-7.4] per 1000 person-years), giving an increased incidence rate difference of 5.2 (95% CI, 3.7-6.7 per 1000 person-years; p<0.0001; Table 4.1) and an unadjusted hazard ratio of 1.74 (95% CI, 1.53-1.98; p<0.0001). After adjustment for cardiovascular risk factors, the hazard ratio remained significantly increased (adjusted HR, 1.53 [95% CI, 1.34-1.74]; p<0.0001; Figure 4.1).

It was noted that in patients with secondary adrenal insufficiency, the incidence rate of cerebrovascular disease was higher than the incidence rate of ischaemic heart disease. This was in contrast to the findings in controls, adrenal insufficiency of any type, and primary adrenal insufficiency (Table 4.1)

- ❖ Unspecified adrenal insufficiency and controls

This analysis included 821 patients with unspecified adrenal insufficiency and 8064 controls. For composite cardiovascular disease, the incidence rate for the study patients was higher than that for controls (38.5 [95% CI, 32.6-45.5] vs 30.0 [28.3-31.8] per 1000 person-years with follow-up periods of 3607 and 38340 person-years, respectively. The incidence rate difference was increased (8.5 [95% CI, 1.9-15.2] per 1000 person-years, p=0.0033) and the unadjusted hazard ratio was also increased (1.26 [95% CI, 1.05-1.50]; p=0.011). After adjustment for cardiovascular risk factors, the hazard ratio was no longer increased (adjusted HR 0.98, [95% CI, 0.81-1.17]; p=0.80; Suppl. Table 4.1).

For ischaemic heart disease, the incidence rate in the study patients was higher than that in controls (16.5 [95% CI, 12.9-21.1] vs 11.6 [10.6-12.7 per 1000 person-years), giving an increased incidence rate difference of 4.9 (95% CI, 0.7-9.1 per 1000 person-years; p=0.0060) and an unadjusted hazard ratio of 1.39 (95% CI, 1.07-1.81; p=0.014). However, after adjustment for cardiovascular risk factors, the hazard ratio was no longer increased (adjusted HR, 1.07 [95% CI, 0.81-1.40]; p=0.63; Suppl. Table 4.1).

For cerebrovascular disease, in contrast to the finding in primary adrenal insufficiency, the incidence rate for the study patients was similar to that of controls (10.2 [95% CI, 7.5-13.9] vs 9.8 [8.8-10.7] per 1000 person-years), giving an incidence rate difference of 0.4 (95% CI, -2.9 to 3.7 per 1000 person-years; p=0.38) and an unadjusted hazard ratio of 1.03 (95% CI, 0.74-1.42; p=0.87). After adjustment for cardiovascular risk factors, the hazard ratio was also not increased (Suppl. Table 4.1).

❖ Primary and secondary adrenal insufficiency

This analysis compared cardiovascular events between patients with primary and secondary adrenal insufficiency. Sex and age were not primarily matched between patients with primary and secondary adrenal insufficiency, and the proportions of patients having previous cardiovascular disease, diabetes mellitus, hypertension, and dyslipidaemia at baseline were different between those with primary and secondary adrenal insufficiency (See Chapter3; Table 3.3 and 3.4). Therefore, these characteristics were taken into account in multivariable analyses. For composite cardiovascular disease, the incidence rate for patients with primary adrenal insufficiency was slightly lower than for those with secondary adrenal insufficiency, giving an incidence rate difference of -0.6 (95% CI, -9.9 to -2.2) per 1000 person-years (p=0.00013) and an unadjusted hazard ratio of 0.83 (95% CI, 0.73-0.95; p=0.00070). After adjustment for sex and age at diagnosis of adrenal insufficiency, the hazard ratio for patients with primary adrenal insufficiency relative to secondary was no longer decreased (adjusted HR, 0.91 [95% CI, 0.80-1.05]; p=0.19). Also, after adjustment for previous cardiovascular disease, diabetes, hypertension and dyslipidaemia at diagnosis of adrenal insufficiency, and ever smoking, the hazard ratio remained non-significantly decreased (adjusted HR, 0.95 [95% CI, 0.83-1.08]; p=0.42; Table 4.2).

For ischaemic heart disease, the incidence rate for patients with primary adrenal insufficiency was not different from those with secondary disease with an incidence rate difference of -0.6 (95% CI, -2.9 to 1.8) per 1000 person-years (p=0.32). This was consistent with the unadjusted hazard ratio of primary relative to secondary adrenal insufficiency (HR, 0.98 [95% CI, 0.80-1.20]; p=0.83). After adjustment for sex and age of diagnosis, the hazard ratio became slightly increased but remained non-significant (adjusted HR, 1.10 [95% CI, 0.90-1.35]; p=0.36). Also, after adjustment for cardiovascular risk factors at the diagnosis of adrenal insufficiency and

ever smoking, the hazard ratio remained virtually unchanged (adjusted HR, 1.13 [95% CI, 0.92-1.39]; p=0.24; Table 4.2).

For cerebrovascular disease, the incidence rate for patients with primary adrenal insufficiency was markedly lower than in those with secondary disease, giving an incidence rate difference of -5.1 (95% CI, -7.2 to -3.1) per 1000 person-years (p<0.0001). The unadjusted hazard ratio of patients with primary adrenal insufficiency relative to those with secondary disease was also decreased (HR, 0.59 [95% CI, 0.47-0.75]; p<0.0001). After adjustment for sex and age at diagnosis, the hazard ratio was similarly decreased (adjusted HR, 0.62 [95% CI, 0.49-0.79]; p<0.0001). Also, after adjustment for cardiovascular risk factors at the diagnosis of adrenal insufficiency and ever smoking, the hazard ratio remained decreased (adjusted HR, 0.65 [95% CI, 0.51-0.82]; p<0.0001; Table 4.2).

It should be noted that baseline cardiovascular risk factors used for the adjustment in the cardiovascular disease risk evaluation were entered as binary covariables and the severity and control of these risk factors were not taken into account. This might have confounded the risk evaluation. However, data for this study derived from routine clinical care and, consequently, recording of blood pressure, glucose and lipid levels of each participant varied depending on the number of medical encounters and patients' past medical history. It was likely, therefore, that the study patients would have had a higher number of such variables recorded than healthy controls. Therefore, full accounting for 'controllable' cardiovascular risk factors was difficult and might have confounded the risk evaluation.

Outcomes	Composite cardiovascular disease			Ischaemic heart disease			Cerebrovascular disease		
Models	HR	95% CI	P	HR	95%CI	P	HR	95%CI	P
Univariable analysis (Unadjusted)	0.83	0.73-0.95	0.0070	0.98	0.80-1.20	0.83	0.59	0.47-0.75	<0.0001
Adjustment for sex, age in years at start of follow-up	0.90	0.78-1.03	0.11	1.08	0.88-1.33	0.45	0.61	0.48-0.77	<0.0001
Adjustment for sex, age in years at diagnosis	0.91	0.80-1.05	0.19	1.10	0.90-1.35	0.36	0.62	0.49-0.79	<0.0001
Adjustment for previous cardiovascular disease, diabetes, hypertension, dyslipidaemia at start of follow-up, and smoking any time	0.96	0.84-1.10	0.58	1.15	0.94-1.42	0.17	0.65	0.51-0.83	<0.0001
Adjustment for previous cardiovascular disease, diabetes, hypertension, dyslipidaemia at diagnosis, and smoking any time	0.95	0.83-1.08	0.42	1.13	0.92-1.39	0.24	0.65	0.51-0.82	<0.0001
Adjustment for sex, age at start of follow-up, previous cardiovascular disease, diabetes, hypertension, dyslipidaemia at start of follow-up, and smoking any time	0.93	0.81-1.06	0.26	1.13	0.92-1.39	0.25	0.62	0.48-0.78	<0.0001
Adjustment for sex, age at diagnosis, previous cardiovascular disease, diabetes, hypertension, dyslipidaemia at diagnosis, and smoking any time	0.92	0.81-1.06	0.24	1.12	0.91-1.38	0.28	0.62	0.49-0.78	<0.0001

Table 4.2: Unadjusted and adjusted hazard ratios of cardiovascular events in patients with primary adrenal insufficiency, relative to secondary adrenal insufficiency

In summary, in patients with adrenal insufficiency of any type, the risk of cardiovascular events relative to controls was increased. However, after baseline cardiovascular risk factors were considered, the risk for ischaemic heart disease was no longer increased whereas the risk for cerebrovascular disease remained significantly increased.

In patients with primary adrenal insufficiency, the risk for composite cardiovascular disease was increased, with the risk for ischaemic heart disease but not cerebrovascular disease appearing to be increased. Similar to the finding in the whole cohort, after baseline cardiovascular risk factors were considered, the risk for composite cardiovascular disease was no longer increased.

In patients with secondary adrenal insufficiency, the risks for composite cardiovascular disease and cerebrovascular disease were increased. Moreover, after cardiovascular risk factors were considered, the risks remained significantly increased. However, the risk for ischaemic heart disease was not increased whether or not cardiovascular risk factors were taken into account.

In a comparison between primary and secondary adrenal insufficiency, the risks for composite cardiovascular disease and ischaemic heart disease were similar. However, the risk for cerebrovascular disease was higher in those with secondary adrenal insufficiency than primary disease.

4.1.2 Incidence rates and hazard ratios for risk of composite cardiovascular, ischaemic heart disease and cerebrovascular events associated with adrenal insufficiency, categorised by earlier and recent calendar years

In this analysis, the participants were divided into two equal sized groups according to the calendar year in which they received clinical care: previous care (before 1st July 2007) and

recent care (on or after 1st July 2007). Similar to the analysis of all participants, incidence rates and hazard ratios for cardiovascular events were examined. The hazard ratios were also adjusted for 'cardiovascular risk factors', consisting of previous cardiovascular disease, baseline diabetes mellitus, hypertension and dyslipidaemia at the start of follow-up, and ever smoking at any time

- Adrenal insufficiency of any type and matched controls

There were 3455 study patients and 34214 controls receiving previous care whereas in recent care there were 3366 patients and 33350 controls. For composite cardiovascular disease in those with previous care, the incidence rate of the study patients was higher than that of controls (30.9 [95% CI, 28.9-33.2] vs 23.6 [23.0-24.2] per 1000 person-years) with follow-up periods of 26176 and 268998 person-years, respectively, giving an incidence rate difference of 7.3 (95% CI, 5.1-9.5) per 1000 person-years ($p<0.0001$; Suppl. Table 4.2). The unadjusted hazard ratio was slightly increased (HR, 1.30 [95%CI, 1.21-1.40]; $p<0.0001$). After adjustment for cardiovascular risk factors, the hazard ratio was diminished but remained significant (adjusted HR, 1.11 [95%CI, 1.30-1.20]; $p=0.0060$). In those with recent care, the incidence rate of composite cardiovascular disease in the study patients was also higher than that of controls (32.6 [95% CI, 29.3-36.2] vs 26.6 [25.6-27.7] per 1000 person-years) with follow-up periods of 10316 and 33350 person-years, respectively, giving an incidence rate difference of 6.0 (95% CI, 2.3-9.6) per 1000 person-years ($p<0.0001$). The unadjusted hazard ratio was increased (HR, 1.24 [95% CI, 1.11-1.39]; $p<0.0001$) but after adjustment for cardiovascular risk factors, it was no longer significantly increased (adjusted HR, 0.94 [95% CI, 0.83-1.06]; $p=0.28$); Table 4.3)

For ischaemic heart disease in participants with previous care, the incidence rate for the study patients was slightly higher than that of controls (12.5 [95% CI, 11.2-13.8] vs 10.7 [10.3-11.1]) per 1000 person-years, giving an incidence rate difference of 1.8 (95% CI, 0.4-3.1) per 1000

person-years (p=0.0038; Suppl. Table 4.2). The unadjusted hazard ratio was also slightly increased (HR, 1.16 [95% CI, 1.03-1.29]; p=0.011) but after adjustment for cardiovascular risk factors, it was not significantly increased (adjusted HR, 0.94 [95% CI, 0.84-1.05]; p=28). In those with recent care, the incidence rate for the study patients was also slightly higher than controls (11.7 [95% CI, 9.8-13.9] vs 10.0 [9.4-10.6]) per 1000 person-years, giving an incidence rate difference of 1.7 (95% CI, -0.4 to 3.8) per 1000 person-years (p=0.051). The unadjusted hazard ratio was not significantly increased (HR, 1.19 [95%CI, 0.99-1.43]; p=0.063) and after adjustment, it remained not increased (adjusted HR, 0.91 [95% CI, 0.75-1.11]; p=0.34). The hazard ratio for ischaemic heart disease of the patients receiving recent care was not statistically different from that observed in those with previous care (p for interaction=0.69; Table 4.3).

For cerebrovascular disease in participants with previous care the incidence rate for the study patients was higher than that of controls (10.5 [95% CI, 9.4-11.8] vs 7.2 [6.9-75] per 1000 person-years), giving an incidence rate difference of 3.3 (95% CI, 2.1-4.6) per 1000 person-years (p<0.0001; Suppl. Table 4.2). The hazard ratio was increased (HR, 1.46 [95% CI, 1.29-1.65]; p<0.0001) and after adjustment, it remained increased (adjusted HR, 1.31 [95% CI, 1.16-1.48]; p<0.0001). In those with recent care, the incidence rate of cerebrovascular disease in the study patients was also higher than controls (10.2 [95% CI, 8.5-12.3] vs 7.3 [6.8-7.9] per 1000 person-years), giving an incidence rate difference of 2.9 (95%CI, 0.9-4.8) per 1000 person-years (p=0.0010) and an unadjusted hazard ratio of 1.41 (95% CI, 1.15-1.72; p=0.0010). After adjustment for cardiovascular risk factors, the hazard ratio was reduced and ceased to be significant (adjusted HR, 1.11 [95% CI, 0.90-1.37]; p=0.33). However, the adjusted hazard ratio of those with recent care was not statistically different from those with previous care (p=0.60; Table 4.3).

Outcome	Unadjusted HR (95% CI)				Adjusted HR (95% CI)				P for interaction
	Previous (<01/07/2007)	p	Recent (≥01/07/2007)	p	Previous (<01/07/2007)	p	Recent (≥01/07/2007)	p	
Adrenal insufficiency of any type									
Composite cardiovascular disease	1.30 (1.12-1.40)	<0.0001	1.24 (1.11-1.39)	<0.0001	1.11 (1.03-1.20)	0.0060	0.94 (0.83-1.06)	0.28	0.076
Ischaemic heart disease	1.16 (1.03-1.29)	0.011	1.19 (0.99-1.43)	0.063	0.94 (0.84-1.05)	0.28	0.91 (0.75-1.11)	0.34	0.69
Cerebrovascular disease	1.46 (1.29-1.65)	<0.0001	1.41 (1.15-1.72)	0.0010	1.31 (1.16-1.48)	<0.0001	1.11 (0.90-1.37)	0.33	0.60
Primary adrenal insufficiency									
Composite cardiovascular disease	1.18 (1.03-1.35)	0.018	1.28 (1.02-1.61)	0.035	1.05 (0.91-1.21)	0.49	1.05 (0.83-1.34)	0.68	0.86
Ischaemic heart disease	1.10 (0.90-1.34)	0.34	1.34 (0.93-1.91)	0.11	0.95 (0.78-1.16)	0.61	1.04 (0.72-1.51)	0.83	0.64
Cerebrovascular disease	0.99 (0.77-1.28)	0.96	1.34 (0.89-2.02)	0.15	0.90 (0.69-1.16)	0.40	1.18 (0.77-1.82)	0.43	0.19
Secondary adrenal insufficiency									
Composite cardiovascular disease	1.37 (1.25-1.51)	<0.0001	1.23 (1.07-1.43)	0.0050	1.16 (1.05-1.28)	0.0020	0.94 (0.80-1.09)	0.39	0.085
Ischaemic heart disease	1.16 (1.00-1.34)	0.050	1.06 (0.83-1.36)	0.62	0.93 (0.80-1.07)	0.31	0.84 (0.65-1.09)	0.19	0.42
Cerebrovascular disease	1.81 (1.56-2.10)	<0.0001	1.58 (1.22-2.03)	<0.0001	1.64 (1.42-1.91)	<0.0001	1.19 (0.91-1.56)	0.19	0.27

Table 4.3: Hazard ratios of cardiovascular events in patients with adrenal insufficiency, according to calendar years of clinical care

Note: † Adjustment for previous cardiovascular disease, baseline diabetes mellitus, hypertension and dyslipidaemia, and smoking any time; N for earlier care, All adrenal insufficiency= 3455 vs 34214, Primary= 1137 vs 11189, Secondary= 1962 vs 19495; N for Recent care, All =3366 vs 33350, Primary= 915 vs 9177, Secondary= 1986 vs 19639

❖ Primary adrenal insufficiency and matched controls

There were 1137 study patients with primary adrenal insufficiency and 11189 controls receiving previous care whereas in recent care there were 915 patients and 9177 controls. For composite cardiovascular disease in those with previous care, the incidence rate for the study patients was slightly higher than that of controls (25.7 [95% CI, 22.7-29.2] vs 21.6 [20.7-22.6] per 1000 person-years) with follow-up periods of 9042 and 91980 person-years, respectively, giving an incidence rate difference of 4.0 (95% CI, 0.6-7.4) per 1000 person-years (p=0.0081; Suppl. Table 4.3). The unadjusted hazard ratio was slightly increased (HR, 1.18 [95%CI, 1.03-1.35]; p=0.018). After adjustment for cardiovascular risk factors, the hazard ratio was no longer increased (adjusted HR, 1.05 [95%CI, 0.91-1.21]; p=0.49). In those with recent care, the incidence rate of composite cardiovascular disease in the study patients with primary adrenal insufficiency was also higher than that of controls (30.4 [95% CI, 24.5-37.8] vs 23.8 [22.1-25.8] per 1000 person-years) with follow-up periods of 2696 and 26677 person-years, respectively, giving an incidence rate difference of 6.6 (95% CI, -0.3 to 13.4) per 1000 person-years (p=0.021). The unadjusted hazard ratio was slightly increased (HR, 1.28 [95% CI, 1.02-1.61]; p=0.035). After adjustment for cardiovascular risk factors, it was no longer increased (adjusted HR, 1.05 [95% CI, 0.83-1.34]; p=0.86) and it was similar to the hazard ratio observed in the patients who had received previous care (p for interaction=0.86; Table 4.3).

For ischaemic heart disease in participants receiving previous care, the incidence rate of the study patients was similar to that of controls (11.2 [95% CI, 9.3-13.6] vs 10.1 [9.5-10.8] per 1000 person-years), giving a non-significant incidence rate difference (p=0.15; Suppl. Table 4.3) and an unadjusted hazard ratio of 0.95 (95%CI, 0.78-1.16; p=0.34). After adjustment for cardiovascular risk factors, it remained non-significantly increased (adjusted HR, 0.95 [95% CI, 0.78-1.16]; p=0.61). In those with recent care, the incidence rate for patients with primary

adrenal insufficiency was slightly higher than that of controls (12.1 [95% CI, 8.6-16.9] vs 9.1 [8.1-10.3]) per 1000 person-years, giving an incidence rate difference of 3.0 (95% CI, -1.3 to 7.2) per 1000 person-years (p=0.066). The unadjusted hazard ratio was not significantly increased (HR, 1.34 [95% CI, 0.93-1.91]; p=0.11) and after adjustment, it remained not significantly increased (adjusted HR, 1.04 [95% CI, 0.72-1.51]; p=0.83). The hazard ratio of primary adrenal insufficiency on ischaemic heart disease in those with recent care was not different from that in those receiving previous care (p for interaction=0.64; Table 4.3).

For cerebrovascular disease in participants receiving previous care, the incidence rate of the study patients was similar to that of controls (6.6 [95% CI, 5.2-8.4] vs 6.6 [6.1-7.1]) per 1000 person-years, giving a non-significant incidence rate difference (p=0.49; Suppl. Table 4.3). The unadjusted and adjusted hazard ratios (95% CI) were 0.99 (0.77-1.28; p=0.96) and 0.90 (0.69-1.16; p=0.40), respectively. In those with recent care, the incidence rate of cerebrovascular disease in the study patients was higher than that in controls (9.2 [95% CI, 6.3-13.5] vs 6.9 [6.0-7.9] per 1000 person-years; however, the incidence rate was not significantly different (2.3 [-1.3 to 6.0] per 1000 person-years; p=0.086). The unadjusted hazard ratio was also not significantly increased (HR, 1.34 [95% CI, 0.89-2.02]; p=0.15) and after adjustment for cardiovascular risk factors, it remained not increased (adjusted HR, 1.18 [0.77-1.82]; p=0.43). The hazard ratio of primary adrenal insufficiency on cerebrovascular disease was not statistically different whether the patients received previous or recent care (p for interaction= 0.19; Table 4.3).

❖ Secondary adrenal insufficiency and matched controls

There were 1962 study patients with secondary adrenal insufficiency and 19495 controls receiving previous care whereas in recent care there were 1986 patients and 19639 controls. For composite cardiovascular disease in those with previous care, the incidence rate for the study patients was higher than that for controls (33.3 [95% CI, 30.5-36.4] vs 24.1 [23.3-24.9] per 1000 person-years) with follow-up periods of 14720 and 150595 person-years, respectively, giving an incidence rate difference of 9.2 (95% CI, 6.2-12.3) per 1000 person-years ($p<0.0001$; Suppl. Table 4.4). The unadjusted hazard ratio was also increased (HR, 1.37 [95%CI, 1.25-1.51]; $p<0.0001$). After adjustment for cardiovascular risk factors, the hazard ratio was reduced but remained significantly increased (adjusted HR, 1.16 [95%CI, 1.05-1.28]; $p=0.0020$). In those with recent care, the incidence rate of composite cardiovascular disease in the study patients with secondary adrenal insufficiency was also higher than that of controls (31.6 [95% CI, 27.5-36.2] vs 26.2 [24.9-27.6] per 1000 person-years) with follow-up periods of 6228 and 59120 person-years, respectively, giving an incidence rate difference of 5.4 (95% CI, 0.8-9.9) per 1000 person-years ($p=0.0073$). The unadjusted hazard ratio was slightly increased (HR, 1.23 [95% CI, 1.07-1.43]; $p=0.0050$). After adjustment for cardiovascular risk factors, it was no longer increased (adjusted HR, 0.94 [95% CI, 0.80-1.09]; $p=0.39$). However, the hazard ratio of secondary adrenal insufficiency on composite cardiovascular disease in those with recent care was similar to that in previous care (p for interaction=0.085; Table 4.3).

For ischaemic heart disease in participants receiving previous care, the incidence rate for the study patients was slightly higher than that for controls (12.7 [95% CI, 11.0-14.5] vs 10.9 [10.4-11.4] per 1000 person-years), giving an incidence rate difference of 1.8 (-0.0 to 3.6) per 1000 person-years ($p=0.021$; Suppl. Table 4.4) and an unadjusted hazard ratio of 1.16 (95%CI, 1.00-1.34; $p=0.050$). After adjustment for cardiovascular risk factors, it remained not significantly

increased (adjusted HR, 0.93 [95% CI, 0.80-1.07]; p=0.31). In those with recent care, the incidence rate for ischaemic heart disease in the study patients with secondary adrenal insufficiency was similar to that in controls (10.4 [95% CI, 8.2-13.1] vs 10.1 [9.3-10.9]) per 1000 person-years, giving a non-significant incidence rate difference (p=0.40). The unadjusted hazard ratio was also not significantly increased (HR, 1.06 [95% CI, 0.83-1.36]; p=0.62) and after adjustment, it remained not increased (adjusted HR, 0.84 [95% CI, 0.65-1.09]; p=0.19). The hazard ratio of secondary adrenal insufficiency on ischaemic heart disease in those with recent care was not different from that in those receiving previous care (p for interaction=0.42; Table 4.3).

For cerebrovascular disease in participants receiving previous care, the incidence rate for the study patients was significantly higher than that for controls (13.1 [95% CI, 11.4-15.0] vs 7.2 [6.8-7.6]) per 1000 person-years, giving an incidence rate difference of 5.9 (95% CI, 4.0-7.7) per 1000 person-years (p<0.0001; Suppl. Table 4.4). The unadjusted hazard ratio was also significantly increased (HR, 1.81 [95% CI, 1.56-2.10]; p<0.0001) and after adjustment for cardiovascular risk factor, it remained significant (adjusted HR, 1.64, [95% CI, 1.42-1.91]; p<0.0001). In those with recent care, the incidence rate of cerebrovascular disease in the study patients was also higher than that in controls (10.4 [95% CI, 8.2-13.2] vs 6.7 [6.1-7.4] per 1000 person-years, giving an incidence rate difference of 3.7 (95% CI, 1.2-6.2) per 1000 person-years (p=0.0006). The unadjusted hazard ratio was also increased (HR, 1.58 [95% CI, 1.22-2.03]; p<0.0001). However, after adjustment for cardiovascular risk factors, it ceased to be significantly increased (adjusted HR, 1.19 [0.91-1.56]; p=0.19). The hazard ratio of secondary adrenal insufficiency on cerebrovascular disease in those with recent care was not statistically different from in those receiving previous care (p for interaction= 0.27; Table 4.3).

In summary, the risk of cardiovascular events including ischaemic heart disease and cerebrovascular disease in patients with adrenal insufficiency of any type was similar whether the patients had started receiving clinical care before or after mid-2007. This was also the case in patients with primary or secondary adrenal insufficiency considered separately.

4.2 Cardiovascular events stratified by sex, age, and comorbidity at baseline

This analysis compared the incidence rate of cardiovascular events for the study patients with that of controls according to sex, age, pre-existing diabetes mellitus and cardiovascular disease, and the use of statins. Similar to Section 4.1, cardiovascular events included fatal and non-fatal events first recorded in CPRD during the follow-up period. The outcomes consisted of composite cardiovascular disease, ischaemic heart disease, and cerebrovascular disease. Hazard ratios were adjusted for 'cardiovascular risk factors', consisting of previous cardiovascular disease, diabetes mellitus, hypertension and dyslipidaemia at baseline, and ever smoking at any time. Additional adjustments for sex and age at the start of follow-up were performed in multivariable Cox regression analysis stratified by comorbidity.

4.2.1 Incidence rates and hazard ratios for risk of cardiovascular events associated with adrenal insufficiency, categorised by men and women

Full results for incidence rates and incidence rate differences of cardiovascular events in patients with adrenal insufficiency of any kind, primary and secondary adrenal insufficiency, and their matched controls, categorised by sex are shown in the Appendix (Suppl. Table 4.5, 4.6 and 4.7). Unadjusted and adjusted hazard ratios for risk of cardiovascular events categorised by sex are shown here in Table 4.4.

Outcome	Unadjusted HR (95% CI)				Adjusted HR (95% CI) †				P for interaction
	Men	p	Women	p	Men	p	Women	p	
Adrenal insufficiency of any type									
Composite cardiovascular disease	1.18 (1.09-1.28)	<0.0001	1.41 (1.29-1.55)	<0.0001	1.02 (0.94-1.12)	0.57	1.14 (1.04-1.25)	0.0050	**0.0030**
Ischaemic heart disease	1.07 (0.95-1.22)	0.26	1.30 (1.12-1.51)	<0.0001	0.92 (0.81-1.05)	0.22	1.00 (0.86-1.16)	0.97	0.078
Cerebrovascular disease	1.36 (1.17-1.58)	<0.0001	1.53 (1.32-1.76)	<0.0001	1.24 (1.06-1.44)	0.0060	1.31 (1.13-1.52)	<0.0001	0.32
Primary adrenal insufficiency									
Composite cardiovascular disease	1.15 (0.97-1.36)	0.11	1.25 (1.07-1.47)	0.0060	1.02 (0.86-1.22)	0.78	1.11 (0.94-1.31)	0.20	0.21
Ischaemic heart disease	1.03 (0.80-1.32)	0.82	1.28 (1.01-1.64)	0.045	0.90 (0.70-1.16)	0.40	1.09 (0.85-1.40)	0.48	0.17
Cerebrovascular disease	1.01 (0.72-1.43)	0.93	1.12 (0.84-1.47)	0.44	0.95 (0.67-1.34)	0.75	1.04 (0.78-1.38)	0.78	0.57
Secondary adrenal insufficiency									
Composite cardiovascular disease	1.21 (1.09-1.34)	<0.0001	1.53 (1.36-1.74)	<0.0001	1.06 (0.96-1.18)	0.25	1.18 (1.04-1.35)	0.010	**0.016**
Ischaemic heart disease	1.08 (0.92-1.26)	0.33	1.22 (0.99-1.52)	0.066	0.95 (0.81-1.11)	0.49	0.89 (0.71-1.11)	0.28	0.62
Cerebrovascular disease	1.55 (1.31-1.85)	<0.0001	2.01 (1.67-2.41)	<0.0001	1.41 (1.18-1.69)	<0.0001	1.68 (1.39-2.04)	<0.0001	0.097

Table 4.4: Hazard ratios of cardiovascular events in patients with adrenal insufficiency, according to sex

Note: † Adjustment for previous cardiovascular disease, baseline diabetes mellitus, hypertension and dyslipidaemia, and smoking any time; N for male cohorts, All adrenal insufficiency= 3173 vs 31283, Primary= 860 vs 8483, Secondary= 1971 vs 19474; N for female cohorts, All =3648 vs 36281, Primary= 1192 vs 11883, Secondary= 1977 vs 19660

In Table 4.4, the hazard ratio for risk of composite cardiovascular events associated with adrenal insufficiency was significantly higher in women, compared with men, although this was only applicable to patients with adrenal insufficiency of any kind or with secondary adrenal insufficiency (p for interaction = 0.0030 and 0.016, respectively), whereas for those with primary disease, it was not significantly different (p for interaction= 0.21). The hazard ratios for risk of incident ischaemic heart disease and cerebrovascular disease associated with adrenal insufficiency of any type were not significantly different between men and women (p for interaction =0.078 and 0.32, respectively). Neither were they significantly different observed in primary adrenal insufficiency (p for interaction =0.17 and 0.57, respectively) nor in secondary adrenal insufficiency (p for interaction =0.62 and 0.097, respectively).

In summary, in patients with adrenal insufficiency of any type and secondary adrenal insufficiency, the risk of composite cardiovascular disease appeared to be higher in women. However, the risk of ischaemic heart disease or cerebrovascular disease separately was not different between the sexes. In patients with primary adrenal insufficiency, there was no sex difference in the risk for any cardiovascular events.

The higher risk of composite cardiovascular disease in women than men was observed only in patients with secondary adrenal insufficiency. This might have resulted from the contribution of concomitant female hypogonadotropic hypogonadism and oestrogen replacement therapy. However, as the biochemical tests were not available in this study, it was not feasible to distinguish those with hypogonadotropic hypogonadism from those using oestrogen for menopause, so that it was beyond the scope of extrapolation in this study.

4.2.2 Incidence rates and hazard ratios for risk of cardiovascular events associated with adrenal insufficiency, categorised by younger and older age

Full results for incidence rates and incidence rate differences of cardiovascular events in patients with adrenal insufficiency of any kind, primary and secondary adrenal insufficiency, and their matched controls, categorised by whether the participants were at younger (<50 y) or older age (≥50 y) at the start of follow-up are shown in the Appendix (Suppl. Tables 4.8, 4.9 and 4.10). Unadjusted and adjusted hazard ratios for risk of cardiovascular events, categorised by age at the start of follow-up, are shown here in Table 4.5.

Outcome	Unadjusted HR (95% CI)				Adjusted HR (95% CI) †				P for interaction
	Age <50	p	Age ≥50	p	Age <50	p	Age ≥50	p	
Adrenal insufficiency of any type									
Composite cardiovascular disease	1.95 (1.61-2.35)	<0.0001	1.27 (1.19-1.36)	<0.0001	1.49 (1.22-1.81)	<0.0001	1.12 (1.04-1.19)	0.0010	**<0.0001**
Ischaemic heart disease	1.38 (1.01-1.87)	0.040	1.17 (1.06-1.30)	0.0020	0.97 (0.70-1.33)	0.84	1.00 (0.90-1.10)	0.95	0.098
Cerebrovascular disease	3.02 (2.25-4.06)	<0.0001	1.38 (1.24-1.55)	<0.0001	2.77 (2.05-3.76)	<0.0001	1.27 (1.13-1.42)	<0.0001	**<0.0001**
Primary adrenal insufficiency									
Composite cardiovascular disease	1.66 (1.18-2.32)	0.0030	1.22 (1.08-1.39)	0.0020	1.23 (0.86-1.77)	0.26	1.13 (0.99-1.28)	0.061	0.051
Ischaemic heart disease	1.54 (0.96-2.47)	0.072	1.15 (0.96-1.39)	0.13	1.10 (0.66-1.83)	0.71	1.02 (0.84-1.23)	0.86	0.14
Cerebrovascular disease	1.72 (0.87-3.37)	0.11	1.09 (0.87-1.37)	0.45	1.73 (0.87-3.46)	0.12	1.03 (0.82-1.30)	0.77	0.18
Secondary adrenal insufficiency									
Composite cardiovascular disease	2.07 (1.62-2.64)	<0.0001	1.30 (1.20-1.42)	<0.0001	1.58 (1.22-2.03)	<0.0001	1.14 (1.04-1.24)	0.0030	**<0.0001**
Ischaemic heart disease	1.03 (0.65-1.63)	0.90	1.16 (1.02-1.32)	0.028	0.71 (0.44-1.15)	0.16	0.99 (0.86-1.13)	0.84	0.95
Cerebrovascular disease	3.90 (2.79-5.46)	<0.0001	1.62 (1.41-1.85)	<0.0001	3.67 (2.60-5.17)	<0.0001	1.48 (1.28-1.71)	<0.0001	**<0.0001**

Table 4.5: Hazard ratios of cardiovascular events in patients with adrenal insufficiency, according to age at the start of follow-up

Note: † Adjustment for previous cardiovascular disease, baseline diabetes mellitus, hypertension and dyslipidaemia, and smoking any time; N for younger cohorts, All adrenal insufficiency= 2930 vs 29407, Primary= 960 vs 9602, Secondary= 1673 vs 16833; N for older cohorts, All =3891 vs 38157, Primary= 1092 vs 10764, Secondary= 2275 vs 22301

In Table 4.5, the hazard ratios for risk of composite cardiovascular events and cerebrovascular events associated with adrenal insufficiency of any type were significantly higher in those younger age, compared with older individuals (p for interaction<0.0001 and <0.0001, respectively), and this was also applicable to patients with secondary adrenal insufficiency, with the same p-values. In those with primary adrenal insufficiency, the hazard ratios for risk of composite cardiovascular events and cerebrovascular events were not significantly different between younger and older patients (p for interaction= 0.051 and 0.18, respectively). The hazard ratio for risk of ischaemic heart disease events associated with adrenal insufficiency was not significantly different according to age (p for interaction =0.098). Neither was it significantly different in primary adrenal insufficiency (p for interaction =0.14) nor in secondary adrenal insufficiency (p for interaction =0.95) considered separately.

In summary, in patients with adrenal insufficiency of any type or secondary adrenal insufficiency, the risk for composite cardiovascular disease and cerebrovascular disease relative to controls was increased in both younger and older individuals but the magnitude of this increase was significantly higher in younger individuals. The risk for ischaemic heart disease was not different according to age. In patients with primary adrenal insufficiency, the risk for cardiovascular events of any kind was also not different according to age.

4.2.3 Incidence rates and hazard ratios for risk of cardiovascular events associated with adrenal insufficiency, categorised by non-diabetes and diabetes at baseline

In this analysis, the participants were classified into two groups depending on whether or not they had co-morbid diabetes mellitus at the start of follow-up (diabetes and non-diabetes groups). The incidence rate of cardiovascular events for the study patients was compared with that for controls within the same diabetes group. While sex and age were closely matched, cardiovascular risk factors (including diabetes at baseline) of the study patients were not matched with controls. Therefore, in the group of participants with the same diabetes status, the proportions of sex and baseline cardiovascular risk factors, and age at the start of follow-up in the study patients were different from those in controls (details shown in the Appendix, Suppl. Table 4.11). Age, sex, and cardiovascular risk factors at the start of follow-up were used to adjust in multivariable Cox regression analysis.

Full results for incidence rates and incidence rate differences of cardiovascular events in patients with adrenal insufficiency of any kind, primary and secondary adrenal insufficiency, and their matched controls, according to diabetes status are shown in the Appendix (Suppl. Tables 4.12, 4.13 and 4.14). It was noted that among those with diabetes, the incidence rate of cardiovascular events in controls was higher than that in the study patients. This was likely due to controls having older age and the higher proportions of men, previous cardiovascular disease and hypertension, compared with the study patients in the diabetes group (Suppl. Table 4.11).

Unadjusted and adjusted hazard ratios for risk of cardiovascular events, categorised by diabetes status, are shown here in Table 4.6.

Outcome	Unadjusted HR (95% CI)				Adjusted HR (95% CI) †				P for interaction
	Non-diabetes	p	Diabetes	p	Non-diabetes	p	Diabetes	p	
Adrenal insufficiency of any type									
Composite cardiovascular disease	1.27 (1.19-1.36)	<0.0001	0.77 (0.65-0.90)	0.0010	1.20 (1.12-1.29)	<0.0001	1.02 (0.86-1.22)	0.81	0.94
Ischaemic heart disease	1.14 (1.02-1.26)	0.016	0.77 (0.61-0.97)	0.030	1.02 (0.92-1.14)	0.68	0.90 (0.70-1.17)	0.43	0.90
Cerebrovascular disease	1.49 (1.33-1.66)	<0.0001	0.71 (0.52-0.97)	0.031	1.48 (1.33-1.66)	<0.0001	1.13 (0.81-1.58)	0.46	0.23
Primary adrenal insufficiency									
Composite cardiovascular disease	1.17 (1.02-1.33)	0.020	0.67 (0.50-0.89)	0.0060	1.16 (1.02-1.32)	0.029	0.99 (0.72-1.35)	0.94	0.52
Ischaemic heart disease	1.05 (0.86-1.29)	0.59	0.76 (0.52-1.12)	0.17	0.98 (0.80-1.20)	0.86	1.04 (0.68-1.58)	0.86	0.21
Cerebrovascular disease	1.12 (0.89-1.41)	0.35	0.44 (0.24-0.82)	0.010	1.14 (0.90-1.45)	0.26	0.84 (0.44-1.60)	0.58	0.57
Secondary adrenal insufficiency									
Composite cardiovascular disease	1.34 (1.23-1.46)	<0.0001	0.83 (0.67-1.05)	0.11	1.26 (1.16-1.38)	<0.0001	1.06 (0.83-1.35)	0.65	0.50
Ischaemic heart disease	1.13 (0.99-1.29)	0.078	0.76 (0.54-1.07)	0.11	1.02 (0.89-1.17)	0.80	0.85 (0.59-1.22)	0.37	0.64
Cerebrovascular disease	1.80 (1.58-2.06)	<0.0001	0.90 (0.60-1.36)	0.62	1.79 (1.56-2.06)	<0.0001	1.33 (0.86-2.07)	0.20	0.24

Table 4.6: Hazard ratios of cardiovascular events in patients with adrenal insufficiency, according to diabetes status at baseline

Note: † Adjustment for sex, age at the start of follow-up, previous cardiovascular disease, baseline diabetes mellitus, hypertension and dyslipidaemia, and smoking any time; N for non-diabetes cohorts, All adrenal insufficiency= 6109 vs 64347, Primary= 1792 vs 19525, Secondary= 3590 vs 37192; N for diabetes cohorts, All =712 vs 3217, Primary= 260 vs 841, Secondary= 358 vs 1942

In Table 4.6, the hazard ratios for risk of composite cardiovascular events, ischaemic heart disease and cerebrovascular events associated with adrenal insufficiency of any type were not significantly different between those with diabetes and those without diabetes at baseline (p for interaction = 0.94, 0.90 and 0.23, respectively). Neither were they significantly different in primary adrenal insufficiency (p for interaction = 0.52, 0.21 and 0.57, respectively) nor in secondary adrenal insufficiency (p for interaction = 0.50, 0.64 and 0.24, respectively).

In summary, the risks of adrenal insufficiency of any type including primary and secondary adrenal insufficiency on cardiovascular events did not differ according to baseline diabetes status. Therefore, the risks were considered to be similar to the whole population of each type of adrenal insufficiency, regardless of baseline diabetes status. It should be noted that among participants with diabetes, although the unadjusted hazard ratios for all cardiovascular events associated with adrenal insufficiency appeared to be decreased, there was a relatively small number of participants in the diabetes cohort.

4.2.4 Incidence rates and hazard ratios for risk of cardiovascular events associated with adrenal insufficiency, categorised by non-cardiovascular disease and cardiovascular disease at baseline

In this analysis, the participants were classified into two groups depending on their co-morbid cardiovascular disease at the start of follow-up (non-cardiovascular disease vs cardiovascular disease at baseline). Baseline cardiovascular disease was defined using the same set of diagnostic codes as for the outcome of composite cardiovascular disease. Similar to the preceding section (4.2.3), the incidence of cardiovascular events occurring for the first time during the follow-up period of the study patients was compared with that of controls each within the same baseline cardiovascular disease category. The proportions of sex and baseline cardiovascular risk factors, and age in the study patients and in controls who had the same category are shown in the Appendix (Suppl. Table 4.15). These factors were used to adjust in multivariable Cox regression analysis.

Full results for incidence rates and incidence rate differences of cardiovascular events in patients with adrenal insufficiency of any kind, primary and secondary adrenal insufficiency, and their matched controls, according to the baseline status of cardiovascular disease are shown in the Appendix (Suppl. Tables 4.16, 4.17 and 4.18). Unadjusted and adjusted hazard ratios for risk of cardiovascular events categorised by cardiovascular disease status, are shown here in Table 4.7.

Outcome	Unadjusted HR (95% CI)				Adjusted HR (95% CI) †				P for interaction
	Non-CVD	p	CVD	p	Non-CVD	p	CVD	p	
Adrenal insufficiency of any type									
Composite cardiovascular disease	1.21 (1.11-1.31)	<0.0001	0.94 (0.86-1.03)	0.21	1.30 (1.20-1.42)	<0.0001	1.02 (0.93-1.13)	0.64	**0.0040**
Ischaemic heart disease	1.04 (0.91-1.20)	0.55	0.89 (0.78-1.02)	0.090	1.09 (0.95-1.26)	0.22	0.89 (0.78-1.02)	0.10	0.27
Cerebrovascular disease	1.41 (1.24-1.61)	<0.0001	1.10 (0.93-1.29)	0.26	1.60 (1.39-1.83)	<0.0001	1.22 (1.03-1.45)	0.019	**0.043**
Primary adrenal insufficiency									
Composite cardiovascular disease	1.13 (0.97-1.32)	0.11	0.98 (0.81-1.18)	0.81	1.26 (1.08-1.47)	0.0030	1.03 (0.86-1.25)	0.73	0.22
Ischaemic heart disease	1.07 (0.84-1.36)	0.59	0.94 (0.73-1.21)	0.61	1.11 (0.86-1.42)	0.42	0.94 (0.73-1.22)	0.63	0.46
Cerebrovascular disease	0.91 (0.68-1.23)	0.54	1.08 (0.78-1.48)	0.64	1.09 (0.81-1.47)	0.57	1.14 (0.82-1.58)	0.43	0.59
Secondary adrenal insufficiency									
Composite cardiovascular disease	1.26 (1.13-1.40)	<0.0001	0.95 (0.84-1.07)	0.40	1.35 (1.21-1.50)	<0.0001	1.05 (0.92-1.19)	0.48	**0.030**
Ischaemic heart disease	0.99 (0.82-1.19)	0.90	0.86 (0.73-1.03)	0.099	1.04 (0.86-1.26)	0.67	0.86 (0.72-1.03)	0.11	0.70
Cerebrovascular disease	1.83 (1.56-2.14)	<0.0001	1.15 (0.93-1.43)	0.18	2.05 (1.75-2.42)	<0.0001	1.29 (1.04-1.62)	0.022	**0.0030**

Table 4.7: Hazard ratios of cardiovascular events in patients with adrenal insufficiency, according to baseline status of cardiovascular disease (non-CVD vs CVD)

Note: † Adjustment for sex, age at the start of follow-up, baseline diabetes mellitus, hypertension and dyslipidaemia, and smoking any time; N for non-CVD cohorts, All adrenal insufficiency= 5631 vs 59978, Primary= 1734 vs 18311, Secondary= 3268 vs 34696; N for CVD cohorts, All =1190 vs 7586, Primary= 318 vs 2055, Secondary= 680 vs 4438

In Table 4.7, the hazard ratios for risk of composite cardiovascular events and cerebrovascular events associated with adrenal insufficiency of any type among those with baseline cardiovascular disease were significantly less increased than among those without (p for interaction= 0.0040 and 0.043, respectively). Similarly, in secondary adrenal insufficiency, they were significantly less increased among those with cardiovascular disease at baseline (p for interaction= 0.030 and 0.0030, respectively). However, in primary adrenal insufficiency, the hazard ratios for risk of composite cardiovascular and cerebrovascular events were not statistically different according to baseline cardiovascular disease status (p for interaction= 0.22 and 0.59, respectively). The hazard ratios for risk of ischaemic heart disease events associated with adrenal insufficiency were also not significantly different according to baseline cardiovascular disease status and this was applicable to patients with adrenal insufficiency of any type, primary and secondary adrenal insufficiency (p for interaction= 0.27, 0.46, and 0.70, respectively).

In summary, in patients with adrenal insufficiency of any type and secondary adrenal insufficiency, the increased risks of composite cardiovascular disease and cerebrovascular disease but not ischaemic heart disease in those without previous cardiovascular disease were greater than in those with previous cardiovascular disease. By contrast, in patients with primary adrenal insufficiency, the risks of cardiovascular events of any kind were not different according to the previous status of cardiovascular disease. Therefore, the risks were considered to be similar to the whole population of primary adrenal insufficiency, regardless of the previous status of cardiovascular disease.

4.2.5 Incidence rates and hazard ratios for risk of cardiovascular events associated with adrenal insufficiency, categorised by non-statin use and statin use

This analysis classified the participants into two groups according to whether or not they received statins at the start of follow-up (non-statin use vs statin use). As for the preceding sections, the incidence of cardiovascular events for the study patients was compared with that for controls within the same category of statin use. The proportions of sex and baseline cardiovascular risk factors, and age in the study patients and in controls according to statin use category are shown in the Appendix (Suppl. Table 4.19). Sex, age, and cardiovascular risk factors were used to adjust in the multivariable Cox regression analysis.

Full results for incidence rates and incidence rate differences of cardiovascular events in patients with adrenal insufficiency of any kind, primary and secondary adrenal insufficiency, and their matched controls, according to statin use at baseline are shown in the Appendix (Suppl. Tables 4.20, 4.21 and 4.22). Unadjusted and adjusted hazard ratios for risk of cardiovascular events, categorised by statin use, are shown here in Table 4.8.

Outcome	Unadjusted HR (95% CI)				Adjusted HR (95% CI) †				P for interaction
	Non-statin use	p	Statin use	p	Non-statin use	p	Statin	p	
Adrenal insufficiency of any type									
Composite cardiovascular disease	1.09 (1.01-1.17)	0.023	1.03 (0.91-1.17)	0.60	1.21 (1.12-1.30)	<0.0001	1.15 (1.01-1.30)	0.032	0.97
Ischaemic heart disease	0.91 (0.81-1.02)	0.12	1.02 (0.86-1.21)	0.81	0.98 (0.87-1.11)	0.75	1.10 (0.92-1.31)	0.29	0.086
Cerebrovascular disease	1.29 (1.14-1.45)	<0.0001	1.19 (0.95-1.49)	0.12	1.48 (1.31-1.67)	<0.0001	1.36 (1.08-1.70)	0.0080	0.52
Primary adrenal insufficiency									
Composite cardiovascular disease	1.03 (0.90-1.18)	0.65	1.06 (0.83-1.35)	0.63	1.16 (1.01-1.33)	0.037	1.15 (0.90-1.47)	0.25	0.54
Ischaemic heart disease	0.92 (0.74-1.13)	0.42	1.03 (0.75-1.42)	0.86	0.99 (0.80-1.23)	0.92	1.10 (0.79-1.53)	0.57	0.29
Cerebrovascular disease	0.88 (0.68-1.14)	0.33	1.29 (0.83-2.01)	0.25	1.02 (0.79-1.32)	0.89	1.52 (0.97-2.37)	0.067	0.12
Secondary adrenal insufficiency									
Composite cardiovascular disease	1.12 (1.02-1.23)	0.020	1.02 (0.88-1.20)	0.76	1.26 (1.14-1.38)	<0.0001	1.21 (1.03-1.42)	0.021	0.96
Ischaemic heart disease	0.89 (0.76-1.04)	0.13	0.93 (0.74-1.17)	0.55	0.96 (0.82-1.13)	0.65	1.06 (0.84-1.33)	0.63	0.24
Cerebrovascular disease	1.61 (1.39-1.86)	<0.0001	1.24 (0.93-1.65)	0.13	1.87 (1.61-2.16)	<0.0001	1.45 (1.09-1.94)	0.011	0.097

Table 4.8: Hazard ratios of cardiovascular events in patients with adrenal insufficiency, according to statin use at baseline (non-statin use vs statin use)

Note: † Adjustment for sex, age at the start of follow-up, previous cardiovascular disease, baseline diabetes mellitus, hypertension and dyslipidaemia, and smoking any time; N for non-statin cohorts, All adrenal insufficiency= 5482 vs 64259, Primary= 1722 vs 19438, Secondary= 3120 vs 37193; N for statin cohorts, All =1339 vs 3305, Primary= 330 vs 928, Secondary= 828 vs 1941

In Table 4.8, the hazard ratios for risk of composite cardiovascular disease, ischaemic heart disease and cerebrovascular disease associated with adrenal insufficiency of any type were not significantly different between statin users and non-statin users (p for interaction= 0.97, 0.086 and 0.52, respectively). Neither were they significantly different in primary adrenal insufficiency (p for interaction= 0.54, 0.29 and 0.12, respectively) nor in secondary adrenal insufficiency (p for interaction= 0.96, 0.24 and 0.097, respectively).

In summary, the risks of adrenal insufficiency of any type including primary and secondary adrenal insufficiency on cardiovascular events were not different according to statin use at baseline. Therefore, the risks were considered to be similar to the whole population of each type of adrenal insufficiency, regardless of statin use.

4.3: Overall cardiovascular mortality

Results for the principal causes of death according to adrenal insufficiency were described in Chapter 3. In this chapter, more detailed consideration is given to death from cardiovascular disease and adrenal insufficiency. The principal cause of death considered here is diseases of the circulatory system, which included deaths from both atherosclerotic and non-atherosclerotic processes. In addition, the specific cause of death from atherosclerotic diseases of the circulatory system (ischaemic heart disease and cerebrovascular disease) were also differentiated. The participants evaluated for cardiovascular mortality included only those having data linked with ONS.

Incidence rates and hazard ratios for risk of mortality from disease of the circulatory system, ischaemic heart disease and cerebrovascular disease associated with adrenal insufficiency

Similar to the analysis of cardiovascular events, the mortality rates for disease of the circulatory system, ischaemic heart disease and cerebrovascular disease were calculated in the study patients with any, primary, secondary or unspecified adrenal insufficiency and controls, and the mortality rate difference was calculated. The unadjusted hazard ratio for each kind of cardiovascular mortality was analysed and was adjusted for ‘cardiovascular risk factors’, consisting of: previous cardiovascular disease, baseline diabetes mellitus, hypertension, dyslipidaemia at the start of follow-up, and ever smoking at any time. Also, as for the analysis of cardiovascular events, a similar analysis was performed to compare cardiovascular mortality between patients with primary and secondary adrenal insufficiency.

❖ Adrenal insufficiency of any type and controls

This analysis included 3547 patients with adrenal insufficiency of any type and 34944 controls, with follow-up periods of 18592 and 34944 person-years, respectively. For disease of the circulatory system, the mortality rates of the study patients and controls were 9.9 (95% CI, 8.6-11.4) and 6.4 (6.1-6.8) per 1000 person-years, respectively, giving a mortality rate difference of 3.5(2.0-4.9) per 1000 person-years ($p<0.0001$; Table 4.9). The unadjusted hazard ratio was 1.54 (95% CI, 1.32-1.80; $p <0.0001$) and, after adjustment for cardiovascular risk factors, the hazard ratio remained increased (adjusted HR 1.31, [95% CI, 1.12-1.54]; $p=0.0010$; Figure 4.2).

For ischaemic heart disease, the mortality rate in the study patients was also higher than that in controls (4.9 [95% CI, 4.0-6.1] vs 2.7 [2.5-3.0] per 1000 person-years), giving a mortality rate difference of 2.2 (95% CI, 1.2-3.3; $p<0.0001$; Table 4.9) and an unadjusted hazard ratio of 1.82 (95% CI, 1.46-2.28; $p<0.0001$). After adjustment for cardiovascular risk factors, the hazard ratio remained increased (adjusted HR, 1.49 [95% CI, 1.18-1.88]; $p=0.0010$; Figure 4.2).

For cerebrovascular disease, the mortality rate for the study patients was not different from that for controls (2.5 [95%CI, 1.9-3.3] vs 2.0 [1.8-2.3] per 1000 person-years), giving a non-significant mortality rate difference of 0.4 (95% CI, -0.3 to 1.2) per 1000 person-years ($p=0.10$; Table 4.9). The unadjusted hazard ratio was not significantly increased (1.22 [95% CI, 0.90-1.66]; $p=0.20$) and after adjustment for cardiovascular risk factors, the hazard ratio remained not increased (adjusted HR, 1.03 [95% CI, 0.75-1.41]; $p=0.85$; Figure 4.2).

Principal cause of death	Study patients			Controls			Mortality rate difference per 1000 person-years (95% CI)	P
	No. death	Person-years	Mortality per 1000 person-years (95% CI)	No. death	Person-years	Mortality per 1000 person-years (95% CI)		
Adrenal insufficiency of any type (N= 3547 vs 34944)								
Disease of the circulatory system	184	18592	9.9 (8.6-11.4)	1157	179833	6.4 (6.1-6.8)	3.5 (2.0 to 4.9)	<0.0001
Ischaemic heart disease	92	18592	4.9 (4.0-6.1)	487	179833	2.7 (2.5-3.0)	2.2 (1.2 to 3.3)	<0.0001
Cerebrovascular disease	46	18592	2.5 (1.9-3.3)	366	179833	2.0 (1.8-2.3)	0.4 (-0.3 to 1.2)	0.10
Primary adrenal insufficiency (N= 1015 vs 10025)								
Disease of the circulatory system	58	5474	10.6 (8.2-13.7)	331	54933	6.0 (5.4-6.7)	4.6 (1.8 to 7.4)	0.0001
Ischaemic heart disease	31	5474	5.7 (4.0-8.1)	144	54933	2.6 (2.2-3.1)	3.0 (1.0 to 5.1)	0.0002
Cerebrovascular disease	10	5474	1.8 (1.6-2.3)	104	54933	1.9 (1.6-2.3)	-0.1 (-1.3 to 1.1)	0.47
Secondary adrenal insufficiency (N= 2136 vs 20991)								
Disease of the circulatory system	110	11377	9.7 (8.0-11.7)	686	106850	6.4 (6.0-6.9)	3.2 (1.4 to 5.1)	0.0001
Ischaemic heart disease	53	11377	4.7 (3.6-6.1)	283	106850	2.6 (1.4-3.0)	2.0 (0.7 to 3.3)	0.0002
Cerebrovascular disease	34	11377	3.0 (2.1-4.2)	222	106850	2.1 (1.8-2.4)	0.9 (-0.1 to 2.0)	0.028

Table 4.9: Mortality rates from cardiovascular disease in patients with adrenal insufficiency and matched controls

Note: † Adjustment for previous cardiovascular disease, baseline diabetes mellitus, hypertension and dyslipidaemia, and smoking at any time

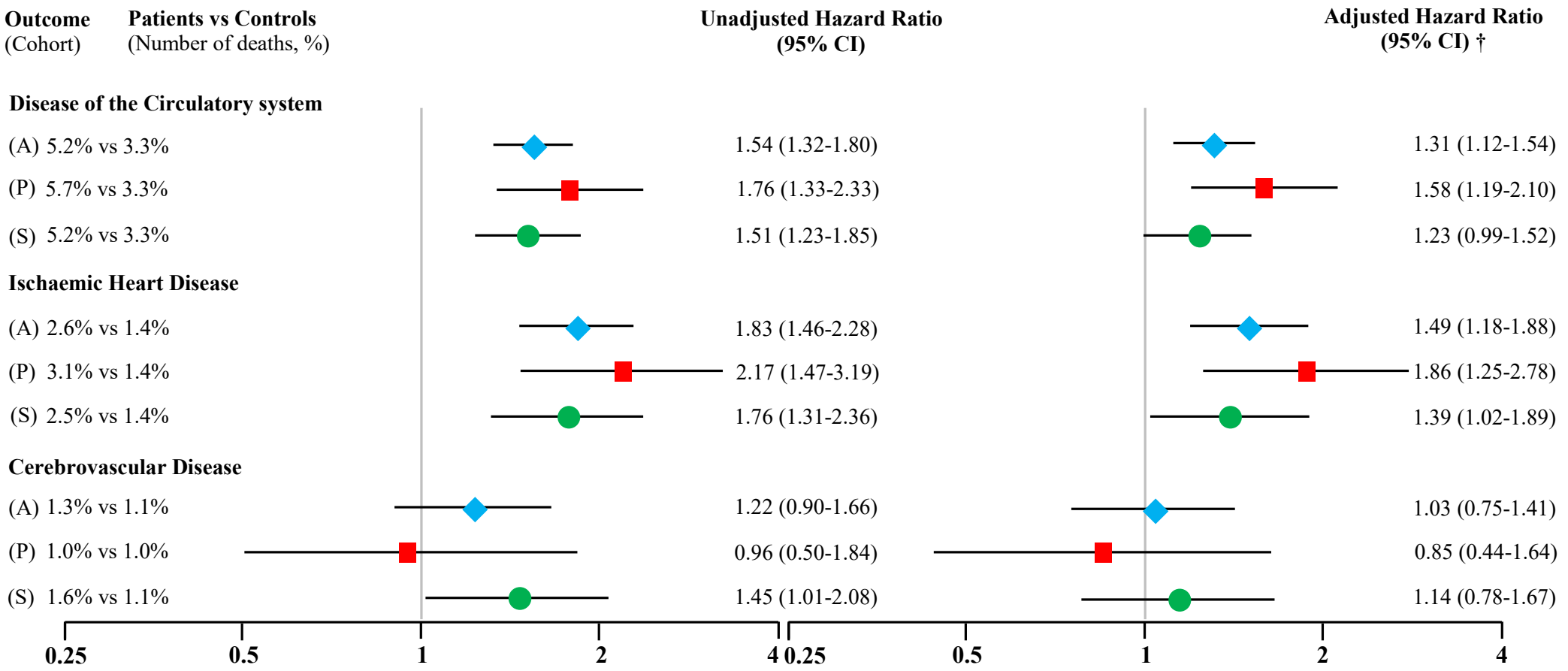


Figure 4.2: Unadjusted and adjusted hazard ratios of cardiovascular mortality in patients with adrenal insufficiency of any type, primary and secondary adrenal insufficiency

Note: † Adjustment for previous cardiovascular disease, baseline diabetes mellitus, hypertension and dyslipidaemia, and smoking any time; (A)-Adrenal insufficiency of any type; (P)-Primary adrenal insufficiency; (S)-Secondary adrenal insufficiency

❖ Primary adrenal insufficiency and controls

This analysis included 1015 patients with primary adrenal insufficiency and 10025 controls, with follow-up periods of 5474 and 54933 person-years, respectively. For disease of the circulatory system, the mortality rate of the study patients with primary adrenal insufficiency was higher than controls (10.6 [95% CI, 8.2-13.7] vs 6.0 [5.4-6.7] per 1000 person-years), giving a mortality rate difference of 4.6 (95% CI, 1.8-4.7) per 1000 person-years (p=0.0001; Table 4.9). The unadjusted hazard ratio was also increased (1.76 [95% CI, 1.33-2.33]; p<0.0001) and after adjustment for cardiovascular risk factors, the hazard ratio remained increased (adjusted HR 1.58, [95% CI, 1.19-2.10]; p=0.20; Figure 4.2).

For ischaemic heart disease, the mortality rate of the study patients with primary adrenal insufficiency was significantly higher than that of controls (5.7 [95% CI, 4.0-8.1] vs 2.6 [2.2-3.1] per 1000 person-years), giving a mortality rate difference of 3.0 (95% CI, 1.0 to 5.1) per 1000 person-years (p=0.0002; Table 4.9). The unadjusted hazard ratio was also increased (HR, 2.17 [95% CI, 1.47-3.19]; p<0.0001) and after adjustment for cardiovascular risk factors, the hazard ratio remained increased (adjusted HR, 1.86 [95% CI, 1.25-2.78]; p=0.0020; Figure 4.2).

For cerebrovascular disease, the mortality rate of the study patients with primary adrenal insufficiency was similar to controls (1.8 [95% CI, 1.6-2.3] vs 1.9 [1.6-2.3] per 1000 person-years), giving a mortality rate difference of -0.1 (-1.3 to 1.1 per 1000 person-years; p=0.47; Table 4.9) and an unadjusted hazard ratio of 0.96 (95% CI, 0.50-1.84; p=0.90). After adjustment for cardiovascular risk factors, the hazard ratio remained not significant (Figure 4.2).

❖ Secondary adrenal insufficiency and controls

This analysis included 2136 patients with secondary adrenal insufficiency and 20991 controls with follow-up periods of 11377 and 106850 person-years, respectively. For disease of the circulatory system, the mortality rate of the study patients with secondary adrenal insufficiency was higher than that of controls (9.7 [95% CI, 8.0-11.7] vs 6.4 [6.0-6.9] per 1000 person-years), giving a mortality rate difference of 3.2 (95% CI, 1.4 to 5.1) per 1000 person-years (p=0.001; Table 4.9). The unadjusted hazard ratio was 1.51 (95% CI, 1.23-1.85; p<0.0001). However, after adjustment for cardiovascular risk factors, the hazard ratio was lower and no longer significant (adjusted HR 1.23, [95% CI, 0.99-1.52]; p=0.058; Figure 4.2).

For ischaemic heart disease, the mortality rate of the study patients with secondary adrenal insufficiency was higher than that of controls (4.7 [95% CI, 3.6-6.1] vs 2.6 [1.4-3.0] per 1000 person-years), giving a mortality rate difference of 2.0 (95% CI, 0.7 to 3.3) per 1000 person-years (p<0.0001; Table 4.9). The unadjusted hazard ratio was also increased (HR, 1.76 [95% CI, 1.31-2.36]; p<0.0001). After adjustment for cardiovascular risk factors, the hazard ratio was lower but remained significantly increased (adjusted HR, 1.39 [95% CI, 1.02-1.89]; p=0.038; Figure 4.2).

For cerebrovascular disease, the mortality rate of the study patients with secondary adrenal insufficiency was slightly higher than that of controls (3.0 [95% CI, 2.1-4.2] vs 2.1 [1.8-2.4] per 1000 person-years), giving a mortality rate difference of 0.9 (95% CI, -0.1 to 2.0) per 1000 person-years (p=0.028; Table 4.9). The unadjusted hazard ratio was marginally significant (1.45 [95% CI, 1.01-2.08]; p=0.044) but after adjustment for cardiovascular risk factors, the hazard ratio was no longer significant (adjusted HR, 1.14 [95% CI, 0.78-1.67]; p=0.48; Figure 4.2).

❖ Unspecified adrenal insufficiency and controls

This analysis included 396 patients with unspecified adrenal insufficiency and 3928 controls. For disease of the circulatory system, the mortality rate of the study patients with unspecified adrenal insufficiency was slightly higher than that of controls (9.2 [95% CI, 5.6-15.0] vs 7.8 [6.6-9.2] per 1000 person-years) with follow-up periods of 1741 and 18050 person-years, respectively. The mortality rate difference was not significantly increased (1.4 [95% CI, -3.3 to 6.1] per 1000 person-years, p=0.25). The unadjusted hazard ratio was not increased (1.18 [95% CI, 0.70-1.98]; p=0.52) and after adjustment for cardiovascular risk factors, the hazard ratio was also not increased (adjusted HR 1.07, [95% CI, 0.63-1.84]; p=0.79; Suppl. Table 4.23).

For ischaemic heart disease, the mortality rate of the study patients with unspecified adrenal insufficiency was also slightly higher than that of controls (4.6 [95% CI, 2.3-9.2] vs 3.3 [2.6-4.3 per 1000 person-years), giving a mortality rate difference of 1.3 (95% CI, -2.0 to 4.6 per 1000 person-years; p=0.19). The unadjusted hazard ratio was not significantly increased 1.37 (95% CI, 0.66-2.87; p=0.40) and after adjustment for cardiovascular risk factors, the hazard ratio was also not increased (adjusted HR, 1.05 [95% CI, 0.48-2.27]; p=0.90; Suppl. Table 4.23).

For cerebrovascular disease, only two deaths were observed among the study patients with unspecified adrenal insufficiency and forty deaths among the controls. Therefore, the mortality rate of either the study patients or controls was low (1.1 [95% CI, 0.3-4.6] vs 2.2 [1.6-3.0] per 1000 person-years) and the hazard ratios did not reach significance (Suppl. Table 4.23).

❖ Primary and secondary adrenal insufficiency

This analysis compared cardiovascular mortality of patients with primary with those with secondary adrenal insufficiency. Similar to the analysis of cardiovascular events, the differences in sex, age, and cardiovascular risk factors were taken into account in this analysis. For disease of the circulatory system, the mortality rate of patients with primary adrenal insufficiency was slightly higher than that of secondary adrenal insufficiency, giving an mortality rate difference of 0.9 (95% CI, -2.3 to 4.2) per 1000 person-years (p=0.28) and an unadjusted hazard ratio of 1.10 (95% CI, 0.80-1.51; p=0.57). After adjustment for sex and age of adrenal insufficiency, the hazard ratio of patients with primary adrenal insufficiency relative to secondary was higher but remained non-significant (adjusted HR, 1.24 [95% CI, 0.90-1.71]; p=0.19). Also, after adjustment for previous cardiovascular disease, diabetes, hypertension and dyslipidaemia at adrenal insufficiency diagnosis, and ever smoking, the hazard ratio for death from the disease of circulatory system remained non-significantly increased (adjusted HR, 1.22 [95% CI, 0.88-1.68]; p=0.23; Table 4.10).

For ischaemic heart disease, the mortality rate of patients with primary adrenal insufficiency was also slightly higher than in those with secondary disease with a mortality rate difference of 1.0 (95% CI, -1.4 to 3.4) per 1000 person-years (p=0.19). The unadjusted hazard ratio of primary relative to secondary adrenal insufficiency was 1.22 (95% CI, 0.78-1.90; p=0.38). After adjustment for sex and age of diagnosis, the hazard ratio was higher but remained not significant (adjusted HR, 1.45 [95% CI, 0.93-2.29]; p=0.10). Also, after adjustment for cardiovascular risk factors at the diagnosis of adrenal insufficiency and ever smoking, the hazard ratio remained not significantly increased (adjusted HR, 1.32 [95% CI, 0.84-2.08]; p=0.22; Table 4.10).

Cardiovascular causes of death	**Circulatory system**			**Ischaemic heart disease**			**Cerebrovascular disease**		
Models	HR	95%CI	P	HR	95%CI	P	HR	95%CI	P
Univariable analysis (Unadjusted)	1.10	0.80-1.51	0.57	1.22	0.78-1.90	0.38	0.61	0.30-1.24	0.17
Adjustment for sex, age in years at start of follow-up	1.21	0.88-1.68	0.24	1.43	0.91-2.24	0.12	0.69	0.34-1.42	0.31
Adjustment for sex, age in years at diagnosis	1.24	0.90-1.71	0.19	1.45	0.93-2.29	0.10	0.71	0.35-1.45	0.34
Adjustment for previous cardiovascular disease, diabetes, hypertension, dyslipidaemia at start of follow-up, and smoking any time	1.26	0.91-1.74	0.16	1.38	0.88-2.18	0.16	0.75	0.37-1.54	0.43
Adjustment for previous cardiovascular disease, diabetes, hypertension, dyslipidaemia at diagnosis, and smoking any time	1.22	0.88-1.68	0.23	1.32	0.84-2.08	0.22	0.72	0.35-1.45	0.35
Adjustment for sex, age at start of follow-up, previous cardiovascular disease, diabetes, hypertension, dyslipidaemia at start of follow-up, and smoking any time	1.20	0.86-1.67	0.28	1.38	0.87-2.18	0.17	0.75	0.36-1.55	0.43
Adjustment for sex, age at diagnosis, previous cardiovascular disease, diabetes, hypertension, dyslipidaemia at diagnosis, and smoking any time	1.19	0.86-1.66	0.29	1.35	0.85-2.14	0.19	0.72	0.35-1.49	0.38

Table 4.10: Unadjusted and adjusted hazard ratios of cardiovascular mortality in patients with primary adrenal insufficiency, relative to secondary adrenal insufficiency

For cerebrovascular disease, the mortality rate of patients with primary adrenal insufficiency was lower than that of those with secondary disease, giving a mortality rate difference of -1.2 (95% CI, -2.7 to 0.4) per 1000 person-years (p=0.083). The unadjusted hazard ratio of patients with primary adrenal insufficiency relative to those with secondary disease was decreased but not significantly (HR, 0.61 [95% CI, 0.30-1.24]; p=0.17). After adjustment for sex and age at diagnosis, (adjusted HR, 0.71 [95% CI, 0.35-1.45]; p=0.34) and after adjustment for cardiovascular risk factors at the diagnosis of adrenal insufficiency and ever smoking, the hazard ratio remained non-significantly decreased (adjusted HR, 0.72 [95% CI, 0.35-1.45]; p=0.35; Table 4.10).

In summary, in a comparison with controls, the risk of death from circulatory system and ischaemic heart disease was increased in patients with adrenal insufficiency of any type, including primary and secondary disease. The risk remained significantly increased even after taking cardiovascular risk factors into account. As death from disease of the circulatory system has included 'unspecified disorders of circulatory system' and 'hypotension', death from adrenal crisis might have been ascertained as death from circulatory system disease. The risk of death from cerebrovascular disease was not increased, possibly because of the low mortality rates in both study patients and controls. In a comparison between type of adrenal insufficiency, the risk of cardiovascular mortality, including ischaemic heart disease and cerebrovascular disease, in patients with primary was not different from the risk in those with secondary adrenal insufficiency.

4.4: Cardiovascular mortality stratified by sex, age, and comorbidity at baseline

This analysis compared the mortality rate from cardiovascular disease of the study patients with controls. As in Section 4.3, the outcomes consisted of mortality from disease of the circulatory system, ischaemic heart disease, and cerebrovascular disease. Identical to Section 4.2, the mortality rate and hazard ratio were evaluated based on the category of sex, age at start of follow-up, and the pre-existing comorbidities of diabetes mellitus and cardiovascular disease and the use of statins, although the population in this analysis included only participants having data linked with ONS.

Hazard ratios were adjusted for 'cardiovascular risk factors': previous cardiovascular disease, diabetes mellitus, hypertension and dyslipidaemia at baseline, and ever smoking at any time. Additional adjustment for sex and age at the start of follow-up were performed in multivariable Cox regression analysis stratified by comorbidity.

4.4.1 Mortality rates and hazard ratios for risk of cardiovascular mortality associated with adrenal insufficiency, categorised by men and women

Full results for rates of mortality from cardiovascular disease and mortality rate differences in patients with adrenal insufficiency of any kind, primary and secondary adrenal insufficiency, and their matched controls, categorised by sex are shown in the Appendix (Suppl. Table 4.24, 4.25 and 4.26). It was noted that the mortality rates from cerebrovascular disease were low across the population stratified by sex. Unadjusted and adjusted hazard ratios for risk of cardiovascular mortality categorised by sex are shown here in Table 4.11.

Principal cause of death	Unadjusted HR (95% CI)				Adjusted HR (95% CI) †				P for interaction
	Men	p	Women	p	Men	p	Women	p	
Adrenal insufficiency of any type									
Disease of the circulatory system	1.56 (1.26-1.93)	<0.0001	1.52 (1.22-1.91)	<0.0001	1.36 (1.09-1.70)	0.0070	1.27 (1.00-1.60)	0.046	0.97
Ischaemic heart disease	1.75 (1.31-2.34)	<0.0001	1.97 (1.39-2.79)	<0.0001	1.43 (1.06-1.94)	0.021	1.61 (1.12-2.31)	0.010	0.49
Cerebrovascular disease	1.57 (1.03-2.37)	0.034	0.95 (0.60-1.50)	0.82	1.43 (0.93-2.20)	0.10	0.76 (0.48-1.21)	0.25	0.12
Primary adrenal insufficiency									
Disease of the circulatory system	1.44 (0.91-2.27)	0.11	2.02 (1.42-2.88)	<0.0001	1.37 (0.86-2.21)	0.18	1.79 (1.25-2.57)	0.0020	0.21
Ischaemic heart disease	1.92 (1.11-3.34)	0.020	2.49 (1.44-4.31)	0.0010	1.64 (0.92-2.94)	0.095	2.24 (1.28-3.93)	0.0050	0.39
Cerebrovascular disease	0.84 (0.26-2.72)	0.77	1.02 (0.47-2.23)	0.95	0.93 (0.28-3.09)	0.90	0.85 (0.39-1.87)	0.68	0.73
Secondary adrenal insufficiency									
Disease of the circulatory system	1.57 (1.21-2.05)	0.0010	1.43 (1.05-1.96)	0.025	1.33 (1.01-1.75)	0.046	1.12 (0.81-1.55)	0.50	0.70
Ischaemic heart disease	1.67 (1.15-2.41)	0.0070	1.97 (1.21-3.19)	0.0060	1.36 (0.92-2.01)	0.12	1.51 (0.91-2.50)	0.11	0.53
Cerebrovascular disease	1.96 (1.24-3.10)	0.0040	0.98 (0.54-1.78)	0.95	1.62 (1.00-2.63)	0.051	0.74 (0.40-1.37)	0.34	0.088

Table 4.11: Hazard ratios of cardiovascular mortality in patients with adrenal insufficiency, according to sex

Note: † Adjustment for previous cardiovascular disease, baseline diabetes mellitus, hypertension and dyslipidaemia, and smoking any time; N for male cohorts, All adrenal insufficiency= 1629 vs 16059, Primary= 410 vs 4077, Secondary= 1054 vs 10343; N for female cohorts, All =1918 vs 1885, Primary= 605 vs 5948, Secondary= 1082 vs 10648

In Table 4.11, the hazard ratios for risk of death from disease of the circulatory system, ischaemic heart disease and cerebrovascular disease associated with adrenal insufficiency of any type were not significantly different between men and women (p for interaction= 0.97, 0.49 and 0.12, respectively). Neither were they significantly different in primary adrenal insufficiency (p for interaction= 0.21, 0.39 and 0.73, respectively) nor in secondary adrenal insufficiency (p for interaction= 0.70, 0.53 and 0.088, respectively).

In summary, the risks of mortality from disease of the circulatory system and ischaemic heart disease in men were similar to women with adrenal insufficiency, including primary and secondary disease. However, in cerebrovascular disease, the mortality rate across the participants stratified by sex was low, and the mortality risks in adrenal insufficiency of any type, including primary and secondary disease were not different according to sex.

4.4.2 Mortality rates and hazard ratios for risk of cardiovascular mortality associated with adrenal insufficiency, categorised by younger and older age at the start of follow-up

Full results for cardiovascular mortality rates and mortality rate differences in patients with adrenal insufficiency of any kind, primary and secondary adrenal insufficiency, and their matched controls, categorised by whether the participants were at younger (<50 y) or older age (≥50 y) at the start of follow-up are shown in the Appendix (Suppl. Table 4.27, 4.28 and 4.29). It was noted that the mortality rates in younger participants were low across all categories of cardiovascular mortality, particularly for cerebrovascular disease (2 patient and 6 control deaths; Suppl. Table 4.27). Unadjusted and adjusted hazard ratios for risk of cardiovascular mortality categorised by age are shown here in Table 4.12.

Principal cause of death	Unadjusted HR (95% CI)				Adjusted HR (95% CI) †				P for interaction
	Age <50	p	Age ≥50	p	Age <50	p	Age ≥50	p	
Adrenal insufficiency of any type									
Disease of the circulatory system	5.43 (2.73-10.77)	<0.0001	1.51 (1.29-1.78)	<0.0001	3.69 (1.75-7.77)	0.0010	1.39 (1.17-1.64)	<0.0001	**<0.0001**
Ischaemic heart disease	4.58 (1.72-12.22)	0.0020	1.82 (1.45-2.29)	<0.0001	2.43 (0.79-7.44)	0.12	1.59 (1.25-2.02)	<0.0001	0.060
Cerebrovascular disease	3.04 (0.61-15.05)	0.17	1.23 (0.90-1.68)	0.20	2.02 (0.37-11.11)	0.41	1.12 (0.81-1.55)	0.48	0.28
Primary adrenal insufficiency									
Disease of the circulatory system	11.09 (3.72-33.01)	<0.0001	1.69 (1.25-2.27)	0.0010	8.21 (2.48-27.22)	0.0010	1.57 (1.16-2.12)	0.0030	**0.0010**
Ischaemic heart disease	11.90 (3.19-44.34)	<0.0001	2.01 (1.32-3.06)	0.0010	7.05 (1.56-31.85)	0.011	1.80 (1.17-2.76)	0.0080	**0.012**
Cerebrovascular disease	No death	..	1.02 (0.53-1.96)	0.94	No death	..	0.95 (0.49-1.83)	0.87	NA
Secondary adrenal insufficiency									
Disease of the circulatory system	3.34 (1.31-8.55)	0.012	1.50 (1.22-1.85)	<0.0001	2.34 (0.86-6.40)	0.096	1.33 (1.07-1.66)	0.010	0.091
Ischaemic heart disease	1.10 (0.14-8.83)	0.92	1.83 (1.36-2.46)	<0.0001	0.62 (0.06-6.02)	0.68	1.57 (1.14-2.15)	0.0050	0.68
Cerebrovascular disease	2.96 (0.60-14.70)	0.18	1.43 (0.99-2.08)	0.058	1.83 (0.32-10.42)	0.49	1.24 (0.84-1.84)	0.27	0.35

Table 4.12: Hazard ratios of cardiovascular mortality in patients with adrenal insufficiency, according to age at the start of follow-up

Note: † Adjustment for previous cardiovascular disease, baseline diabetes mellitus, hypertension and dyslipidaemia, and smoking any time; N for younger cohorts, All adrenal insufficiency= 1565 vs 15641, Primary= 484 vs 4855, Secondary= 931 vs 9277; N for older cohorts, All =1982 vs 19303, Primary= 531 vs 5170, Secondary= 1205 vs 11714

In Table 4.12, the hazard ratio for risk of death from disease of the circulatory system associated with adrenal insufficiency of any type was significantly different according to age at the start of follow-up (p for interaction<0.0001) whereas the hazard ratios for death from ischaemic heart disease and cerebrovascular disease was not significantly different by age (p for interaction=0.060 and 0.28, respectively). In primary adrenal insufficiency, the hazard ratios for risk of death from disease of the circulatory system and ischaemic heart disease in younger patients was significantly higher than those in older age (p for interaction=0.0010 and 0.012, respectively) whereas no death from cerebrovascular disease was observed in younger primary adrenal insufficiency patients and controls. In secondary adrenal insufficiency, the hazard ratios for risk of death from disease of the circulatory system, ischaemic heart disease and cerebrovascular disease were not different according to age (p for interaction =0.091, 0.68 and 0.35).

In summary, in primary adrenal insufficiency, the risks of death from disease of the circulatory system and ischaemic heart disease in younger patients were higher than in older individuals, even though the overall mortality rates were higher in older individuals. In secondary adrenal insufficiency, the risk of death from these conditions was not different according to age. In cerebrovascular disease, the mortality rate across the participants stratified by age was low and the mortality risk was not different according to age in adrenal insufficiency of any type, or in primary or secondary disease.

4.4.3 Mortality rates and hazard ratios for risk of cardiovascular mortality associated with adrenal insufficiency, categorised by non-diabetes and diabetes at baseline

As in Section 4.2.3, the risk of cardiovascular mortality associated with adrenal insufficiency in those with diabetes was compared with those without diabetes. The baseline characteristics and proportions of cardiovascular risk factors in study patients and in controls with the same diabetes status are shown in the Appendix (Suppl. Table 4.30).

Full results for cardiovascular mortality rates and mortality rate differences in patients with adrenal insufficiency of any kind, primary and secondary adrenal insufficiency, and their matched controls, categorised by whether or not the participants had diabetes mellitus at the start of follow-up (diabetes vs non-diabetes) are shown in the Appendix (Suppl. Table 4.31, 4.32 and 4.33). As for cardiovascular events in participants with diabetes (Section 4.2.3), the higher cardiovascular mortality in controls could be ascribed to their higher median age and proportions of men, previous cardiovascular disease and hypertension (Suppl. Table 4.30-4.33).

Unadjusted and adjusted hazard ratios for risk of cardiovascular mortality categorised by diabetes status are shown here in Table 4.13.

Principal cause of death	Unadjusted HR (95% CI)				Adjusted HR (95% CI) †				P for interaction
	Non-diabetes	p	Diabetes	p	Non-diabetes	p	Diabetes	p	
Adrenal insufficiency of any type									
Disease of the circulatory system	1.58 (1.34-1.87)	<0.0001	0.79 (0.53-1.18)	0.25	1.55 (1.31-1.85)	<0.0001	1.43 (0.93-2.20)	0.10	0.99
Ischaemic heart disease	1.69 (1.31-2.18)	<0.0001	1.36 (0.85-2.19)	0.20	1.62 (1.25-2.11)	<0.0001	2.15 (1.27-3.63)	0.0040	0.15
Cerebrovascular disease	1.41 (1.02-1.94)	0.035	0.24 (0.08-0.78)	0.018	1.33 (0.96-1.84)	0.088	0.57 (0.17-1.92)	0.36	0.12
Primary adrenal insufficiency									
Disease of the circulatory system	1.72 (1.26-2.35)	0.0010	0.95 (0.49-1.85)	0.89	1.76 (1.28-2.41)	<0.0001	1.91 (0.92-3.96)	0.082	0.94
Ischaemic heart disease	1.82 (1.14-2.88)	0.011	1.73 (0.77-3.88)	0.18	1.92 (1.20-3.07)	0.0060	2.64 (1.09-6.40)	0.031	0.40
Cerebrovascular disease	1.00 (0.48-2.05)	0.99	0.39 (0.09-1.73)	0.21	0.96 (0.46-1.99)	0.90	1.20 (0.25-5.79)	0.82	0.89
Secondary adrenal insufficiency									
Disease of the circulatory system	1.57 (1.27-1.95)	<0.0001	0.80 (0.46-1.38)	0.42	1.49 (1.19-1.87)	0.0010	1.23 (0.68-2.24)	0.48	0.86
Ischaemic heart disease	1.73 (1.24-2.40)	0.0010	1.21 (0.62-2.34)	0.57	1.60 (1.13-2.26)	0.0080	1.76 (0.84-3.70)	0.13	0.60
Cerebrovascular disease	1.70 (1.18-2.46)	0.0050	0.16 (0.02-1.20)	0.075	1.54 (1.05-2.27)	0.029	0.27 (0.04-2.08)	0.20	0.11

Table 4.13: Hazard ratios of cardiovascular mortality in patients with adrenal insufficiency, according to diabetes status at baseline

Note: † Adjustment for sex, age at the start of follow-up, previous cardiovascular disease, baseline hypertension and dyslipidaemia, and smoking any time; N for non-diabetes cohorts, All adrenal insufficiency= 3171 vs 33071, Primary= 885 vs 9575, Secondary= 1930 vs 19819; N for diabetes cohorts, All =376 vs 1873, Primary= 130 vs 450, Secondary= 206 vs 1172

In Table 4.13, the hazard ratios for mortality risk from disease of the circulatory system, ischaemic heart disease and cerebrovascular disease associated with adrenal insufficiency of any type were not significantly different according to whether or not the participants had diabetes mellitus at baseline (p for interaction= 0.99, 0.15 and 0.12, respectively). Neither were they significantly different in primary adrenal insufficiency (p for interaction= 0.94, 0.40 and 0.89, respectively) nor in secondary adrenal insufficiency (p for interaction= 0.86, 0.60 and 0.11, respectively).

In summary, the risks of adrenal insufficiency of any type including primary and secondary adrenal insufficiency on cardiovascular mortality were not different according to the difference in baseline diabetes status. Therefore, the risks were considered to be similar to the whole population of each type of adrenal insufficiency, regardless of baseline diabetes status. The risks included death from disease of the circulatory system, ischaemic heart disease, and cerebrovascular disease.

4.4.4 Mortality rates and hazard ratios for risk of cardiovascular mortality associated with adrenal insufficiency, categorised by non-cardiovascular disease and cardiovascular disease at baseline

As in Section 4.2.4, the risk of cardiovascular mortality associated with adrenal insufficiency in those with cardiovascular disease was compared with those without cardiovascular disease. The baseline characteristics and proportions of cardiovascular risk factors in study patients and in controls with the same status of cardiovascular disease are shown in the Appendix (Suppl. Table 4.34).

Full results for cardiovascular mortality rates and mortality rate differences in patients with adrenal insufficiency of any kind, primary and secondary adrenal insufficiency, and their matched controls, categorised by whether or not the participants had cardiovascular disease at the start of follow-up (cardiovascular disease vs non- cardiovascular disease) are shown in the Appendix (Suppl. Table 4.35, 4.36 and 4.37). Unadjusted and adjusted hazard ratios for risk of cardiovascular mortality categorised by baseline status of cardiovascular disease are shown here in Table 4.14.

Principal cause of death	Unadjusted HR (95% CI)				Adjusted HR (95% CI) †				P for interaction
	Non-CVD	p	CVD	p	Non-CVD	p	CVD	p	
Adrenal insufficiency of any type									
Disease of the circulatory system	1.66 (1.35-2.03)	<0.0001	1.08 (0.85-1.37)	0.52	1.87 (1.52-2.31)	<0.0001	1.26 (0.98-1.62)	0.071	**0.016**
Ischaemic heart disease	1.97 (1.47-2.66)	<0.0001	1.28 (0.92-1.80)	0.14	2.18 (1.61-2.96)	<0.0001	1.39 (0.97-1.98)	0.070	0.074
Cerebrovascular disease	1.22 (0.80-1.86)	0.36	0.93 (0.60-1.45)	0.75	1.39 (0.90-2.14)	0.13	1.10 (0.69-1.74)	0.68	0.49
Primary adrenal insufficiency									
Disease of the circulatory system	2.05 (1.45-2.89)	<0.0001	1.23 (0.76-1.99)	0.39	2.44 (1.72-3.46)	<0.0001	1.19 (0.73-1.95)	0.49	**0.010**
Ischaemic heart disease	2.32 (1.41-3.82)	0.0010	1.82 (0.98-3.39)	0.060	2.72 (1.64-4.52)	<0.0001	1.67 (0.87-3.19)	0.12	0.18
Cerebrovascular disease	1.08 (0.46-2.50)	0.86	0.72 (0.26-2.00)	0.53	1.30 (0.56-3.06)	0.54	0.70 (0.25-1.98)	0.50	0.34
Secondary adrenal insufficiency									
Disease of the circulatory system	1.60 (1.22-2.09)	0.0010	1.04 (0.77-1.41)	0.78	1.76 (1.33-2.32)	<0.0001	1.20 (0.87-1.66)	0.26	0.10
Ischaemic heart disease	2.10 (1.44-3.06)	<0.0001	1.03 (0.64-1.64)	0.91	2.26 (1.53-3.35)	<0.0001	1.10 (0.67-1.82)	0.71	**0.042**
Cerebrovascular disease	1.32 (0.79-2.23)	0.29	1.16 (0.71-1.92)	0.55	1.44 (0.84-2.48)	0.18	1.34 (0.79-2.27)	0.28	0.88

Table 4.14: Hazard ratios of cardiovascular mortality in patients with adrenal insufficiency, according to baseline status of cardiovascular disease (non-CVD vs CVD)

Note: † Adjustment for sex, age at the start of follow-up, baseline diabetes mellitus, hypertension and dyslipidaemia, and smoking any time; N for non-CVD cohorts, All adrenal insufficiency= 2969 vs 31122, Primary= 875 vs 9073, Secondary= 1788 vs 18647; N for CVD cohorts, All =578 vs 3822, Primary= 140 vs 952, Secondary= 348 vs 2344

In Table 4.14, according to the baseline status of cardiovascular disease, the hazard ratio for mortality risk from disease of the circulatory system associated with adrenal insufficiency of any type was significantly greater for non-cardiovascular disease (p for interaction= 0.016) whereas the hazard ratios for death from ischaemic heart disease and cerebrovascular disease were not statistically different (p for interaction= 0.074 and 0.49). Patients with primary adrenal insufficiency showed a similar pattern of differences (p for interaction= 0.010, 0.18 and 0.34, respectively). In secondary adrenal insufficiency, the hazard ratios for mortality risk from disease of the circulatory system and cerebrovascular disease associated with adrenal insufficiency were not significantly different (p for interaction= 0.10 and 0.88) whereas the hazard ratio for death from ischaemic heart disease appeared to be higher in those without pre-existing cardiovascular disease (p interaction= 0.042).

In summary, in patients with adrenal insufficiency of any type and primary adrenal insufficiency, the risk for death from disease of the circulatory system among those without pre-existing cardiovascular disease was higher than in those with pre-existing disease; however, the risks for death from ischaemic heart disease and from cerebrovascular disease were not different, according to the status of pre-existing cardiovascular disease. In patients with secondary adrenal insufficiency, the risk of death from ischaemic heart disease in those without cardiovascular disease appeared to be higher than those having previous cardiovascular disease, although the risks of death from circulatory system disease and cerebrovascular disease were not different according to the baseline status of cardiovascular disease.

4.4.5 Mortality rates and hazard ratios for risk of cardiovascular mortality associated with adrenal insufficiency, categorised by non-statin use and statin use

As in Section 4.2.5 for cardiovascular events, the risk of cardiovascular mortality associated with adrenal insufficiency in those using statins was compared with those not using statins. The baseline characteristics and proportions of cardiovascular risk factors in study patients and controls within each statin group are shown in the Appendix (Suppl. Table 4.38).

Full results for cardiovascular mortality rates and mortality rate differences in patients with adrenal insufficiency of any kind, primary and secondary adrenal insufficiency, and their matched controls, categorised by whether or not the participants received statins at the start of follow-up (statin use vs non-statin use) are shown in the Appendix (Suppl. Table 4.39, 4.40 and 4.41). Unadjusted and adjusted hazard ratios for risk of cardiovascular mortality categorised by statin use are shown here in Table 4.15.

Principal cause of death	Unadjusted HR (95% CI)				Adjusted HR (95% CI) †				P for interaction
	Non-statin use	p	Statin use	p	Non-statin use	p	Statin use	p	
Adrenal insufficiency of any type									
Disease of the circulatory system	1.35 (1.12-1.62)	0.0020	1.14 (0.84-1.56)	0.40	1.63 (1.36-1.97)	<0.0001	1.32 (0.97-1.81)	0.078	0.37
Ischaemic heart disease	1.46 (1.10-1.92)	0.0080	1.45 (0.95-2.19)	0.082	1.78 (1.35-2.35)	<0.0001	1.61 (1.06-2.44)	0.026	0.87
Cerebrovascular disease	0.98 (0.67-1.44)	0.92	1.17 (0.65-2.08)	0.60	1.17 (0.80-1.71)	0.41	1.33 (0.74-2.39)	0.34	0.53
Primary adrenal insufficiency									
Disease of the circulatory system	1.49 (1.07-2.08)	0.018	1.81 (1.02-3.20)	0.042	1.68 (1.21-2.34)	0.0020	2.07 (1.16-3.72)	0.015	0.49
Ischaemic heart disease	1.56 (0.95-2.56)	0.076	2.70 (1.31-5.57)	0.0070	1.81 (1.10-2.97)	0.019	2.82 (1.32-6.03)	0.0070	0.23
Cerebrovascular disease	0.94 (0.46-1.93)	0.86	0.68 (0.15-3.11)	0.61	1.01 (0.49-2.08)	0.97	0.87 (0.18-4.20)	0.85	0.74
Secondary adrenal insufficiency									
Disease of the circulatory system	1.35 (1.06-1.71)	0.016	0.90 (0.60-1.33)	0.58	1.71 (1.34-2.18)	<0.0001	1.01 (0.68-1.52)	0.94	**0.049**
Ischaemic heart disease	1.52 (1.06-2.17)	0.023	1.01 (0.57-1.76)	0.98	1.92 (1.34-2.75)	<0.0001	1.15 (0.65-2.02)	0.63	0.18
Cerebrovascular disease	1.13 (0.71-1.79)	0.61	1.17 (0.60-2.26)	0.64	1.42 (0.90-2.25)	0.13	1.24 (0.64-2.43)	0.52	0.93

Table 4.15: Hazard ratios of cardiovascular mortality in patients with adrenal insufficiency, according to statin use at baseline (non-statin use vs statin use)

Note: † Adjustment for sex, age at the start of follow-up, previous cardiovascular disease, baseline diabetes mellitus, hypertension and dyslipidaemia, and smoking any time; N for non-statin cohorts, All adrenal insufficiency= 2809 vs 33058, Primary= 844 vs 9505, Secondary= 1659 vs 19866; N for statin cohorts, All =738 vs 1886, Primary= 171 vs 520, Secondary= 477 vs 1125

In Table 4.15, the hazard ratios for mortality risk from disease of the circulatory system, ischaemic heart disease and cerebrovascular disease associated with adrenal insufficiency of any type were not significantly different, according to whether or not the patients used statins at baseline (p for interaction= 0.37, 0.87 and 0.53, respectively). This was also the case for patients with primary adrenal insufficiency (p for interaction= 0.49, 0.23 and 0.74, respectively). In secondary adrenal insufficiency, the hazard ratios for mortality risk from ischaemic heart disease and cerebrovascular disease were also not significantly different according to statin use (p for interaction= 0.18 and 0.93), although the hazard ratios for death from disease of the circulatory system appeared to be marginally higher in those not using statins (p for interaction= 0.049).

In summary, the risks of adrenal insufficiency of any type including primary and secondary adrenal insufficiency on cardiovascular mortality was not different according to statin use at baseline. Therefore, the risks were considered to be similar to the whole population of each type of adrenal insufficiency, regardless of statin use. The risk included death from disease of the circulatory system, ischaemic heart disease, and cerebrovascular disease.

It is important to recall that these mortality analyses included only participants having linkage to ONS mortality records and that participants are further sub-categorised according to sex, age or comorbidities. Compared with the analyses of cardiovascular events, the smaller numbers for the mortality analyses will have resulted in relatively lower study power.

4.5 Incident hospital admissions due to cardiovascular disease

This analysis focused on the incidence of hospital admissions with the primary diagnosis of cardiovascular disease for the first time during the follow-up period. Similar to the analysis of cardiovascular mortality (Section 4.3), cardiovascular disease defined here was disease of the circulatory system, ischaemic heart disease, or cerebrovascular disease, and participants were included only if they had data linked with HES.

Incidence rates and hazard ratios for risk of hospitalisation due to disease of the circulatory system, ischaemic heart disease and cerebrovascular disease associated with adrenal insufficiency

The incidence rates of hospitalisation in all study patients were compared with those in controls, and the incidence rate differences and hazard ratios were calculated. As for Sections 4.1 and 4.3, hazard ratios were adjusted for 'cardiovascular risk factors' and an additional analysis was performed to compare rates and risk of hospitalisation between patients with primary or secondary adrenal insufficiency.

- ❖ Adrenal insufficiency of any type and controls

This analysis included 3547 patients with adrenal insufficiency of any type and 34944 controls. For hospitalisation from disease of the circulatory system, the rate in the study patients was higher than that in controls (30.9 [95% CI, 28.3-33.6] and 19.0 [18.4-19.7] per 1000 person-years) with follow-up periods of 16916 and 168937 person-years, respectively, giving a hospitalisation rate difference of 11.8 (95% CI, 9.1-14.5) per 1000 person-years ($p<0.0001$, Table 4.16). The unadjusted hazard ratio was 1.62 (95% CI, 1.48-1.78; $p <0.0001$) and after adjustment for cardiovascular risk factors, the hazard ratio remained increased (adjusted HR 1.41, [95% CI, 1.28-1.55]; $p<0.0001$; Figure 4.3).

For ischaemic heart disease, the hospitalisation rate in the study patients was slightly higher than that in controls (7.7 [95% CI, 6.5-9.0] vs 6.3 [5.9-6.7] per 1000 person-years), giving a hospitalisation rate difference of 1.4 (95% CI, 0.0-2.7; p=0.017; Table 4.16) and an unadjusted hazard ratio of 1.22 (95% CI, 1.02-1.45; p=0.029). After adjustment for cardiovascular risk factors, the hazard ratio was no longer increased (adjusted HR, 0.97 [95% CI, 0.81-1.17]; p=0.76; Figure 4.3).

For cerebrovascular disease, the hospitalisation rate of the study patients was significantly higher than that of controls (6.8 [95%CI, 5.7-8.1] vs 3.9 [6.7-4.2] per 1000 person-years; p=0.20), giving a hospitalisation rate difference of 2.9 (95% CI, 1.7-4.1) per 1000 person-years (p<0.0001; Table 4.16). The unadjusted hazard ratio was significantly increased (1.74 [95% CI, 1.44-2.10]; p<0.0001). After adjustment for cardiovascular risk factors, the hazard ratio was lower but remained increased (adjusted HR, 1.46 [95% CI, 1.20-1.78]; p<0.0001; Figure 4.3).

Cause of hospitalisation	Study patients			Controls			Incidence rate difference per 1000 person-years (95% CI)	P
	No. 1st event	Person-years	Incidence per 1000 person-years (95% CI)	No. 1st event	Person-years	Incidence per 1000 person-years (95% CI)		
Adrenal insufficiency of any type (N= 3547 vs 34944)								
Disease of the circulatory system	522	16916	30.9 (28.3-33.6)	3217	168937	19.0 (18.4-19.7)	11.8 (9.1 to 14.5)	<0.0001
Ischaemic heart disease	139	18150	7.7 (6.5-9.0)	1107	175614	6.3 (5.9-6.7)	1.4 (0.0 to 2.7)	0.017
Cerebrovascular disease	125	18210	6.8 (5.7-8.1)	703	178481	3.9 (6.7-4.2)	2.9 (1.7 to 4.1)	<0.0001
Primary adrenal insufficiency (N= 1015 vs 10025)								
Disease of the circulatory system	145	4989	29.1 (24.7-34.2)	917	51481	17.8 (16.7-19.0)	11.3 (6.4 to 16.1)	<0.0001
Ischaemic heart disease	40	5352	7.5 (5.5-10.2)	322	53641	6.0 (5.4-6.7)	1.5 (-0.9 to 3.9)	0.098
Cerebrovascular disease	24	5440	4.4 (3.0-6.6)	210	54504	3.9 (3.4-4.4)	0.6 (-1.3 to 2.4)	0.26
Secondary adrenal insufficiency (N= 2136 vs 20991)								
Disease of the circulatory system	311	10329	30.1 (26.9-33.6)	1953	100483	19.4 (18.6-20.3)	10.7 (7.2 to 14.1)	<0.0001
Ischaemic heart disease	84	11084	7.6 (6.1-9.4)	673	104318	6.5 (6.0-7.0)	1.1 (-0.6 to 2.8)	0.084
Cerebrovascular disease	88	11147	7.9 (6.4-9.7)	424	106035	4.0 (3.6-4.4)	3.9 (2.2 to 5.6)	<0.0001

Table 4.16: Incidence rates of hospitalisation from cardiovascular disease in patients with adrenal insufficiency and matched controls

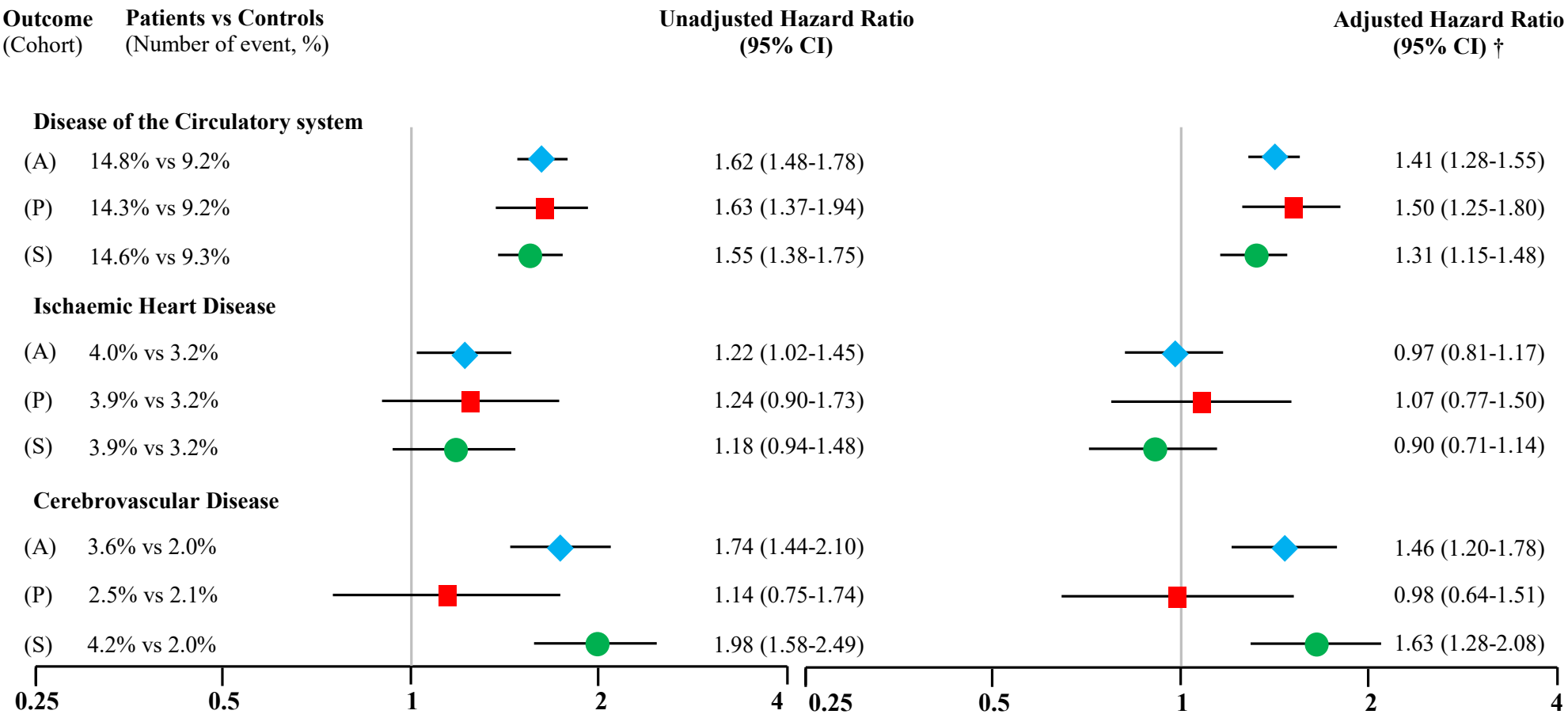


Figure 4.3: Unadjusted and adjusted hazard ratios of hospitalisation from cardiovascular disease in patients with adrenal insufficiency of any type, primary and secondary adrenal insufficiency

Note: † Adjustment for previous cardiovascular disease, baseline diabetes mellitus, hypertension and dyslipidaemia, and smoking any time; (A)-Adrenal insufficiency of any type; (P)-Primary adrenal insufficiency; (S)-Secondary adrenal insufficiency

❖ Primary adrenal insufficiency and controls

This analysis included 1015 patients with primary adrenal insufficiency and 10025 controls. For disease of the circulatory system, the hospitalisation rate in the study patients with primary adrenal insufficiency was higher than in controls (29.1 [95% CI, 24.7-34.2] vs 17.8 [16.7-19.0] per 1000 person-years) with follow-up periods of 4989 and 51481 person-years, respectively giving a hospitalisation rate difference of 11.3 (95% CI, 6.4-16.1) per 1000 person-years ($p<0.0001$; Table 4.16). The unadjusted hazard ratio was also increased (HR, 1.63 [95% CI, 1.37-1.94]; $p<0.0001$) and after adjustment for cardiovascular risk factors, the hazard ratio remained increased (adjusted HR 1.50, [95% CI, 1.25-1.80]; $p<0.0001$; Figure 4.3).

For ischaemic heart disease, the hospitalisation rate in the study patients with primary adrenal insufficiency was slightly higher than that in controls (7.5 [95% CI, 5.5-10.2] vs 6.0 [5.4-6.7] per 1000 person-years), giving a hospitalisation rate difference of 1.5 (95% CI, -0.9 to 3.9) per 1000 person-years ($p=0.098$; Table 4.16). The unadjusted hazard ratio was not significantly increased (HR, 1.24 [95% CI, 0.90-1.73]; $p=0.19$) and after adjustment for cardiovascular risk factors, the hazard ratio was also not increased (adjusted HR, 1.07 [95% CI, 0.77-1.50]; $p=0.67$; Figure 4.3).

For cerebrovascular disease, the hospitalisation rate of the study patients with primary adrenal insufficiency was similar to controls (4.4 [95% CI, 3.0-6.6] vs 3.9 [3.4-4.4] per 1000 person-years), giving a hospitalisation rate difference of 0.6 (-1.3 to 2.4 per 1000 person-years; $p=0.26$; Table 4.16) and an unadjusted hazard ratio of 1.14 (95% CI, 0.75-1.74; $p=0.53$). After adjustment for cardiovascular risk factors, the hazard ratio remained not significant (unadjusted HR, 0.98 [95% CI, 0.64-1.51]; $p=0.94$; Figure 4.3).

- Secondary adrenal insufficiency and controls

This analysis included 2136 patients with secondary adrenal insufficiency and 20991 controls. For disease of the circulatory system, the hospitalisation rate of the study patients was higher than that of controls (30.1 [95% CI, 26.9-33.6] vs 19.4 [18.6-20.3] per 1000 person-years) with follow-up periods of 10329 and 20991 person-years, respectively, giving a hospitalisation rate difference of 10.7 (95% CI, 7.2-14.1) per 1000 person-years ($p<0.0001$; Table 4.16). The unadjusted hazard ratio was 1.55 (95% CI, 1.38-1.75; $p<0.0001$) and after adjustment for cardiovascular risk factors, the hazard ratio was lower but remained significantly increased (adjusted HR 1.31, [95% CI, 1.15-1.48]; $p<0.0001$; Figure 4.3).

For ischaemic heart disease, the hospitalisation rate in the study patients with secondary adrenal insufficiency was similar to that in controls (7.6 [95% CI, 6.1-9.4] vs 6.5 [6.0-7.0] per 1000 person-years), giving a hospitalisation rate difference of 1.1 (95% CI, -0.6 to 2.8) per 1000 person-years ($p=0.084$). The hazard ratio was equally not increased (adjusted HR, 0.90 [95% CI, 0.71-1.14]; $p=0.38$; Figure 4.3).

For cerebrovascular disease, the hospitalisation rate of the study patients with secondary adrenal insufficiency was significantly higher than that of controls (7.9 [95% CI, 6.4-9.7] vs 4.0 [3.6-4.4] per 1000 person-years), giving a hospitalisation rate difference of 3.9 (95% CI, 2.2-5.6) per 1000 person-years ($p<0.0001$; Table 4.16). The unadjusted hazard ratio was significant (1.98 [95% CI, 1.58-2.49]; $p<0.0001$) and after adjustment for cardiovascular risk factors, the hazard ratio remained increased (adjusted HR, 1.63 [95% CI, 1.28-2.08]; $p<0.0001$; Figure 4.3).

- Unspecified adrenal insufficiency and controls

This analysis included 396 patients with unspecified adrenal insufficiency and 3928 controls. For disease of the circulatory system, the hospitalisation rate of the study patients was higher than that of controls (41.3 [95% CI, 32.4-52.6] vs 20.4 [18.4-22.7] per 1000 person-years) with follow-up periods of 1598 and 16973 person-years, respectively. The hospitalisation rate difference was significantly increased (20.9 [95% CI, 10.7-31.0] per 1000 person-years, p<0.0001). The unadjusted hazard ratio was significantly increased (2.02 [95% CI, 1.55-2.63]; p<0.0001) and after adjustment for cardiovascular risk factors, it remained increased (adjusted HR 1.72, [95% CI, 1.31-2.26]; p<0.0001; Suppl. Table 4.42).

For ischaemic heart disease, the hospitalisation rate in the study patients with unspecified adrenal insufficiency was slightly higher than that in controls (8.7 [95% CI, 5.3-14.5] vs 6.3 [5.3-7.6] per 1000 person-years), giving a hospitalisation rate difference of 2.4 (95% CI, -2.2 to 7.0 per 1000 person-years; p=0.21). The unadjusted hazard ratio was not significantly increased 1.39 (95% CI, 0.81-2.38; p=0.23) and after adjustment for cardiovascular risk factors, the hazard ratio was also not increased (adjusted HR, 1.11 [95% CI, 0.64-1.95]; p=0.70; Suppl. Table 4.42).

For cerebrovascular disease, the hospitalisation rate in the study patients with unspecified adrenal insufficiency was significantly higher than that in controls (7.5 [95% CI, 4.4-13.0] vs 3.8 [3.0-4.9] per 1000 person-years), giving a hospitalisation rate difference of 3.7 (-0.5 to 7.9) per 1000 person-years (p=0.018). The unadjusted hazard ratio was increased (HR, 1.96 [1.08-3.54]; p=0.026) and after adjustment for cardiovascular risk factors, it remained increased (Suppl. Table 4.42).

❖ Primary and secondary adrenal insufficiency

This analysis compared hospital admission due to cardiovascular disease between patients with primary and those with secondary adrenal insufficiency. Similar to the analysis of cardiovascular events and mortality, the differences in sex, age, and cardiovascular risk factors were taken into account in this analysis.

For disease of the circulatory system, the hospitalisation rate of patients with primary adrenal insufficiency was similar to that of secondary adrenal insufficiency, giving a hospitalisation rate difference of -1.0 (95% CI, -6.8 to 4.7) per 1000 person-years (p=0.36) and an unadjusted hazard ratio of 0.97 (95% CI, 0.79-1.18; p=0.74). After adjustment for sex and age of adrenal insufficiency, the hazard ratio for patients with primary adrenal insufficiency relative to secondary remained not increased (adjusted HR, 1.08 [95% CI, 0.89-1.32]; p=0.42). Also, after adjustment for previous cardiovascular disease, diabetes, hypertension and dyslipidaemia at adrenal insufficiency diagnosis, and ever smoking, the hazard ratio for hospitalisation from the disease of circulatory system remained not significantly increased (adjusted HR, 1.14 [95% CI, 0.93-1.39]; p=0.19; Table 4.17).

For ischaemic heart disease, the hospitalisation rate of patients with primary adrenal insufficiency was also similar to that of secondary disease, giving a hospitalisation rate difference of -0.1 (95% CI, -2.9 to 2.7) per 1000 person-years (p=0.47). The unadjusted hazard ratio of primary relative to secondary adrenal insufficiency was 0.99 (95% CI, 0.68-1.45; p=0.96). After adjustment for sex and age of diagnosis, the hazard ratio was higher but remained not significantly increased (adjusted HR, 1.17 [95% CI, 0.80-1.72]; p=0.41). After adjustment for cardiovascular risk factors at the diagnosis of adrenal insufficiency and ever smoking, the hazard ratio was higher but remained not significantly increased (adjusted HR, 1.25 [95% CI, 0.85-1.83]; p=0.25; Table 4.17).

Cardiovascular causes of hospitalisation	Circulatory system			Ischaemic heart disease			Cerebrovascular disease		
Models	HR	95%CI	P	HR	95%CI	P	HR	95%CI	P
Univariable analysis (Unadjusted)	0.97	0.79-1.18	0.74	0.99	0.68-1.45	0.96	0.56	0.36-0.88	0.012
Adjustment for sex, age in years at start of follow-up	1.06	0.87-1.30	0.55	1.15	0.79-1.68	0.47	0.59	0.38-0.94	0.025
Adjustment for sex, age in years at diagnosis	1.08	0.89-1.32	0.42	1.17	0.80-1.72	0.41	0.61	0.38-0.96	0.031
Adjustment for previous cardiovascular disease, diabetes, hypertension, dyslipidaemia at start of follow-up, and smoking any time	1.17	0.96-1.43	0.11	1.32	0.90-1.94	0.16	0.67	0.43-1.06	0.089
Adjustment for previous cardiovascular disease, diabetes, hypertension, dyslipidaemia at diagnosis, and smoking any time	1.14	0.93-1.39	0.19	1.25	0.85-1.83	0.25	0.66	0.42-1.04	0.071
Adjustment for sex, age at start of follow-up, previous cardiovascular disease, diabetes, hypertension, dyslipidaemia at start of follow-up, and smoking any time	1.16	0.95-1.42	0.15	1.30	0.88-1.92	0.18	0.64	0.40-1.01	0.057
Adjustment for sex, age at diagnosis, previous cardiovascular disease, diabetes, hypertension, dyslipidaemia at diagnosis, and smoking any time	1.15	0.94-1.41	0.17	1.25	0.85-1.84	0.25	0.63	0.40-1.00	0.052

Table 4.17: Unadjusted and adjusted hazard ratios of hospitalisation from cardiovascular disease in patients with primary adrenal insufficiency, relative to secondary adrenal insufficiency

For cerebrovascular disease, the hospitalisation rate of patients with primary adrenal insufficiency was significantly lower than for those with secondary disease, giving a hospitalisation rate difference of -3.5 (95% CI, -5.9 to -1.1) per 1000 person-years (p=0.0043). The unadjusted hazard ratio for patients with primary adrenal insufficiency relative to those with secondary disease was significantly decreased (HR, 0.56 [95% CI, 0.36-0.88]; p=0.012). After adjustment for sex and age at diagnosis, the hazard ratio remained significantly decreased (adjusted HR, 0.61 [95% CI, 0.38-0.96]; p=0.031). However, after adjustment for cardiovascular risk factors at the diagnosis of adrenal insufficiency and ever smoking, the hazard ratio was no longer significantly decreased (adjusted HR, 0.66 [95% CI, 0.42-1.04]; p=0.071; Table 4.17).

In summary, in patients with adrenal insufficiency and secondary adrenal insufficiency, the risks of hospitalisation from disease of the circulatory system and cerebrovascular disease were increased, even when cardiovascular risk factors were taken into account, although the risk of hospitalisation from ischaemic heart disease was not increased. In patients with primary adrenal insufficiency, the risk of hospitalisation from disease of the circulatory system was increased but the risk was not increased when cardiovascular disease specific to atherosclerosis (ischaemic heart disease or cerebrovascular disease) was distinguished.

The increased risk for hospitalisation from disease of the circulatory system across all types of adrenal insufficiency while the risk for hospitalisation from ischaemic heart disease was not increased, suggested that the primary disease was likely to be a non-atherosclerotic process such as valvular heart disease, in which adrenal insufficiency might have had an adverse effect and contributed to hospital admissions.

4.6 Hospital admissions due to cardiovascular disease stratified by sex and age

This analysis compared the hospitalisation rate from cardiovascular disease of the study patients with controls within each sex or age category. As in Section 4.5, the outcomes consisted of hospitalisation from disease of the circulatory system, ischaemic heart disease and cerebrovascular disease, and the participants included were only those having linked data. The hospitalisation rate and hazard ratio were evaluated based on the category of sex and age at start of follow-up. Hazard ratios were adjusted for 'cardiovascular risk factors'.

4.6.1 Incidence rates and hazard ratios for risk of hospitalisation due to cardiovascular disease associated with adrenal insufficiency, categorised by men and women

Full results for incidence rates and incidence rate differences of hospitalisation due to cardiovascular disease in patients with adrenal insufficiency of any type, primary and secondary adrenal insufficiency and their matched controls, categorised by sex are shown in the Appendix (Suppl. Table 4.43, 4.44 and 4.45). Unadjusted and adjusted hazard ratios for risk of hospitalisation due to cardiovascular disease, categorised by sex, are shown here in Table 4.18.

Cause of hospitalisation	Unadjusted HR (95% CI)				Adjusted HR (95% CI) †				P for interaction
	Men	p	Women	p	Men	p	Women	p	
Adrenal insufficiency of any type									
Disease of the circulatory system	1.56 (1.38-1.77)	<0.0001	1.71 (1.49-1.96)	<0.0001	1.37 (1.20-1.56)	<0.0001	1.47 (1.28-1.69)	<0.0001	0.22
Ischaemic heart disease	1.19 (0.95-1.49)	0.13	1.29 (0.97-1.72)	0.083	0.97 (0.77-1.23)	0.82	1.00 (0.74-1.34)	0.98	0.44
Cerebrovascular disease	1.74 (1.33-2.28)	<0.0001	1.74 (1.33-2.28)	<0.0001	1.57 (1.19-2.07)	0.0020	1.37 (1.03-1.81)	0.029	0.86
Primary adrenal insufficiency									
Disease of the circulatory system	1.60 (1.23-2.08)	<0.0001	1.65 (1.30-2.09)	<0.0001	1.44 (1.10-1.90)	0.0090	1.55 (1.22-1.97)	<0.0001	0.44
Ischaemic heart disease	1.08 (0.67-1.76)	0.74	1.43 (0.91-2.23)	0.11	0.88 (0.53-1.45)	0.61	1.27 (0.81-2.01)	0.29	0.15
Cerebrovascular disease	0.74 (0.32-1.69)	0.46	1.40 (0.85-2.29)	0.18	0.60 (0.26-1.41)	0.24	1.24 (0.75-2.05)	0.40	0.10
Secondary adrenal insufficiency									
Disease of the circulatory system	1.52 (1.30-1.77)	<0.0001	1.63 (1.35-1.97)	<0.0001	1.31 (1.12-1.54)	0.0010	1.32 (1.09-1.61)	0.0050	0.56
Ischaemic heart disease	1.19 (0.91-1.56)	0.20	1.18 (0.78-1.78)	0.44	0.95 (0.71-1.26)	0.70	0.85 (0.55-1.31)	0.46	0.94
Cerebrovascular disease	2.03 (1.50-2.75)	<0.0001	1.94 (1.36-2.76)	<0.0001	1.85 (1.34-2.54)	<0.0001	1.40 (0.96-2.04)	0.077	0.89

Table 4.18: Hazard ratios of hospitalisation from cardiovascular disease in patients with adrenal insufficiency, according to sex

Note: † Adjustment for previous cardiovascular disease, baseline diabetes mellitus, hypertension and dyslipidaemia, and smoking any time; N for male cohorts, All adrenal insufficiency= 1629 vs 16059, Primary= 410 vs 4077, Secondary= 1054 vs 10343; N for female cohorts, All =1918 vs 18885, Primary= 605 vs 5948, Secondary= 1082 vs 10648

In Table 4.18, the hazard ratios for risk of hospitalisation from disease of the circulatory system, ischaemic heart disease and cerebrovascular disease associated with adrenal insufficiency of any type were not significantly different between men and women (p for interaction= 0.22, 0.44 and 0.86, respectively). Neither were they significantly different in primary adrenal insufficiency (p for interaction= 0.44, 0.15 and 0.10, respectively) nor in secondary adrenal insufficiency (p for interaction= 0.56, 0.94 and 0.89, respectively).

In summary, the risks of hospitalisation from disease of the circulatory system, ischaemic heart disease, or cerebrovascular disease were not different according to sex. This was consistently observed in both primary and secondary adrenal insufficiency. Therefore, the risks on hospitalisation from each cardiovascular disease were considered to be similar to the whole population of each type of adrenal insufficiency, regardless of sex.

4.6.2 Incidence rates and hazard ratios for risk of hospitalisation due to cardiovascular disease associated with adrenal insufficiency, categorised by younger and older age at the start of follow-up

Full results for incidence rates and incidence rate differences of hospitalisation due to cardiovascular disease in patients with adrenal insufficiency of any type, primary and secondary adrenal insufficiency and their matched controls, categorised by whether the participants were at younger (<50 y) and older age (≥50 y) at the start of follow-up are shown in the Appendix (Suppl. Table 4.46, 4.47 and 4.48). Unadjusted and adjusted hazard ratios for risk of hospitalisation due to cardiovascular disease, categorised by age, are shown here in Table 4.19.

Cause of hospitalisation	Unadjusted HR (95% CI)				Adjusted HR (95% CI) †				P for interaction
	Age <50	p	Age ≥50	p	Age <50	p	Age ≥50	p	
Adrenal insufficiency of any type									
Disease of the circulatory system	2.07 (1.65-2.59)	<0.0001	1.61 (1.46-1.79)	<0.0001	1.76 (1.40-2.22)	<0.0001	1.44 (1.30-1.60)	<0.0001	**0.014**
Ischaemic heart disease	1.19 (0.68-2.08)	0.54	1.26 (1.05-1.52)	0.015	0.86 (0.48-1.52)	0.59	1.04 (0.86-1.26)	0.68	0.79
Cerebrovascular disease	4.34 (2.55-7.40)	<0.0001	1.62 (1.32-2.00)	<0.0001	3.97 (2.30-6.86)	<0.0001	1.42 (1.14-1.76)	0.0010	**<0.0001**
Primary adrenal insufficiency									
Disease of the circulatory system	1.91 (1.28-2.84)	0.0020	1.67 (1.37-2.03)	<0.0001	1.65 (1.08-2.53)	0.020	1.55 (1.27-1.89)	<0.0001	0.51
Ischaemic heart disease	1.56 (0.66-3.71)	0.31	1.26 (0.88-1.80)	0.19	1.12 (0.44-2.90)	0.80	1.11 (0.77-1.59)	0.57	0.58
Cerebrovascular disease	1.38 (0.31-6.12)	0.67	1.20 (0.77-1.87)	0.41	1.43 (0.31-6.57)	0.64	1.06 (0.68-1.66)	0.79	0.85
Secondary adrenal insufficiency									
Disease of the circulatory system	2.03 (1.52-2.72)	<0.0001	1.52 (1.34-1.74)	<0.0001	1.80 (1.33-2.43)	<0.0001	1.32 (1.15-1.51)	<0.0001	**0.020**
Ischaemic heart disease	0.81 (0.35-1.87)	0.62	1.25 (0.99-1.59)	0.062	0.57 (0.24-1.36)	0.20	0.99 (0.78-1.27)	0.96	0.56
Cerebrovascular disease	6.26 (3.43-11.42)	<0.0001	1.74 (1.35-2.24)	<0.0001	5.95 (3.20-11.06)	<0.0001	1.48 (1.13-1.94)	0.0040	**<0.0001**

Table 4.19: Hazard ratios hospitalisation from cardiovascular disease in patients with adrenal insufficiency, according to age at the start of follow-up

Note: † Adjustment for previous cardiovascular disease, baseline diabetes mellitus, hypertension and dyslipidaemia, and smoking any time; N for younger cohorts, All adrenal insufficiency= 1565 vs 15641, Primary= 484 vs 4855, Secondary= 931 vs 9277; N for older cohorts, All =1982 vs 19303, Primary= 531 vs 5170, Secondary= 1205 vs 11714

In Table 4.19, the hazard ratios for risk of hospitalisation due to disease of the circulatory system and cerebrovascular disease associated with adrenal insufficiency of any type were significantly higher in the younger age group at the start of follow-up (p for interaction =0.014 and <0.0001) whereas the hazard ratio for risk of hospitalisation due to ischaemic heart disease was not significantly different according to age (p for interaction= 0.79). This was also the case for patients with secondary adrenal insufficiency (p for interaction = 0.020, <0.0001 and 0.56, respectively). In primary adrenal insufficiency, the hazard ratios for risk of hospitalisation due to disease of the circulatory system, cerebrovascular disease and ischaemic heart disease were not significantly different according to age (p for interaction= 0.51, 0.85 and 0.58, respectively).

In summary, in adrenal insufficiency of any type and secondary adrenal insufficiency, the risks of hospitalisation from disease of the circulatory system and cerebrovascular disease in younger patients were higher than in older individuals. However, in these patients, the risk of hospitalisation from ischaemic heart disease was not increased, regardless of age. In primary adrenal insufficiency, the risks of hospitalisation from disease of the circulatory system, ischaemic heart disease, or cerebrovascular disease was not different according to age; therefore, the risks were considered to be similar to risks assessed in the whole cohort.

4.7 Association of cardiovascular disease in patients with adrenal insufficiency with other comorbidities

This analysis comprised two parts: (1) the association between cardiovascular events observed in patients with adrenal insufficiency and death from adrenal crisis; and (2) the association between cerebrovascular events observed in secondary adrenal insufficiency and ever treated with radiotherapy. The associations were expressed as odds ratios and odds ratios adjusted for sex, age at the start of follow-up, and cardiovascular risk factors (previous cardiovascular disease, diabetes mellitus, hypertension and dyslipidaemia at the start of follow-up, and ever smoking at any time).

4.7.1 The association between cardiovascular events and death with adrenal crisis

This analysis included only patients with adrenal insufficiency and compared the mortality from adrenal crisis between those having composite cardiovascular events during the follow-up period and those without cardiovascular events. This was a cause-specific mortality analysis and, therefore, included only patients with ONS linkage.

From a total of 3547 patients with adrenal insufficiency of any type, 518 patients had composite cardiovascular events during the follow-up period whereas 66 patients had adrenal crisis as an associated cause of death (Table 4.20). The proportion of patients who died with adrenal crisis was significantly higher in those with cardiovascular events than those without cardiovascular events (5.0% vs 1.3%; $p<0.0001$), consistent with an unadjusted odds ratio of 3.95 (95% CI, 2.39-6.53; $p<0.0001$). After adjustment for cardiovascular risk factors, the odds ratio was higher (adjusted OR, 4.73 [2.73-8.18]; $p<0.0001$). After adjustment for sex, age, and cardiovascular risk factors, the odds ratio was reduced but remained significantly elevated (adjusted OR, 2.97 [1.72-5.14]; $p<0.0001$).

Cohort	No. death from adrenal crisis/ total patients (%)		P	Unadjusted OR (95% CI)	p	Adjusted OR† (95% CI)	p	Adjusted OR‡ (95% CI)	p
	CVD	No CVD							
All adrenal insufficiency (N= 3547)	26/ 518 (5.0%)	40/ 3029 (1.3%)	<0.0001	3.95 (2.39-6.53)	<0.0001	4.73 (2.73-8.18)	<0.0001	2.97 (1.72-5.14)	<0.0001
Primary adrenal insufficiency (N= 1015)	25/ 126 (19.8%)	36/ 889 (4.1%)	<0.0001	5.86 (3.38-10.17)	<0.0001	6.95 (3.76-12.83)	<0.0001	4.76 (2.57-8.82)	<0.0001
Secondary adrenal insufficiency (N= 2136)	1/ 338 (0.3%)	2/ 1798 (0.1%)	0.40	2.66 (0.24-29.47)	0.42	3.47 (0.31-38.82)	0.31	4.10 (0.25-66.16)	0.32

Table 4.20: The association between cardiovascular events and death with adrenal crisis

Note: † Adjustment for previous cardiovascular disease, baseline diabetes mellitus, hypertension and dyslipidaemia, and smoking any time
‡ Adjustment for sex, age at start of follow-up, baseline diabetes mellitus, hypertension and dyslipidaemia, and smoking any time

CVD: having cardiovascular events having cardiovascular events (composite cardiovascular disease) during the follow-up period

From a total of 1015 patients with primary adrenal insufficiency, 126 patients had composite cardiovascular events during the follow-up period whereas 61 patients had adrenal crisis as an associated cause of death (Table 4.20). Similar to patients with adrenal insufficiency of any type, the proportion of patients who died with adrenal crisis was markedly higher in those with cardiovascular events than those without cardiovascular events (19.8% vs 4.1%; p<0.0001), consistent with an unadjusted odds ratio of 5.86 (95% CI, 3.38-10.17; p<0.0001). After adjustment for cardiovascular risk factors, the odds ratio was higher (adjusted OR, 6.95 [3.76-12.83]; p<0.0001). After adjustment for sex, age, and cardiovascular risk factors, the odds ratio remained significantly increased (adjusted OR, 4.76 [2.57-8.82]; p<0.0001).

From a total of 2136 patients with secondary adrenal insufficiency, 338 patients had composite cardiovascular events during the follow-up period whereas only three patients had adrenal crisis as an associated cause of death (Table 4.20). The proportion of patients who died with adrenal crisis was higher in those with cardiovascular events than those without cardiovascular events, although not significantly (0.3% vs 0.1%; p=0.40). The number of deaths with adrenal crisis in secondary adrenal insufficiency was small and neither the unadjusted nor the adjusted odds ratios reached statistical significance (Table 4.20).

In summary, there was a strong association between incident cardiovascular events and death with adrenal crisis in patients with adrenal insufficiency, in particular primary adrenal insufficiency. For patients with secondary adrenal insufficiency, as the number of deaths with adrenal crisis was low, the association could not be reliably investigated.

4.7.2 The association between cerebrovascular events and ever treated with radiotherapy in patients with secondary adrenal insufficiency

According to Section 4.1, there was an increase in the hazard ratio for cerebrovascular disease, restricted to patients with secondary adrenal insufficiency and the hazard ratio remained significantly increased after adjustment for cardiovascular risk factors. This suggested that the increased risk of cerebrovascular disease was independent of cardiovascular risk factors. Moreover, despite the risk of cerebrovascular disease being increased, the hazard ratio for ischaemic heart disease was not increased, suggesting that the increased risk of cerebrovascular disease in patients with secondary adrenal insufficiency might have not been associated with a systemic atherosclerotic process. In addition, according to previous literature, there is a strong association between cranial radiation and mortality, particularly from cerebrovascular disease, in patients with pituitary disorders. Therefore, this analysis examined whether radiotherapy could increase the risks for: 1) cerebrovascular events, 2) ischaemic heart disease events, 3) all-cause mortality, 4) death from cerebrovascular disease, and 5) hospitalisation due to cerebrovascular disease in patients with secondary adrenal insufficiency.

From a total of 3948 patients with secondary adrenal insufficiency, 520 patients had received radiotherapy whereas 281 patients had cerebrovascular events, 271 had ischaemic heart disease events, and 746 died from any cause during the follow-up period (Table 4.21).

Outcomes	**Radiotherapy**, No. events/ total patients (%)		P	**Unadjusted OR (95%CI)**	**p**	**Adjusted OR (95%CI) †**	**p**	**Adjusted OR (95%CI) ‡**	**p**
	Yes	No							
Cerebrovascular disease events (N = 3948)	59/ 520 (11.4)	222/ 3428 (6.5)	<0.0001	1.85 (1.36-2.50)	<0.0001	1.86 (1.37-2.53)	<0.0001	1.94 (1.42-2.64)	<0.0001
Ischaemic heart disease events (N = 3948)	35/ 520 (6.7)	236/ 3428 (6.9)	0.89	0.98 (0.68-1.41)	0.89	0.99 (0.67-1.45)	0.94	1.00 (0.68-1.48)	0.98
All-cause mortality (N= 3948)	127/ 520 (24.4)	619/ 3428 (18.1)	0.0010	1.47 (1.18-1.82)	0.0010	1.52 (1.21-1.91)	<0.0001	1.69 (1.32-2.16)	<0.0001
Death from cerebrovascular disease (N =2136)	7/ 264 (2.7)	27/ 1872 (1.4)	0.14	1.86 (0.80-4.32)	0.14	1.92 (0.81-4.53)	0.13	2.20 (0.91-5.31)	0.078
Hospitalisation from cerebrovascular disease (N =2136)	24/ 264 (9.1)	65/ 1872 (3.5)	<0.0001	2.78 (1.71-4.52)	<0.001	2.92 (1.77-4.80)	<0.0001	2.98 (1.80-4.90)	<0.0001

Table 4.21: Cerebrovascular disease, ischaemic heart disease, and mortality in patients with secondary adrenal insufficiency undergoing radiotherapy

Note: † Adjustment for previous cardiovascular disease, baseline diabetes mellitus, hypertension and dyslipidaemia, and smoking any time

‡ Adjustment for sex, age at start of follow-up, baseline diabetes mellitus, hypertension and dyslipidaemia, and smoking any time

Regarding cerebrovascular events, the proportion of patients with incident events was significantly higher in those with radiotherapy than those without radiotherapy (11.4% vs 6.5%; p<0.0001), consistent with an unadjusted odds ratio of 1.85 (95% CI, 1.36-2.50; p<0.0001). After adjustment for cardiovascular risk factors, the odds ratio for cerebrovascular events was almost unchanged (adjusted OR, 1.86 [1.37-2.53]; p<0.0001). After adjustment for sex, age, and cardiovascular risk factors, the odds ratio was further increased (adjusted OR, 1.94 [1.42-2.64]; p<0.0001).

Regarding ischaemic heart disease events, the proportion of patients with incident events was similar between those with and without radiotherapy (6.7% vs 6.9%; p=0.89), giving an unadjusted odds ratio of 0.98 (95% CI, 0.68-1.41; p=0.89). After adjustment for age, sex, and cardiovascular risk factors, the odds ratio remained not increased (Table 4.21).

Regarding all-cause mortality, the proportion of deaths in patients with radiotherapy was also higher than those without radiotherapy (24.4% vs 18.1%; p=0.0010), consistent with an unadjusted odds ratio of 1.47 (95% CI, 1.18-1.82; p=0.0010). After adjustment for cardiovascular risk factors, the odds ratio remained increased (adjusted OR, 1.52 [95% CI, 1.21-1.91]; p<0.0001). After adjustment for sex, age, and cardiovascular risk factors, the odds ratio was further increased (adjusted OR, 1.69 [95% CI, 1.32-2.16]; p<0.0001); Table 4.62).

From a total of 2136 patients with secondary adrenal insufficiency having linked HES/ ONS data, 34 died from cerebrovascular disease and 89 patients were admitted to hospital from cerebrovascular disease (Table 4.21).

Regarding cerebrovascular mortality, the proportion of deaths in those with radiotherapy was not significantly higher than those without (2.7% vs 1.4%; p=0.14). The unadjusted odds ratio was also not significant (OR, 1.86 [95% CI, 0.80-4.32]; p=0.14) and after adjustment, the odds ratios remained not significantly increased (Table 4.21).

Regarding hospitalisation from cerebrovascular disease, the proportion of admitted patients was also higher in those with radiotherapy than those without (9.1% vs 3.5%; p<0.0001), giving an unadjusted odds ratio of 2.78 (95% CI, 1.71-4.52; p<0.0001). After adjustment for cardiovascular risk factors, the odds ratio was further increased (adjusted OR, 2.92 [95% CI, 1.77-4.80]; p<0.0001) and it was almost unchanged after further adjustment for sex and age at the start of follow-up (adjusted OR, 2.98 [95% CI, 1.80-4.90]; p<0.0001; Table 4.21).

In summary, in patients with secondary adrenal insufficiency, there was an association of radiotherapy with cerebrovascular events, all-cause mortality, and hospitalisation from cerebrovascular disease. Furthermore, the associations remained significant after sex, age, and cardiovascular risk factors were taken into account. By contrast, no association between radiotherapy and ischaemic heart disease was observed. This suggested the increased risk for cerebrovascular disease observed in secondary adrenal insufficiency patients who underwent radiotherapy was unlikely to be related with a systemic atherosclerosis process. However, the association between radiotherapy and cerebrovascular mortality could not be reliably investigated since the number of deaths from this cause was low.

CHAPTER 5: SENSITIVITY ANALYSIS

This chapter presents analyses aiming to validate the classification of the study patients, the assignment of death and cardiovascular disease in CPRD GOLD, and the assignment of smoking status for all participants. In addition, baseline characteristics of the participants who had been diagnosed with adrenal insufficiency before the start of study were evaluated.

5.1 The validation of diagnostic codes used to define adrenal insufficiency in CPRD

Since the diagnosis of adrenal insufficiency was mainly confirmed in the hospital setting where dynamic biochemical tests can be performed, the record of adrenal insufficiency in the primary care setting might have been inaccurate. This analysis aimed to validate the diagnostic codes used to define adrenal insufficiency in CPRD (Medical codes or Read codes). The codes for each type of adrenal insufficiency were validated separately using the diagnostic codes (ICD-10 codes) described in hospital admissions from HES data as a standard reference. ICD-10 codes used for validating the diagnosis of primary adrenal insufficiency consisted of the codes describing primary adrenal insufficiency and adrenal crisis. As an ICD-10 code describing secondary adrenal insufficiency was not available, the codes describing hypopituitarism, hypothalamic pituitary disorders, pituitary adenoma, and adrenal crisis were used to validate the diagnosis of secondary adrenal insufficiency (Appendix, Suppl. Table 5.1). Study patients assigned as primary (or secondary) adrenal insufficiency in CPRD who were admitted to hospital were extracted and their ICD-10 codes (including primary and secondary diagnoses and comorbidities) in hospital admissions were examined. Positive predictive value for the diagnosis of primary (or secondary) adrenal insufficiency was calculated from the proportion

of patients having ICD-10 codes for primary (or related to secondary) adrenal insufficiency in HES data to the total number of primary (or secondary) adrenal insufficiency patients in CPRD who were admitted to hospitals.

Hospital admission information of the 1015 patients with primary and 2136 patients with secondary adrenal insufficiency with linked HES data and start date from 1997 onwards was evaluated. For primary adrenal insufficiency, a total of 976 patients were admitted to hospital. Of these, 859 patients had ICD-10 codes for primary adrenal insufficiency and 30 did not have valid ICD-10 codes for hospital admissions, giving the positive predictive value for the diagnosis of primary adrenal insufficiency in CPRD of 90.7% (859/ [976-30]). For secondary adrenal insufficiency, a total of 2056 patients were admitted to the hospitals. Of these, 1529 patients had ICD-10 codes related to secondary adrenal insufficiency and 113 did not have valid ICD-10 codes in hospital admissions, giving the positive predictive value for the diagnosis of secondary adrenal insufficiency in CPRD of 78.7% (1529/ [2056-113]).

In summary, the diagnosis of primary and secondary adrenal insufficiency using CPRD data in conjunction with having a glucocorticoid prescription as inclusion criteria in this study yielded acceptable reliability as the in-hospital diagnosis was used as a standard reference. However, the positive predictive value for diagnosis of secondary adrenal insufficiency was lower, which might have resulted from the unavailability of a direct code for secondary adrenal insufficiency.

5.2 The validation of the assignment of death status in CPRD

Approximately 50% of participants in this study did not have data linked to ONS information. This analysis aimed to validate the reliability of mortality information recorded in CPRD by using ONS information as a reference standard. The mortality status of participants linked with ONS data and having the start date from 1997 onwards was investigated. False negative and false positive rates were calculated overall and separately for patients with adrenal insufficiency and controls. The false negative rate was the proportion of the number of participants recorded as having died by ONS but with no death recorded in CPRD to the total number of deaths recorded in ONS. The false positive rate was the proportion of participants recorded as having died in CPRD but with no death recorded in ONS to the total number of alive participants in ONS. In addition, the risk for all-cause mortality of adrenal insufficiency using the mortality status and the date of death recorded in CPRD and in ONS was calculated separately using univariable Cox logistic regression analysis.

The mortality status of 38491 participants (3547 study patients and 34944 controls) were examined, for whom 4336 and 4383 deaths were recorded in ONS and CPRD, respectively. Of the 4336 deaths recorded in ONS, 60 did not have death recorded in CPRD, giving a false negative rate of 1.4%. Of 34155 alive participants in ONS, 107 were recorded as having died in CPRD, giving a false positive rate of 0.3% (Table 5.1).

Similarly, the mortality status of the 3547 study patients was examined, for whom 639 and 646 deaths were recorded in ONS and CPRD, respectively. In study patients, the false negative and false positive rates of CPRD mortality status were 1.1% and 0.5%, respectively. Also, the mortality status of the 34944 controls was examined, for whom 3697 and 3737 deaths were recorded in ONS and CPRD, respectively. In controls, the false negative and false positive rates were 1.4% and 0.3%, respectively (Table 5.1).

Regarding the risk of adrenal insufficiency on all-cause mortality, the unadjusted hazard ratio using CPRD mortality status was identical to that using ONS information (HR, 1.68 [95% CI, 1.54-1.82]; p<0.0001; Table 5.2).

In summary, the record of death in CPRD was highly consistent with the ONS dataset, as illustrated by the low false negative and false positive rates. In addition, the risk for all-cause mortality using CPRD was indistinguishable from that evaluated using the ONS dataset.

	Total participants (N= 38491)			**Patients with adrenal insufficiency (N= 3547)**			**Controls (N= 34944)**		
	ONS alive	ONS death	Total	ONS alive	ONS death	Total	ONS alive	ONS death	Total
CPRD alive	34048 (99.7%)	60 **(1.4%)**	34108	289 (99.5%)	7 **(1.1%)**	2901	31154 (99.7%)	53 **(1.4%)**	31207
CPRD death	107 (**0.3%**)	4276 (98.6%)	4383	14 **(0.5%)**	632 (98.9%)	646	93 **(0.3%)**	3644 (98.6%)	3737
Total	34155 (100%)	4336 (100%)	38491	2908 (100%)	639 (100%)	3547	31247 (100%)	3697 (100%)	34944

Table 5.1: The validation of the assignment of death status in Clinical Practice Research Datalink (CPRD) using Office for National Statistics (ONS) mortality data

Source of data	Adrenal insufficiency N= 3547			Controls N= 34944			Unadjusted HR (95%)	p
	No. death	Person-years	Mortality per 1000 person-years (95% CI)	No. death	Person-years	Mortality per 1000 person-years (95% CI)		
CPRD	646	18603	34.7 (32.1-37.5)	3733 †	179888	20.8 (20.1-21.4)	1.68 (1.54-1.82)	<0.0001
ONS	639	18592	34.4 (31.8-37.1)	3696 ‡	179833	20.6 (19.9-21.2)	1.68 (1.54-1.82)	<0.0001

Table 5.2: The hazard ratio of adrenal insufficiency for all-cause mortality using mortality data from Clinical Practice Research Datalink (CPRD) using Office for National Statistics (ONS)

Note: † fours and ‡ one controls were excluded from the analysis because the date of death was recorded before the start of follow-up

5.3 The validation of diagnostic codes used to define cardiovascular disease in CPRD

Cardiovascular disease was commonly diagnosed in the hospital setting but the primary outcome of cardiovascular events in this study was defined using CPRD data, based on a primary care record. This analysis aimed to validate the record of specific cardiovascular disease (ischaemic heart disease and cerebrovascular disease including transient ischaemic attack) in CPRD using HES information as a reference standard. In the HES dataset, ICD-10 codes were used (Appendix, Suppl. Table 2.7). All in-hospital diagnoses, consisting of primary and secondary diagnoses and comorbidities, were examined in participants who had linked HES data and a start of follow-up from 1997 onwards, and who were admitted to the hospital during the follow-up period. The false positive and false negative rates were calculated overall and separately between the study patients and controls. The false positive rate was the proportion of participants having a cardiovascular disease record in CPRD but no record in HES to the number of participants admitted to hospital without a diagnosis of cardiovascular disease. The false negative rate was the proportion of participants having cardiovascular disease in HES without a record in CPRD to the number of participants admitted to hospital with a diagnosis of cardiovascular disease.

A total of 18636 participants with HES linked data (2674 study patients and 15962 controls) were admitted to hospital during the follow-up period. For ischaemic heart disease, 2865 participants had a record in HES and 15771 participants had no record. Of those recorded as having ischaemic heart disease in HES, 729 had no such record in CPRD, giving a false negative rate of 25.5%. Of those with no record of ischaemic heart disease in HES, 639 had a record in CPRD, giving a false positive rate of 4.1%. Similarly, the record of ischaemic heart disease in CPRD was evaluated in the study patients and controls. The false negative rate was

24.9% and 25.5% whereas the false positive rate was 3.5% and 4.1% in the study patients and controls, respectively (Table 5.3).

For cerebrovascular disease, 1477 participants had a record and 17159 had no record in HES. Of those with cerebrovascular disease recorded in HES, 507 were not recorded in CPRD, giving a false negative rate of 34.6%. Of those not recorded in HES, 1117 were recorded in CPRD, giving a false positive rate of 6.5%. Similarly, the record of cerebrovascular disease in CPRD was evaluated in the study patients and controls. The false negative rate was 34.6% and 34.3% whereas the false positive rate was 6.7% and 6.5% in the study patients and controls, respectively (Table 5.4).

In summary, the false positive rates of recording ischaemic heart disease and cerebrovascular disease in either study patients or controls were acceptable. The false negative rates, in which ischaemic heart disease and cerebrovascular disease were recorded in HES but not in CPRD, were high, suggesting that cardiovascular disease was mainly diagnosed in the hospital setting rather than in primary care. However, the false negative rates of the study patients were similar to those in controls. This similarity in false negative rates was therefore less likely to distort the risk evaluated in the patients relative to controls.

	Total participants (N= 18636)			**Patients with adrenal insufficiency (N= 2674)**			**Controls (N= 15962)**		
	HES not recorded	HES recorded	Total	HES not recorded	HES recorded	Total	HES not recorded	HES recorded	Total
CPRD not recorded	15132 (96.0%)	**729 (25.5%)**	15861	2216 (96.5%)	**94 (24.9%)**	2310	12916 (95.9%)	**635 (25.5%)**	13551
CPRD recorded	**639 (4.1%)**	2136 (74.6%)	2775	**81 (3.5%)**	283 (75.1%)	364	**558 (4.1%)**	1853 (74.5%)	2441
Total	15771 (100%)	2865 (100%)	18636	2297 (100%)	377 (100%)	2674	13474 (100%)	2488 (100%)	15962

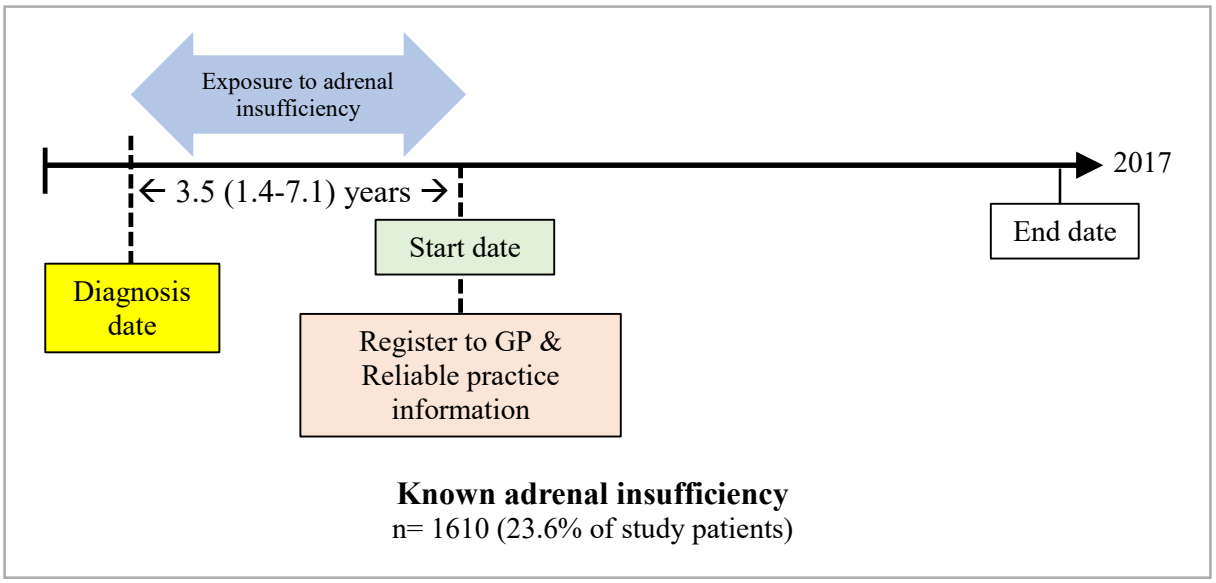
Table 5.3: The validation of the record of ischaemic heart disease in Clinical Practice Research Datalink (CPRD) using Hospital Episode Statistics (HES) data

	Total participants (N= 18636)			**Patients with adrenal insufficiency (N= 2674)**			**Controls (N= 15962)**		
	HES not recorded	HES recorded	Total	HES not recorded	HES recorded	Total	HES not recorded	HES recorded	Total
CPRD not recorded	16042 (93.5%)	**507 (34.3%)**	16549	2272 (93.3%)	**83 (34.6%)**	2355	13770 (93.5%)	**424 (34.3%)**	14194
CPRD recorded	**1117 (6.5%)**	970 (65.7%)	2087	**162 (6.7%)**	157 (65.4%)	319	**955 (6.5%)**	813 (65.7%)	1768
Total	17159 (100%)	1477 (100%)	18636	2434 (100%)	240 (100%)	2674	14725 (100%)	1237 (100%)	15962

Table 5.4: The validation of the record of cerebrovascular disease in Clinical Practice Research Datalink (CPRD) using Hospital Episode Statistics (HES) data

5.4 A comparison of baseline characteristics and cardiovascular risk factors in patients diagnosed with adrenal insufficiency before and at the study entry (Known vs New adrenal insufficiency)

At the start of follow-up, the prevalence of baseline cardiovascular risk factors including previous cardiovascular disease, diabetes mellitus, hypertension and dyslipidaemia in patients with adrenal insufficiency was higher than that of controls (Chapter 3, Table 3.2). Meanwhile, some patients were diagnosed with adrenal insufficiency prior to study entry (known adrenal insufficiency) since the start of follow-up in this study was in line with the recommendation from CPRD that the follow-up should begin after the research-standard information for each participant was certain (Detailed in Chapter 2, section 2.4: Follow-up period). It could be speculated that these patients, who had been exposed to adrenal insufficiency prior to the start of follow-up, might have developed cardiovascular risk factors (such as previous cardiovascular disease, diabetes, and hypertension) already at the start of follow-up (Figure 5.1). Also, after their study entry, this group of patients might have a higher risk for developing cardiovascular disease than those diagnosed with adrenal insufficiency later at the start of follow-up (new adrenal insufficiency), which could cause inconsistent results for the risk of cardiovascular disease evaluated in the main analysis. This analysis therefore compared demographic data and the prevalence of cardiovascular disease for patients with known adrenal insufficiency or with new adrenal insufficiency. In addition, the risk for all-cause mortality and cardiovascular disease in patients with known and new adrenal insufficiency, compared with their matched controls were separately evaluated.



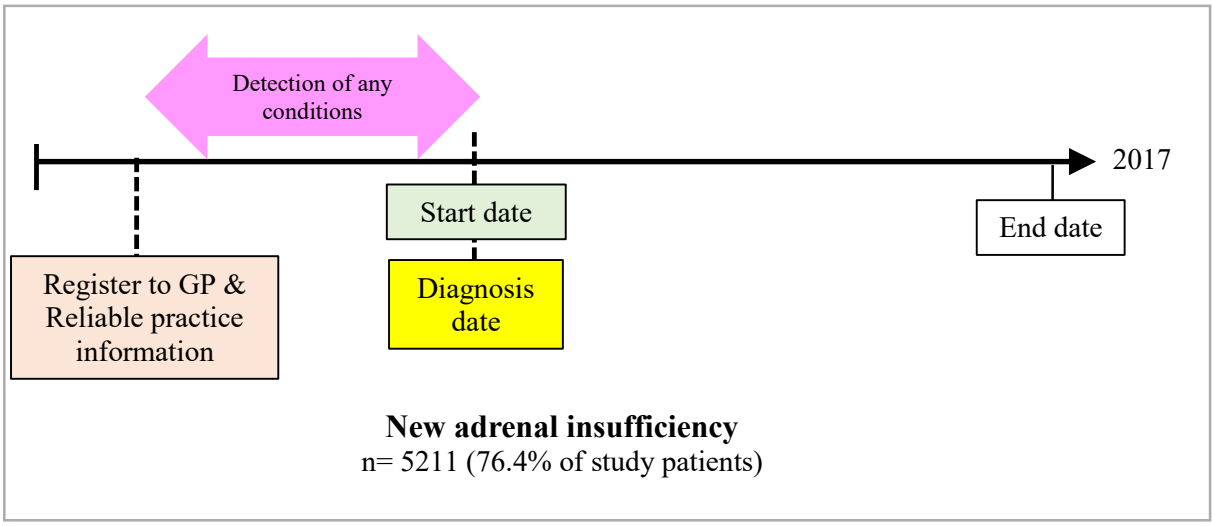


Figure 5.1: Classification of study patients according to time at the diagnosis of adrenal insufficiency (Known vs New adrenal insufficiency)

Note: GP- General practitioners

5.4.1 Demographic data and cardiovascular risk factors at baseline of patients with known and new adrenal insufficiency and their matched controls

From a total of 6821 adrenal insufficiency patients, 1610 (23.6%) were diagnosed with adrenal insufficiency before the study entry (known adrenal insufficiency) and 5211 (76.4%) had adrenal insufficiency at the start of follow-up (new adrenal insufficiency). In those with known adrenal insufficiency, the median time from the diagnosis to the start of follow was 3.5 (IQR, 1.4 to 7.1) years (Figure 5.1). Each patient had up to ten matched controls, thereby there were 16079 controls matched with known adrenal insufficiency and 51485 matched with new adrenal insufficiency.

The proportion of women was similar between patients with known, compared with new adrenal insufficiency (52.2% vs 53.9%, p=0.22). Age at the start of follow-up was also similar (52 [IQR, 37-67] vs 54 [38-68]; p=0.20); however, age at diagnosis was younger in those with known adrenal insufficiency (47 [IQR, 33-62] vs 54 [38-68]; p<0.0001). The period of follow-up was longer in those with known adrenal insufficiency (6.4 [IQR, 2.2-13.4] vs 3.8 [1.6-7.9] years; p<0.0001)) and as expected, the period from the diagnosis of adrenal insufficiency to the end of study was longer in those with known adrenal insufficiency (12.2 [IQR, 6.4-18.7 vs 3.8 [1.6-7.9]; years; p<0.0001; Table 5.5).

Despite having previously been exposed to adrenal insufficiency, patients with known adrenal insufficiency had a lower proportion of baseline cardiovascular risk factors at the start follow-up compared with those with new adrenal insufficiency. For baseline cardiovascular disease, the proportion of known adrenal insufficiency and new adrenal insufficiency was 15.4% and 18.1%, respectively (p=0.013). For hypertension, the proportion of those with known adrenal insufficiency was also lower than of those with new adrenal insufficiency (18.6% vs 23.2%; p<0.0001), as well as for dyslipidaemia (13.9% vs 22.5%; p<0.0001). Smoking was also higher

in those with new adrenal insufficiency (23.5% vs 34.3%; $p<0.0001$). However, the proportion of diabetes in those with new adrenal insufficiency was non-significantly higher than those with known adrenal insufficiency (9.4% vs 10.8%; $p=0.13$; Table 5.6).

	Known adrenal insufficiency			New Adrenal insufficiency			P †	Whole cohort		
	Patients N=1610	Controls N=16079	p	Patients N=5211	Controls N=51485	p		Patients N=6821	Controls N=67564	p
Female, (%)	840 (52.2)	8390 (52.2)	0.99	2808 (53.9)	27891 (54.2)	0.69	0.22	3648 (53.5)	36281 (53.7)	0.73
Age at start; year, median (IQR)	52 (37-67)	52 (37-67)	0.91	54 (38-68)	53 (37-68)	0.16	0.20	53 (38-68)	53 (37-68)	0.20
Age at diagnosis; year, median (IQR)	47 (33-62)	..	NA	54 (38-68)	..	NA	<0.0001	52 (36-67)	..	NA
Total follow-up time, year; median (IQR)	6.4 (2.2-13.4)	7.2 (2.4-14.2)	0.0070	3.8 (1.6-7.9)	3.5 (1.5-7.6)	0.0007	<0.0001	4.3 (1.7-8.8)	4.0 (1.6-9.0)	0.17
Total follow-up time from diagnosis to end date, years; median (IQR)	12.2 (6.4-18.7)	..	NA	3.8 (1.6-7.9)	..	NA	<0.0001	5.2 (2.0-10.5)	..	NA

Table 5.5: Demographic data at baseline of patients diagnosed with adrenal insufficiency before and at the start of follow-up (Known vs New adrenal insufficiency) and their matched controls

Note: † P for a comparison between known and new adrenal insufficiency patients

Cardiovascular risk factors	Known adrenal insufficiency			New Adrenal insufficiency			P †	Whole cohort		
	Patients N=1610	Controls N=16079	p	Patients N=5211	Controls N=51485	p		Patients N=6821	Controls N=67564	p
Cardiovascular disease, (%)	248 (15.4)	1678 (10.4)	<0.0001	942 (18.1)	5908 (11.5)	<0.0001	0.013	1190 (17.5)	7586 (11.2)	<0.0001
Diabetes mellitus, (%)	152 (9.4)	599 (3.7)	<0.0001	560 (10.8)	2618 (5.1)	<0.0001	0.13	712 (10.4)	3217 (4.8)	<0.0001
Hypertension, (%)	300 (18.6)	2202 (13.7)	<0.0001	1208 (23.2)	6989 (13.6)	<0.0001	<0.0001	1508 (22.1)	9191 (13.6)	<0.0001
Dyslipidaemia, (%)	223 (13.9)	1098 (6.8)	<0.0001	1174 (22.5)	2309 (4.5)	<0.0001	<0.0001	1397 (20.5)	3407 (5.0)	<0.0001
Statin use, (%)	206 (12.8)	1059 (6.6)	<0.0001	1133 (21.7)	2246 (4.4)	<0.0001	<0.0001	1339 (19.6)	3305 (4.9)	<0.0001
Ever smoking, (%)	378 (23.5)	3135 (19.5)	<0.0001	1785 (34.3)	10747 (20.9)	<0.0001	<0.0001	2163 (31.7)	13882 (20.6)	<0.0001

Table 5.6: Cardiovascular risk factor at baseline of patients diagnosed with adrenal insufficiency before and at the start of follow-up (Known vs New adrenal insufficiency) and their matched controls

Note: † P for a comparison between known and new adrenal insufficiency patients

The unexpectedly higher proportions of baseline cardiovascular risk factors including smoking in patients with new adrenal insufficiency compared with known adrenal insufficiency suggested that other factors, independent of adrenal insufficiency, might have contributed to this. Patients with new adrenal insufficiency had been registered to the general practice before the start of follow-up and this allowed time for health conditions especially asymptomatic disease (such as hypertension and dyslipidaemia) to be screened and detected (Figure 5.1). In other words, patients with new adrenal insufficiency would have had more medical encounters than those with known adrenal insufficiency, a systematic bias referred to as "Informed presence bias". In addition, in a comparison with their matched controls, patients with known or new adrenal insufficiency both had significantly higher proportions of cardiovascular risk factors, also suggesting "Informed presence bias". In contrast to the study patients, controls' health conditions including cardiovascular risk factors might have been overlooked since they were usually healthy and their start of follow-up might simply have been when they registered to the general practice. When the time to screen and detect health conditions was extended from the start to the end of follow-up, the proportions of cardiovascular risk factors including smoking were increased in both study patients and controls (Table 5.7). Also, by the end of follow-up, the proportions of cardiovascular risk factors in those with known adrenal insufficiency no longer differed from new adrenal insufficiency (Table 5.7). However, by the end of follow-up, the proportions of cardiovascular risk factors, except smoking, remained higher in the study patients compared with controls, suggesting that adrenal insufficiency may have some effect on the increase in the prevalence of cardiovascular risk factors.

Cardiovascular risk factors	Known adrenal insufficiency			New adrenal insufficiency			P †	Whole cohort		
	Patients N=1610	Controls N=16079	P	Patients N=5211	Controls N=51485	P		Patients N = 6821	Controls N = 67564	P
Cardiovascular disease at start, (%)	248 (15.4)	1678 (10.4)	<0.0001	942 (18.1)	5908 (11.5)	<0.0001	0.013	1190 (17.5)	7586 (11.2)	<0.0001
Cardiovascular disease at any time, (%)	450 (28.0)	3500 (21.8)	<0.0001	1380 (26.5)	9609 (18.7)	<0.0001	0.24	1830 (26.8)	13109 (19.4)	<0.0001
Diabetes mellitus at start, (%)	152 (9.4)	599 (3.7)	<0.0001	560 (10.8)	2618 (5.1)	<0.0001	0.13	712 (10.4)	3217 (4.8)	<0.0001
Diabetes at any time, (%)	253 (15.7)	1344 (8.4)	<0.0001	811 (15.6)	4381 (8.5)	<0.0001	0.88	1064 (15.6)	5725 (8.5)	<0.0001
Hypertension at start, (%)	300 (18.6)	2202 (13.7)	<0.0001	1208 (23.2)	6989 (13.6)	<0.0001	<0.0001	1508 (22.1)	9191 (13.6)	<0.0001
Hypertension at any time, (%)	470 (29.2)	3956 (24.6)	<0.0001	1541 (29.6)	10898 (21.2)	<0.0001	0.77	2011 (29.5)	14854 (22.0)	<0.0001
Dyslipidaemia at start, (%)	223 (13.9)	1098 (6.8)	<0.0001	1174 (22.5)	2309 (4.5)	<0.0001	<0.0001	1397 (20.5)	3407 (5.0)	<0.0001
Dyslipidaemia at any time, (%)	549 (34.1)	4155 (25.8)	<0.0001	1858 (35.7)	12532 (24.3)	<0.0001	0.25	2407 (35.3)	16687 (24.7)	<0.0001
Ever smoking at start, (%)	378 (23.5)	3135 (19.5)	<0.0001	1785 (34.3)	10747 (20.9)	<0.0001	<0.0001	2163 (31.7)	13882 (20.6)	<0.0001
Ever smoking at any time, (%)	665 (41.3)	6777 (42.2)	0.51	2263 (43.4)	22337 (43.4)	0.95	0.13	2928 (42.9)	29114 (43.1)	0.79

Table 5.7: Cardiovascular risk factor at the start of follow-up and at any time of patients with known and new adrenal insufficiency and their matched controls

Note: † P for a comparison between known and new adrenal insufficiency patients

5.4.2 The risks for all-cause mortality and cardiovascular disease in patients with known and new adrenal insufficiency

This analysis evaluated the risks for all-cause mortality and cardiovascular disease in patients diagnosed with adrenal insufficiency before and at the start of follow-up (known vs new adrenal insufficiency), relative to their matched controls. The analysis consisted of 1610 known adrenal insufficiency patients compared with 16079 matched controls, and 5211 new adrenal insufficiency patients compared with 51845 matched controls.

For all-cause mortality, in known adrenal insufficiency, there were 400 deaths of the study patients and 2588 deaths of controls whereas in new adrenal insufficiency, there were 1035 deaths of the study patients and 5974 deaths of controls. The unadjusted hazard ratio of patients with known adrenal insufficiency was not different from those with new adrenal insufficiency (HR, 1.64 [95% CI, 1.48-1.83] vs 1.68 [1.58-1.80]) and these were similar to the hazard ratio in all patients (Table 5.8).

For composite cardiovascular disease, in known adrenal insufficiency, there were 323 patients and 2712 controls with an incident whereas in new adrenal insufficiency, there were 823 patients and 6241 controls with an event. The unadjusted hazard ratio of patients with known adrenal insufficiency was also not different from those with new adrenal insufficiency (HR, 1.26 [95% CI, 1.12-1.41] vs 1.29 [1.20-1.39]) as well as in all patients (Table 5.8).

Population	All-cause mortality				Composite cardiovascular events			
	No. death/ Total No. (%)		Hazard ratio (95% CI)	p	No. event/ Total No. (%)		Hazard ratio (95% CI)	p
	Patients	Controls			Patients	Controls		
Known adrenal insufficiency (1610 vs 16079)	400 (24.8)	2588 (16.1)	1.64 (1.48-1.83)	<0.0001	323 (20.1)	2712 (16.9)	1.26 (1.12-1.41)	<0.0001
New adrenal insufficiency (5211 vs 51845)	1035 (19.9)	5974 (11.5)	1.68 (1.58-1.80)	<0.0001	823 (15.8)	6241 (12.1)	1.29 (1.20-1.39)	<0.0001
All participants (6821 vs 67564)	1435 (21.0)	8562 (12.7)	1.68 (1.58-1.77)	<0.0001	1146 (16.8)	8953 (13.3)	1.28 (1.20-1.36)	<0.0001

Table 5.8: The hazard ratio of adrenal insufficiency for all-cause mortality and cardiovascular events in patients diagnosed with adrenal insufficiency before and at the start of follow-up (Known vs New adrenal insufficiency)

In summary, nearly a quarter of the study patients had a diagnosis of adrenal insufficiency before the start of follow-up. Previous exposure to adrenal insufficiency might have resulted in increased cardiovascular risk factors. In fact, the prevalence of cardiovascular risk factors was lower in these patients, compared with the patients having the diagnosis of adrenal insufficiency at the start of follow-up. The prevalence of cardiovascular risk factors for both groups of patients turned out to be comparable when the observation period was extended to the end of the study, implying that differences at the start of follow-up could have been caused by informed presence bias. However, the risks for mortality and cardiovascular disease, relative to matched controls, in both groups (known and new adrenal insufficiency) were virtually identical.

5.5 A comparison of all-cause mortality and cardiovascular events in participants with different smoking status

This analysis evaluated whether the imputation of smoking status could contribute to alteration of the primary outcomes: all-cause mortality and composite cardiovascular events. In the main analysis (Chapter 3 and 4), participants having only ex-smoker codes were considered as smokers and those with missing smoking information were considered as non-smokers.

5.5.1 Classifications of participants using different definitions of smoking status

The participants were classified into five groups according to their medical codes (Appendix, Suppl. Table 2.10) related to smoking status recorded in the CPRD Clinical file, Referral file, Test file, or Immunisation file in the different time periods (Table 5.9). Group 1 (smoking at start) consisted of the participants with smoking codes recorded before or at the start of follow-up, regardless of whether they were concomitantly recorded with ex-smoking or non-smoking codes. Group 2 (smoking during the follow-up period) included the participants with smoking codes recorded after the start but before or at the end of follow-up, regardless concomitantly ex-smoking or non-smoking codes recorded. Group 3 (ex-smoking at any time) included the participants recorded with ex-smoking codes at any time before the end of follow-up, without concomitantly smoking codes recorded. Group 4 (non-smoking at any time) included the participants recorded with non-smoking codes at any time before the end of follow-up, without concomitantly smoking or ex-smoking codes recorded. Group 5 (missing smoking data) was the participants who did not have any smoking related medical codes recorded in CPRD dataset.

At the start of follow-up, the proportion of study patients with smoking codes was higher than that of controls (19% vs 11%) but during the follow-up period, the proportion of recording smoking codes was higher in controls (5% vs 10%), thereby, when recording at any time

(smoking at any time) was considered, the proportion of smoking codes in the study patients appeared to be not different from controls (25% vs 21%). Also, when recording ex-smoking codes at any time was included (ever smoking) the proportion of the study patients was similar to controls (43% vs 43%). For the record of non-smoking codes, the proportion of the study patients was higher than controls (21% vs 13%). As expected, the proportion of missing smoking information in controls was higher than in the study patients (36% vs 44%; Table 5.9). Because of the high proportion of missing smoking data and the difference in proportions between study patients and controls across the different smoking categories, the following analysis was conducted to ensure that the different smoking status of the participants did not significantly affect the influence of adrenal insufficiency on the primary outcomes (all-cause mortality and cardiovascular events).

Smoking classification	Study patients (N= 6821) No. (%)	Controls (N= 67564) No. (%)	All participants (N= 74385) No. (%)
1. Smoking at start	1316 (19.3)	7540 (11.2)	8856 (11.9)
2. Smoking during the follow-up period	366 (5.4)	6934 (10.3)	7300 (9.8)
3. Ex-smoking at any time	1246 (18.3)	14640 (21.7)	15886 (21.4)
4. Non-smoking at any time	1449 (21.2)	8489 (12.6)	9938 (13.4)
5. Missing smoking data	2444 (35.8)	29961 (44.3)	32405 (43.6)
Smoking at any time (1. &2.)	1682 (24.7)	14474 (21.4)	16156 (21.7)
Ever smoking (1. &2. &3.) †	2928 (42.9)	29114 (43.1)	32042 (43.1)

Table 5.9: Classification of participants according to smoking-related codes recorded in different periods

Note: † Parameter used for defining smoking status in the main analysis (ever smoking)

5.5.2 The risk of adrenal insufficiency on all-cause mortality and cardiovascular events in the selected participants in different categories of smoking status

This analysis compared the unadjusted hazard ratios of adrenal insufficiency on all-cause mortality and composite cardiovascular events in different groups of participants according to their smoking-related codes including the combination groups of those with smoking and ex-smoking codes (ever smoking), and those with any smoking codes (All participants without missing smoking information).

Regarding all-cause mortality, the hazard ratio in those with missing smoking data was 1.60 (95% CI, 1.45-1.77), which was similar to those with non-smoking codes (HR, 1.65 [95% CI, 1.47-1.86]) and those without missing smoking information (HR, 1.74 [95% CI, 1.63-1.86]). In those with ex-smoking codes at any time, the hazard ratio was lower than those with smoking codes at any time (HR, 1.67 [95% CI, 1.48-1.88] vs 2.05 [1.82-2.30]). However, when the ex-smokers were considered as smokers (ever smoking), the hazard ratio was not different from the hazard ratio of all participants (HR, 1.81 [95% CI, 1.67-1.97] vs 1.68 [1.58-1.77]); Table 5.10)

Regarding composite cardiovascular events, similar to the comparison of hazard ratios for mortality, the hazard ratio evaluated in those with missing smoking data was similar to those with non-smoking codes and those without missing smoking information (HR, 1.29 [95% CI, 1.13-1.46] vs 1.24 [1.09-1.42] vs 1.24 [1.16-1.33]). In those with ex-smoking codes, the hazard ratio of adrenal insufficiency was lower than in those with smoking codes (1.19 [95% CI, 1.06-1.35] vs 1.41 [1.25-1.59]). However, when the ex-smokers were considered as smokers, the hazard ratio was not different from the hazard ratio of all participants (HR, 1.26 [95% CI, 1.16-1.38] vs 1.28 [1.20-1.36]); Table 5.10)

In summary, the risks of adrenal insufficiency on mortality and cardiovascular disease in those with missing smoking-related codes were similar to those with non-smoking codes. In those with ex-smoking codes, the risks were lower than those with smoking codes; however, when ex-smokers were combined with smokers, the risks were not different from the risks evaluated in the whole cohort. It was noted that the risks in ex-smokers were closer to the risks in those with non-smoking codes than those with smoking codes. The following analysis then distinguished the risk of adrenal insufficiency on mortality and cardiovascular disease when ex-smokers were considered as non-smokers from the risk when ex-smokers were considered as smokers.

Population	All-cause mortality				Composite cardiovascular events			
	No. death/ Total No. (%)		Hazard ratio (95% CI)	p	No. event/ Total No. (%)		Hazard ratio (95% CI)	p
	Patients	Controls			Patients	Controls		
1. Smoking at start	285/ 1316 (21.7)	796/ 7540 (10.6)	2.07 (1.81-2.37)	<0.0001	238/ 1316 (18.1)	939/ 7540 (12.5)	1.49 (1.29-1.72)	<0.0001
2. Smoking during the follow-up period	69/ 366 (18.9)	881/ 6934 (12.7)	1.23 (0.96-1.58)	0.094	75/ 366 (20.5)	1162/ 6934 (16.8)	1.05 (0.83-1.32)	0.70
3. Ex-smoking at any time	308/ 1246 (24.7)	2220/ 14640 (15.2)	1.67 (1.48-1.88)	<0.0001	294/ 1246 (23.6)	2938/ 14640 (20.1)	1.19 (1.06-1.35)	0.0040
4. Non-smoking at any time	334/ 1449 (23.1)	1369/ 8489 (16.1)	1.65 (1.47-1.86)	<0.0001	286/ 1449 (19.7)	1461/ 8489 (17.2)	1.29 (1.13-1.46)	<0.0001
5. Missing smoking data	440/ 2444 (18.0)	3300/ 29961 (11.0)	1.60 (1.45-1.77)	<0.0001	253/ 2444 (10.4)	2453/ 29961 (8.2)	1.24 (1.09-1.42)	0.0010
All participants	1435/ 6821 (21.0)	8562/ 67564 (12.7)	1.68 (1.58-1.77)	<0.0001	1146/ 6821 (16.8)	8953/ 67564 (13.3)	1.28 (1.20-1.36)	<0.0001
Smoking at any time (1.&2.)	354/ 1682 (21.1)	1677/ 14474 (11.6)	2.05 (1.82-2.30)	<0.0001	313/ 1682 (18.6)	2101/ 14474 (14.5)	1.41 (1.25-1.59)	<0.0001
Ever smoking (1.&2.&3.) †	662/ 2928 (22.6)	3987/ 29114 (13.4)	1.81 (1.67-1.97)	<0.0001	607/ 2928 (20.7)	5039/ 29114 (17.3)	1.26 (1.16-1.38)	<0.0001
All participants without missing smoking information (1.&2.&3.&4.)	996/ 4377 (22.8)	5266/ 37603 (14.0)	1.74 (1.63-1.86)	<0.0001	893/ 4377 (20.4)	6500/ 37603 (17.3)	1.24 (1.16-1.33)	<0.0001

Table 5.10: Hazard ratios of adrenal insufficiency for all-cause mortality and cardiovascular events in patients with different smoking status

Note: † Parameter used for defining smoking status in the main analysis (ever smoking)

5.5.3 The risk of adrenal insufficiency associated with smoking on all-cause mortality and cardiovascular events

In this analysis, the hazard ratios of adrenal insufficiency on all-cause mortality and composite cardiovascular events were evaluated when variation in smoking status was taken into account. Bivariable cox regression analyses were performed using alternative categorisations of smoking status: (1) 'smoking at start' analysis, participants having smoking codes were considered to be a smoker whereas those with ex-smoking codes at any time, smoking codes after the start of follow-up, and missing smoking data were considered as non-smokers; (2) 'smoking at any time' analysis, participants having smoking codes at any time before the end of follow-up were considered as smokers whereas those with ex-smoking codes and missing smoking data were considered as non-smokers; and (3) 'ever smoking' analysis, participants having smoking or ex-smoking codes at any time before the end of follow-up were considered as smokers whereas those with missing smoking data were considered as non-smokers. In addition to the analysis in the whole cohort (all participants), similar bivariable cox regression analysis was performed in the subgroup of participants with available smoking-related codes (participants without missing smoking information).

For all-cause mortality, the whole cohort included 1435 deaths of 6821 study patients and 8562 deaths of 67564 controls. The unadjusted hazard ratio of adrenal insufficiency was 1.68 (95% CI, 1.58-1.77). The hazard ratio was almost unchanged whether it was adjusted for 'smoking at start', 'smoking at any time', or 'ever smoking' (Table 5.11). In the subgroup of those with available smoking information, the participants included 996 deaths of 4377 study patients and 5266 deaths of 37603 controls. The unadjusted hazard ratio of adrenal insufficiency was 1.74 (95% CI, 1.63-1.86), which was not different from the whole cohort. After adjustment for

‘smoking at start’, ‘smoking at any time’, or ‘ever smoking’, the hazard ratios were also almost unchanged (Table 5.11).

Variable used for adjustment	All-cause mortality				Composite cardiovascular events			
	All participants (N= 6821 vs 67564)		Participants without missing smoking information (N= 4377 vs 37603)		All participants (N= 6821 vs 67564)		Participants without missing smoking information (N= 4377 vs 37603)	
	Hazard ratio (95% CI)	p	Hazard ratio (95% CI)	p	Hazard ratio (95% CI)	p	Hazard ratio (95% CI)	p
Unadjusted hazard ratio	1.68 (1.58-1.77)	<0.0001	1.74 (1.63-1.86)	<0.0001	1.28 (1.20-1.36)	<0.0001	1.24 (1.16-1.33)	<0.0001
Smoking at start	1.67 (1.58-1.76)	<0.0001	1.71 (1.60-1.84)	<0.0001	1.27 (1.19-1.35)	<0.0001	1.25 (1.16-1.34)	<0.0001
Smoking at anytime	1.68 (1.59-1.78)	<0.0001	1.74 (1.62-1.86)	<0.0001	1.28 (1.20-1.36)	<0.0001	1.24 (1.15-1.33)	<0.0001
Ever smoking †	1.67 (1.58-1.77)	<0.0001	1.76 (1.65-1.89)	<0.0001	1.29 (1.22-1.37)	<0.0001	1.27 (1.19-1.36)	<0.0001

Table 5.11: Hazard ratios of adrenal insufficiency for all-cause mortality and cardiovascular events in all participants and participants without missing smoking data, adjustment for the different variable according to smoking status (Bivariable Cox regression analysis)

Note: † Parameter used for defining smoking status in the main analysis (ever smoking)

For composite cardiovascular disease, the events in the whole cohort were recorded in 1146 patients and 8953 controls from a total of 6821 patients and 67564 controls, respectively. The unadjusted hazard ratio of adrenal insufficiency was 1.28 (95% CI, 1.20-1.36). Similar to the finding in all-cause mortality, the hazard ratio of adrenal insufficiency on cardiovascular disease was almost unchanged whether it was adjusted for 'smoking at start', 'smoking at any time', or 'ever smoking' (Table 5.11). In the subgroup of those with available smoking information, composite cardiovascular events were recorded in 893 patients and 6500 controls from a total of 4377 patients and 37603 controls, respectively. The unadjusted hazard ratio was 1.24 (95% CI, 1.16-1.33), which was not different from the whole cohort. After adjustment for 'smoking at start', 'smoking at any time', or 'ever smoking', the hazard ratios were also almost unchanged (Table 5.11).

In summary, the risks of adrenal insufficiency on all-cause mortality and cardiovascular disease were not different whether participants with ex-smoking codes were assigned as smokers or non-smokers. The risks were virtually unchanged when the participants with missing smoking information were excluded.

CHAPTER 6: DISCUSSION AND CONCLUSION

Previous studies have reported increased mortality and cardiovascular disease in patients with primary adrenal insufficiency and in those with pituitary disorders, some of which can be concomitant with secondary adrenal insufficiency. However, risks were not increased in some studies and uncertainty may have resulted from suboptimal matching between cases and controls. Almost all studies have evaluated the patient risks relative to the general population using standardised mortality or incidence ratios (SMR or SIR), with ages only roughly matched and the location and period of clinical care, which will have influenced the quality of care, remaining unmatched. In addition, population reference data has not allowed any consideration of the influence of variation in established cardiovascular risk factors between cases and controls. The present analysis sought to minimise differences between study patients and the reference population in age, calendar period and location of care and cardiovascular risk factors. Accordingly, the rates of mortality and cardiovascular disease events in patients with adrenal insufficiency, including primary and secondary disease were compared with controls matched for sex, age, residence area, and calendar time of care.

This study has shown that the risk for all-cause mortality relative to controls was increased in patients with adrenal insufficiency of any type including primary and secondary disease. Although the leading cause of death was disease of the circulatory system, death from infectious disease carried a greater relative risk. The mortality rate was highest in the first year of diagnosis and the mortality risk relative to controls was also highest, remaining increased from the first year of follow-up onwards. In the first year after diagnosis, the rate of hospital admission with adrenal crisis was greatest. Adrenal-crisis related death accounted for one in ten deaths in patients with adrenal insufficiency.

Composite cardiovascular events were also increased in patients with adrenal insufficiency of any type but after baseline cardiovascular risk factors were taken into account, the increased risk was only of borderline significance. After adjustment for cardiovascular risk factors, the risk for incident ischaemic heart disease was not increased in both primary and secondary adrenal insufficiency. By contrast, the risk for incident cerebrovascular disease after adjustment remained increased, although only in secondary adrenal insufficiency. In mortality from disease of the circulatory system and ischaemic heart disease, the risks remained increased independently of cardiovascular risk factors. Risk of mortality specific for cerebrovascular disease was increased only in patients with secondary adrenal insufficiency and became non-significant after adjustment for cardiovascular risk factors.

6.1 Increased all-cause mortality risks in primary and secondary adrenal insufficiency

In primary adrenal insufficiency, previous Scandinavian studies using SMRs have reported contradictory results in which three (73-75) but not one (19) reported increased mortality. In secondary adrenal insufficiency, the mortality risk was mainly assessed in patients with pituitary disorders, regardless of concomitant adrenal insufficiency (23, 49, 76-82, 85-90). In subgroup analyses of patients specifically with secondary adrenal insufficiency, results have also been inconsistent, with most studies reporting increased SMRs (78, 81, 82, 86), although a recent study reported no increase in SMR (49). In a comparison with controls matched for age, sex, region, and time of clinical care, the present study confirmed that the mortality risk was significantly increased in patients with adrenal insufficiency of any kind, including primary and secondary adrenal insufficiency. Moreover, this is the first study demonstrating that the mortality risk in patients with primary adrenal insufficiency may be higher than in those with secondary adrenal insufficiency.

6.2 All-cause mortality risk remaining increased over the historical period of medical care

A study in patients with non-functioning pituitary adenoma reported that the mortality risk in those receiving care in 2007 or later was reduced to a non-significant increase in SMR (93). However, to date no study has examined this in patients with primary or secondary adrenal insufficiency. The present study showed that with individual matching for period of care, the increased mortality risk relative to controls in patients with primary adrenal insufficiency was unchanged in those attending recent care (after mid-2007) whereas in secondary adrenal insufficiency, the increased mortality risk was lower in those receiving more recent care, although it remained significantly increased. Clearly, the standard of care for patients with adrenal insufficiency, in particular for those with primary disease, might be further improved to normalise the mortality risk.

6.3 Increased mortality risk and incidence of adrenal crisis from the beginning of the course of disease

An early increase in the mortality rate in patients with adrenal insufficiency was observed, although this was also observed in controls (Chapter 3, Figure 3.13). However, the mortality risk relative to controls was significantly increased from the first year of follow-up, especially in patients with primary adrenal insufficiency (Chapter 3, Table 3.17). Also, in the first year of diagnosis of adrenal insufficiency, the mortality rate was at its maximum (Chapter 3, Table 3.19). As the start of follow-up was, on average, one year after the diagnosis, this indicated that the mortality risk was increased from the beginning of the disease course and this could imply that an acute cause of death, such as infection and adrenal crisis, rather than a slow process (i.e. atherosclerosis) might contribute to the early increase in mortality. In addition, the early increase in mortality was predominantly observed in patients with primary adrenal insufficiency, consistent with adrenal crisis being a major contributor as those with primary

disease have a lesser reserve of adrenocortical function than those with secondary. In accordance with the mortality rate, the rate of in-hospital adrenal crisis was maximum at the first year after diagnosis and this was also prominent in primary adrenal insufficiency. All these findings suggested that adrenal crisis was an important contributor to the increased mortality risk in patients with adrenal insufficiency.

6.4 Adrenal crisis and infection-related deaths

In the present study, adrenal crisis-related death was recorded in up to one in ten, one in three, and one in a hundred of deaths in patients with adrenal insufficiency of any type, primary, and secondary adrenal insufficiency, respectively. However, it is plausible that adrenal crisis-related death was under-estimated in this study, as the mortality rate was only 3.5 deaths per 1000 patient-years for patients with adrenal insufficiency of any kind whereas in a previous report, it was 5 deaths per 1000 patient-years for patients with primary or secondary adrenal insufficiency (103). This might have resulted from a difference in study designs, as the previous study used a prospective review of death certificates and phone contacts while the present study used records from ONS based on coding from death certificates. Adrenal crisis-related death may indeed be under-recognised in any setting, since its symptoms are non-specific, often unexpected, rapidly progressive and can mimic acute cardiovascular events. Sudden deaths in adrenal insufficiency patients have been clinically attributed at the time to be due to myocardial infarction or pulmonary embolism, despite having no evidence of coronary or pulmonary artery occlusion in the autopsies (81). Mistaken attribution of sudden death to cardiovascular events or infection is, therefore, a possibility (81, 110). Conversely, cardiovascular events or infection could precipitate adrenal crisis in patients with adrenal insufficiency without adrenal crisis being recognised as a cause of death.

In people using systemic glucocorticoids for reasons other than adrenal insufficiency, an increased risk of infection has been reported (101). Accordingly, risk of infection in patients with adrenal insufficiency could be increased due to glucocorticoid over-replacement. In the present study, infectious disease carried a markedly increased relative risk of death with up to a 4-fold increment for patients with adrenal insufficiency of any kind or primary adrenal insufficiency and 3-fold for secondary disease. This was in line with previous observations in patients with primary adrenal insufficiency (73, 74) and pituitary disorders (80, 90). Furthermore, in the present study, the majority of deaths from infection were respiratory tract and urinary tract infections but were instead recorded as deaths from the disease of respiratory system and genitourinary system, respectively. When all possible infections were combined, infection became among the leading causes of death in patients with adrenal insufficiency of any type, including primary and secondary disease.

6.5 Cardiovascular events and cardiovascular mortality

Composite cardiovascular events consisted of ischaemic heart and cerebrovascular diseases, and other conditions such as atrial fibrillation and congestive heart failure. The risk for composite cardiovascular events appeared to be increased across all types of adrenal insufficiency. However, after the types of cardiovascular events were distinguished, the patterns of increased risk for cardiovascular disease differed according to the types of cardiovascular disease and the types of adrenal insufficiency.

For ischaemic heart disease events, there was a borderline increase in the risk in both primary and secondary adrenal insufficiency, but after adjustment for cardiovascular risk factors, the risk was no longer increased (Chapter 4, Figure 4.1). This suggested that the increased risk for incident ischaemic heart disease was likely to be influenced by the presence of cardiovascular risk factors. A previous study in primary adrenal insufficiency using matched controls reported

an increase in the risk for ischaemic heart disease even after adjustment (100). However, the parameters used for adjustment included only diabetes and chronic obstructive pulmonary disease, which was used as a surrogate for smoking status; other established cardiovascular risk factors such as previous cardiovascular disease, hypertension and dyslipidaemia were not taken into account (100). More importantly, the study's start date of follow-up was set to be not earlier than 2006 and the majority of patients had a long-standing exposure to adrenal insufficiency before entering to the study (100). In previous studies of patients with pituitary disorders, an increase in the risk for incident ischaemic heart disease was also observed, although these studies reported the risk by comparing with a national database, so there was no accounting for cardiovascular risk factors (79, 130).

For cerebrovascular disease events, the risk was increased in patients with secondary adrenal insufficiency but not in primary disease (Chapter 4, Figure 4.1). This was in line with findings reported by the previous study of primary adrenal insufficiency described above in relation to ischaemic heart disease (100), and with previous studies of patients with pituitary disorders, in which the increased risk for incident cerebrovascular disease was consistently observed (79, 129, 130, 141). The good agreement between the previous studies and the present study confirms that cerebrovascular disease is likely to be strongly associated with pituitary disorders including secondary adrenal insufficiency, and that the increased risk for cerebrovascular disease is specific to secondary not primary adrenal insufficiency. The absence of increased risk in primary disease suggests that adrenal insufficiency *per se* is unlikely to play a major role in increasing risk for cerebrovascular disease. This further implies that concomitant deficiencies in other pituitary hormones might contribute to the increased risk of cerebrovascular disease. However, if deficiencies in other pituitary hormone were important, one might expect ischaemic heart and cerebrovascular disease to be equally affected. Furthermore, after adjustment for cardiovascular risk factors, the risk for cerebrovascular

disease remained increased. Taken together, these considerations suggest that a localised factor associated with hypothalamic-pituitary disorders such as pituitary surgery or radiation might have resulted in the increased risk for cerebrovascular disease. In the present study, a strong association between a history of radiotherapy and cerebrovascular disease was demonstrated and this was in accordance with previous reports in patients with pituitary disorders (78, 90, 92, 141).

As well as cardiovascular events, cardiovascular mortality was also evaluated according to the principal causes of death: disease of the circulatory system, ischaemic heart disease, and cerebrovascular disease, although mortality from disease of the circulatory system included not only ischaemic heart disease and cerebrovascular disease, but also other cardiac disease unrelated to atherosclerosis.

Disease of the circulatory system was the leading cause of death for both patients with adrenal insufficiency and controls. The mortality risk was increased in both primary and secondary adrenal insufficiency and it remained increased after adjustment for cardiovascular risk factors, although with a marginal significance for patients with secondary adrenal insufficiency (Chapter 4, Figure 4.2). This was in line with a previous report in patients with primary adrenal insufficiency (73) and in line with some (23, 89, 90) that reported a borderline increased cardiovascular mortality in patients with pituitary disorders. This was not supported by all (77, 85, 88), however, and all these studies evaluated mortality risk using a standardised mortality ratio (SMR) and the varying definitions for cardiovascular deaths (23, 73, 77, 85, 88-90).

For ischaemic heart disease, the mortality risk in both primary and secondary adrenal insufficiency also remained increased after taking account of cardiovascular risk factors (Chapter 4, Figure 4.2). There appears to be no published information specific for ischaemic heart disease mortality in patients with primary adrenal insufficiency but for secondary adrenal

insufficiency, the increase observed in the present study was consistent with some studies of patients with pituitary disorders (23, 77, 78).

For cerebrovascular disease, mortality risk was not increased in patients with primary adrenal insufficiency but the risk was increased in secondary adrenal insufficiency, although significance was lost after adjustment for cardiovascular risk factors (Chapter 4, Figure 4.2). The present finding in cerebrovascular mortality was, nevertheless, similar to that from cerebrovascular events. As for ischaemic heart disease, there appears to be no published information on the mortality risk for cerebrovascular disease specific to primary adrenal insufficiency. In previous studies of patients with pituitary disorders, the risk for cerebrovascular mortality was increased to a greater extent than in the present study; however, the risk in previous studies was evaluated using SMRs and cardiovascular risk factors were not considered (23, 77, 78, 80, 81, 89, 90, 92).

It is important to note that the increased risk for cerebrovascular events in patients with secondary adrenal insufficiency was independent of cardiovascular risk factors. In contrast, the risk for overall cardiovascular events associated with any adrenal insufficiency was no longer increased after adjustment for cardiovascular risk factors but the risk for cardiovascular mortality remained increased after adjustment. This suggested that the increased risk for cardiovascular events but not cardiovascular mortality was influenced by the presence of established cardiovascular risk factors.

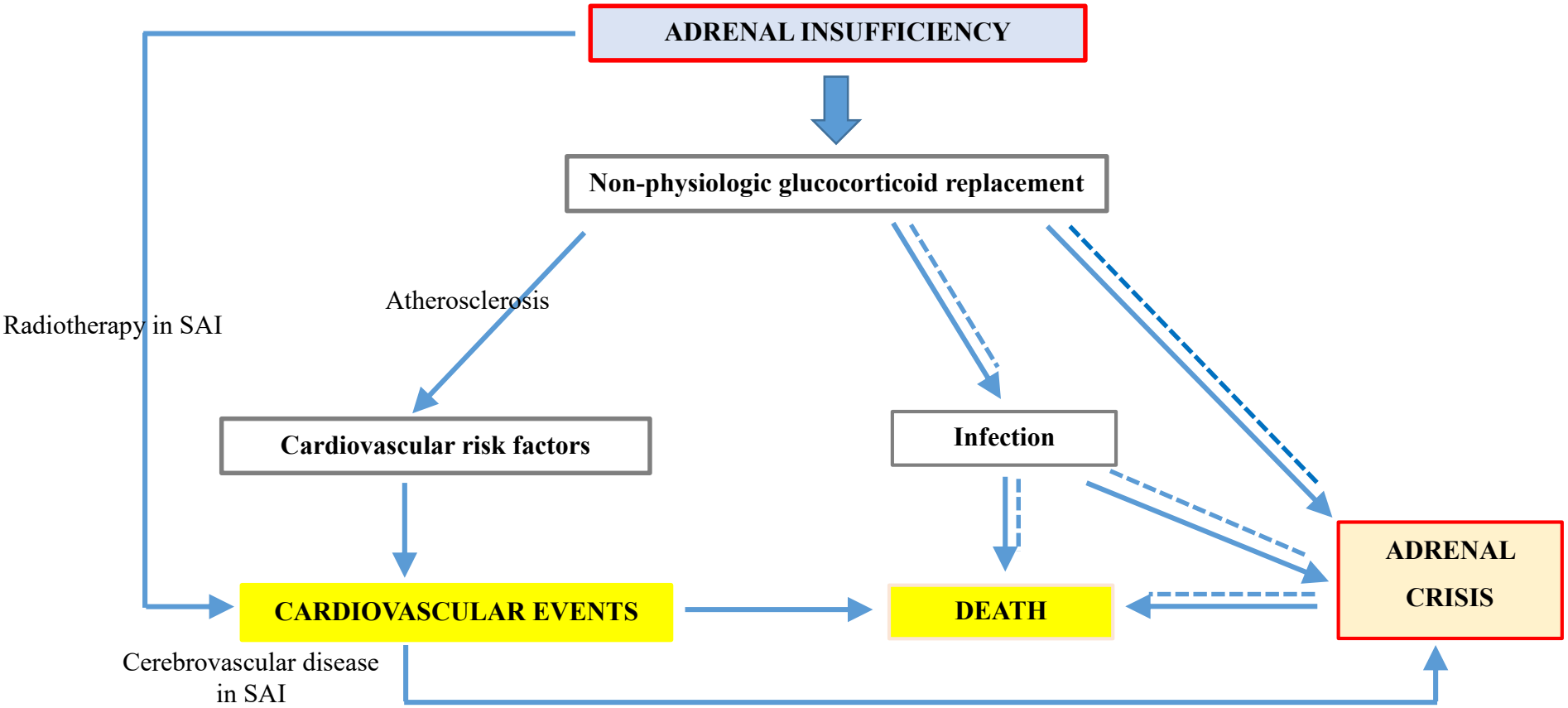


Figure 6.1: An insight into the major factors contributing to the increased mortality and cardiovascular disease in patients with adrenal insufficiency

Note: Dashed lines represented potentially accelerated processes; SAI-secondary adrenal insufficiency

6.6 An insight into the increased risks for cardiovascular disease, cardiovascular and all-cause mortality in patients with adrenal insufficiency

Risk of adrenal crisis is increased early in the course of adrenal insufficiency and is accompanied by early increases in both mortality rates and risks, with the markedly increased risk of deaths from infection. Adrenal crisis offers a potential unifying factor in these associations. Furthermore, after taking account of established cardiovascular risk factors, the risk for cardiovascular events was not increased but cardiovascular mortality remained increased. The increased cardiovascular mortality was more prominent in patients with primary than those with secondary adrenal insufficiency and again adrenal crisis could contribute to the pattern of associations. In addition, in patients ever having had a cardiovascular event, the incidence of adrenal crisis-related death was higher than in those without an event. These considerations suggest a system of interactions involving adrenal crisis, infection, and cardiovascular disease in increasing the mortality risk in patients with adrenal insufficiency (Figure 6.1). Notably, adrenal crisis could play a central role in increased mortality if the level of glucocorticoid is insufficient to maintain normal homeostasis during the acute stresses of infection or cardiovascular disease. Furthermore, adrenal crisis and infection could particularly accelerate the mortality risk soon after the diagnosis of adrenal insufficiency (Figure 6.1).

The findings in this study have suggested that to reduce mortality risk, clinical care for patients with adrenal insufficiency should target the three factors: adrenal crisis, infection and cardiovascular disease, in addition to dose optimisation of routine glucocorticoid therapy. First, the most important, is to prevent adrenal crisis. Education on glucocorticoid dose increment during an intercurrent illness and using hydrocortisone emergency injection kits when needed should be implemented soon after the diagnosis of adrenal insufficiency. Second is the need for increasing awareness of infection and early prescribing of appropriate antimicrobial agents

when there is clinical suspicion. Third is preventing and controlling cardiovascular diseases, which could be especially beneficial in the medium or long terms.

6.7 The risks for all-cause mortality and cardiovascular events according to age, sex, and comorbidities

In patients with primary or secondary adrenal insufficiency, the risk for all-cause mortality relative to controls was higher among those of younger age than those of older age. This is consistent with previous studies of patients with primary adrenal insufficiency (19, 74) and pituitary disorders (77, 78, 80, 89, 90). Since the present study had individual information for the period of follow-up, the absolute mortality rates could be calculated according to age groups in both patients and controls. The present study clearly demonstrates that the absolute mortality rates were higher for older adrenal insufficiency patients than for younger patients, but since younger controls had the best prognosis, adrenal insufficiency conferred a higher relative risk among younger than among older individuals.

The risk for all-cause mortality was not different according to sex in patients with primary adrenal insufficiency and this was in line with previous reports (73, 74). Most of previous studies with pituitary disorders observed that hypopituitarism conferred a higher mortality risk in women than it did in men (23, 76-81, 87-90, 93, 94, 158, 159), and it was believed that hypopituitarism can attenuate the longevity benefit associated with female sex in the general population (160). However, the present study showed that the mortality risk of secondary adrenal insufficiency patients relative to controls was also not statistically different between men and women. Also, the present study clearly demonstrated that as for controls, the absolute mortality rate of female patients remained lower than male patients.

Regarding the mortality risk difference according to comorbidities, the mortality risk of patients with primary adrenal insufficiency relative to controls was not different according to

whether or not they had comorbid cardiovascular disease or diabetes mellitus. It was noted that in the present study, the increased risk of primary adrenal insufficiency patients with diabetes relative to controls with diabetes was relatively low (adjusted HR, 1.83 [95% CI, 1.46-2.29]), compared with a previous study by Chantzichristos et al. using matched controls with diabetes (adjusted HR, 3.89 [95% CI, 2.84-5.32]) (75). The considerably higher HR of the study by Chantzichristos et al. might have resulted from the duration of diabetes in controls being shorter than in their counterpart study patients. In patients with secondary adrenal insufficiency, the mortality risk relative to controls was also not different according to diabetes status. The risk differed according to the status of comorbid cardiovascular disease, in which the risk was slightly higher among those without comorbid cardiovascular disease, although no such information was previously available in patients with pituitary disorders.

Regarding cardiovascular events, risk did not differ according to sex, age, the status of previous cardiovascular disease, baseline diabetes and statin use, in patients with primary or secondary adrenal insufficiency, except that in secondary disease, the risk for cerebrovascular events was higher either in those with younger age or in those without previous cardiovascular disease. No previous studies in patients with primary or secondary adrenal insufficiency have investigated the risk for cardiovascular events according to these categories.

However, it is important to point out that the extent of the risk increment for adrenal insufficiency relative to controls in each sub-category of comorbidities (i.e. diabetes or cardiovascular disease) should be cautiously interpreted. This is because this present study, the comorbidities of the study patients were not initially matched with controls before classifying to the sub-categories, and other factors affecting mortality and cardiovascular disease (such as age, sex, and place and period of care) can differ between the study patients and controls in the same comorbid category. This can confound the estimation of the relative risks.

6.8 Limitations and future research

The present study has enhanced the accuracy of estimating the risks for mortality and cardiovascular disease in patients with adrenal insufficiency by using individually matched controls from a large real-world and quality-controlled database; however, there remain a number of limitations according to the study design and source of data: misclassification, informed presence bias, and unaddressed potential confounders.

With regard to misclassification, the diagnosis of adrenal insufficiency could be misclassified, as it was based on records in the primary care setting which do not provide access to the hormonal evaluation at the time of diagnosis, usually performed at the hospital setting. Misclassification was diminished by adding another inclusion criterion, according to which an oral glucocorticoid had to have been prescribed within three months after the first record of adrenal insufficiency. Classification was also validated by comparing the primary care record with the in-hospital record of adrenal insufficiency using a subgroup of patients who had been admitted to hospital, and this yielded a high positive predictive value of 91% and 79% for primary and secondary adrenal insufficiency, respectively. Similarly, a diagnosis of cardiovascular disease might have been misclassified as cardiovascular disease is also often diagnosed in the hospital setting. Again, the classification was validated by comparing the primary care records with in-hospital records for both the study patients and controls and it yielded an acceptable false positive rate (approximately 5%). In contrast, the false negative rate was somewhat high (up to 34%), although the false negative rate of the study patients and controls was proportional and therefore unlikely to distort the evaluation of risk. In addition, the hazard ratios for incident ischaemic heart disease and cerebrovascular disease recorded in CPRD (Chapter 4, Figure 4.1) were entirely consistent with the hazard ratios for hospitalisation

from the same diseases across all types of adrenal insufficiency patients (Chapter 4, Figure 4.3).

'Informed presence bias' is a common bias in studies using electronic health records, occurring when the study patients have more medical encounters and gain more medical attentions than the controls thus increasing the likelihood of comorbidity detection (161). The present study observed that at baseline, the prevalence of cardiovascular risk factors (e.g. previous cardiovascular disease, diabetes, or hypertension) in the study patients was higher than in controls, as would be expected if informed presence bias was present. Since cardiovascular risk factors, by definition, affect cardiovascular disease, the imbalance of baseline prevalence of these factors was taken into account by their inclusion in multivariable analysis models. Importantly, however, both unadjusted and adjusted relative risks should be cautiously interpreted, as they can only indicate associations, not cause-effect relationships. Informed presence bias can also be problematic in the outcome evaluation, given that study patients may be more likely to have an outcome recorded than their corresponding controls. However, the outcomes evaluated in the present study were hard outcomes (e.g. death, cardiovascular disease), for which there is likely to be an equal possibility for the study patients and controls to be recorded.

There are other confounders that might have influenced mortality and/ or cardiovascular disease that could not be taken into account, as some data was unavailable or missing and the time for conducting the study was limited. These included doses/ types of glucocorticoid used, body mass index, and confounders specific for secondary adrenal insufficiency, including other pituitary hormone deficiencies and their replacement therapy, a history of pituitary surgery and underlying causes of hypothalamic-pituitary disorders.

Future research; Regarding the evaluation of risk for all-cause mortality, it was clear that patients with adrenal insufficiency had increased mortality compared with controls. However, an early increase in mortality risk in patients with adrenal insufficiency at the beginning of the follow-up observed in this study might have been influenced by the systematic bias from the CPRD dataset. This would need to be confirmed by large prospective population-based studies.

Regarding the evaluation of risk for cardiovascular disease, future research in which cardiovascular risk factors of the study patients and controls are individually matched and body mass index is available is needed to confirm that the increased risk for cardiovascular disease in patients with adrenal insufficiency is dependent to the presence of cardiovascular risk factors.

6.9 Conclusions

In this large, case and control-matched, retrospective study, the mortality risk for patients with adrenal insufficiency was unequivocally increased. Cardiovascular disease was the leading cause of death while the relative risk of death from infection was markedly high. Soon after diagnosis, the mortality and hospital admission rates from adrenal crisis were maximum. Overall, the risk of cardiovascular events was not increased but cardiovascular mortality remained increased, even after taking account of cardiovascular risk factors. However, adrenal crisis-related death was associated with concomitant cardiovascular disease. Three factors: adrenal crisis, infection and cardiovascular disease, potentially contributed to the increased mortality in patients with adrenal insufficiency, despite these factors being preventable and treatable. Early education for adrenal crisis prevention, awareness of infection with appropriate treatment, and cardiovascular risk reduction could contribute to mitigating the increased mortality risk in patients with adrenal insufficiency.

References

1. Horrocks PM, Jones AF, Ratcliffe WA, Holder G, White A, Holder R, et al. PATTERNS OF ACTH AND CORTISOL PULSATILITY OVER TWENTY-FOUR HOURS IN NORMAL MALES AND FEMALES. Clinical Endocrinology. 1990;32(1):127-34.

2. Copinschi G, Challet E. Chapter 9 - Endocrine Rhythms, the Sleep-Wake Cycle, and Biological Clocks A2 - Jameson, J. Larry. In: Groot LJD, Kretser DMd, Giudice LC, Grossman AB, Melmed S, Potts JT, et al., editors. Endocrinology: Adult and Pediatric (Seventh Edition). Philadelphia: W.B. Saunders; 2016. p. 147-73.e9.

3. Stewart PM, Newell-Price JDC. The Adrenal Cortex. In: Melmed Se, Polonsky KSe, Larsen PRe, Kronenberg He, editors. Williams textbook of endocrinology. Thirteenth ed. Philadelphia, PA: Elsevier; 2016. p. 490-555.

4. Chrousos GP. Chapter 99 - Glucocorticoid Action: Physiology. In: Groot LJD, Kretser DMd, Giudice LC, Grossman AB, Melmed S, Potts JT, et al., editors. Endocrinology: Adult and Pediatric (Seventh Edition). Philadelphia: W.B. Saunders; 2016. p. 1727-40.e5.

5. Lewis JG, Bagley CJ, Elder PA, Bachmann AW, Torpy DJ. Plasma free cortisol fraction reflects levels of functioning corticosteroid-binding globulin. Clinica Chimica Acta. 2005;359(1):189-94.

6. Funder J, Pearce P, Smith R, Smith A. Mineralocorticoid Action: Target Tissue Specificity Is Enzyme, Not Receptor, Mediated. Science. 1988;242(4878):583.

7. Edwards CR, Stewart PM, Burt D, Brett L, McIntyre MA, Sutanto WS, et al. Localisation of 11 beta-hydroxysteroid dehydrogenase--tissue specific protector of the mineralocorticoid receptor. Lancet. 1988;2(8618):986-9.

8. Ricketts ML, Verhaeg JM, Bujalska I, Howie AJ, Rainey WE, Stewart PM. Immunohistochemical localization of type 1 11beta-hydroxysteroid dehydrogenase in human tissues. J Clin Endocrinol Metab. 1998;83(4):1325-35.

9. Bujalska IJ, Kumar S, Stewart PM. Does central obesity reflect "Cushing's disease of the omentum"? The Lancet. 1997;349(9060):1210-3.

10. Bujalska IJ, Kumar S, Hewison M, Stewart PM. Differentiation of adipose stromal cells: the roles of glucocorticoids and 11beta-hydroxysteroid dehydrogenase. Endocrinology. 1999;140(7):3188-96.

11. Stewart PM. Tissue-specific Cushing's syndrome, 11beta-hydroxysteroid dehydrogenases and the redefinition of corticosteroid hormone action. Eur J Endocrinol. 2003;149(3):163-8.

12. Diederich S, Eigendorff E, Burkhardt P, Quinkler M, Bumke-Vogt C, Rochel M, et al. 11beta-hydroxysteroid dehydrogenase types 1 and 2: an important pharmacokinetic determinant for the activity of synthetic mineralo- and glucocorticoids. The Journal of clinical endocrinology and metabolism. 2002;87(12):5695.

13. Axelrod L. Chapter 100 - Glucocorticoid Therapy2016. 1741-55.e3 p.

14. Munck A, Naray-Fejes-Toth A. The ups and downs of glucocorticoid physiology. Permissive and suppressive effects revisited. Mol Cell Endocrinol. 1992;90(1):C1-4.

15. Barthel A, Willenberg HS, Gruber M, Bornstein SR. Chapter 102 - Adrenal Insufficiency. In: Groot LJD, Kretser DMd, Giudice LC, Grossman AB, Melmed S, Potts JT, et al., editors. Endocrinology: Adult and Pediatric (Seventh Edition). Philadelphia: W.B. Saunders; 2016. p. 1763-74.e4.

16. Kong MF, Jeffcoate W. Eighty-six cases of Addison's disease. Clin Endocrinol (Oxf). 1994;41(6):757-61.

17. Laureti S, Vecchi L, Santeusanio F, Falorni A. Is the prevalence of Addison's disease underestimated? J Clin Endocrinol Metab. 1999;84(5):1762.

18. Lovas K, Husebye ES. High prevalence and increasing incidence of Addison's disease in western Norway. Clin Endocrinol (Oxf). 2002;56(6):787-91.

19. Erichsen MM, Lovas K, Fougner KJ, Svartberg J, Hauge ER, Bollerslev J, et al. Normal overall mortality rate in Addison's disease, but young patients are at risk of premature death. Eur J Endocrinol. 2009;160(2):233-7.

20. Meyer G, Neumann K, Badenhoop K, Linder R. Increasing prevalence of Addison's disease in German females: health insurance data 2008-2012. Eur J Endocrinol. 2014;170(3):367-73.

21. Burt MG, Ho KKY. Chapter 11 - Hypopituitarism and Growth Hormone Deficiency. In: Groot LJD, Kretser DMd, Giudice LC, Grossman AB, Melmed S, Potts JT, et al., editors. Endocrinology: Adult and Pediatric (Seventh Edition). Philadelphia: W.B. Saunders; 2016. p. 188-208.e5.

22. Melmed Se, Kleinberg D. Pituitary Masess and Tumors. In: Melmed Se, Polonsky KSe, Larsen PRe, Kronenberg He, editors. Williams textbook of endocrinology. Thirteenth ed. Philadelphia, PA: Elsevier; 2016. p. 232-99.

23. Nilsson B, Gustavasson-Kadaka E, Bengtsson BA, Jonsson B. Pituitary adenomas in Sweden between 1958 and 1991: incidence, survival, and mortality. J Clin Endocrinol Metab. 2000;85(4):1420-5.

24. Regal M, Paramo C, Sierra SM, Garcia-Mayor RV. Prevalence and incidence of hypopituitarism in an adult Caucasian population in northwestern Spain. Clin Endocrinol (Oxf). 2001;55(6):735-40.

25. Allolio B. Extensive expertise in endocrinology. Adrenal crisis. Eur J Endocrinol. 2015;172(3):R115-24.

26. Bancos I, Hahner S, Tomlinson J, Arlt W. Diagnosis and management of adrenal insufficiency. Lancet Diabetes Endocrinol. 2015;3(3):216-26.

27. Rushworth RL, Torpy DJ, Falhammar H. Adrenal Crisis. N Engl J Med. 2019;381(9):852-61.

28. Murray RD, Ekman B, Uddin S, Marelli C, Quinkler M, Zelissen PM, et al. Management of glucocorticoid replacement in adrenal insufficiency shows notable heterogeneity - data from the EU-AIR. Clin Endocrinol (Oxf). 2017;86(3):340-6.

29. Tomlinson JW, Walker EA, Bujalska IJ, Draper N, Lavery GG, Cooper MS, et al. 11beta-hydroxysteroid dehydrogenase type 1: a tissue-specific regulator of glucocorticoid response. Endocr Rev. 2004;25(5):831-66.

30. Nordenstrom A, Marcus C, Axelson M, Wedell A, Ritzen EM. Failure of cortisone acetate treatment in congenital adrenal hyperplasia because of defective 11beta-hydroxysteroid dehydrogenase reductase activity. J Clin Endocrinol Metab. 1999;84(4):1210-3.

31. Inada H, Imamura T, Nakajima R, Yamano T. Poor response to substitution therapy with cortisone acetate in patients with congenital adrenal hyperplasia. Clin Pediatr Endocrinol. 2004;13(1):11-5.

32. Axelrod L. Chapter 100 - Glucocorticoid Therapy A2 - Jameson, J. Larry. In: Groot LJD, Kretser DMd, Giudice LC, Grossman AB, Melmed S, Potts JT, et al., editors. Endocrinology: Adult and Pediatric (Seventh Edition). Philadelphia: W.B. Saunders; 2016. p. 1741-55.e3.

33. Diederich S, Scholz T, Eigendorff E, Bumke-Vogt C, Quinkler M, Exner P, et al. Pharmacodynamics and pharmacokinetics of synthetic mineralocorticoids and glucocorticoids: receptor transactivation and prereceptor metabolism by 11beta-hydroxysteroid-dehydrogenases. Horm Metab Res. 2004;36(6):423-9.

34. Bornstein SR, Allolio B, Arlt W, Barthel A, Don-Wauchope A, Hammer GD, et al. Diagnosis and Treatment of Primary Adrenal Insufficiency: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2016;101(2):364-89.

35. Fleseriu M, Hashim IA, Karavitaki N, Melmed S, Murad MH, Salvatori R, et al. Hormonal Replacement in Hypopituitarism in Adults: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2016;101(11):3888-921.

36. Derendorf H, Mollmann H, Barth J, Mollmann C, Tunn S, Krieg M. Pharmacokinetics and oral bioavailability of hydrocortisone. J Clin Pharmacol. 1991;31(5):473-6.

37. Forss M, Batcheller G, Skrtic S, Johannsson G. Current practice of glucocorticoid replacement therapy and patient-perceived health outcomes in adrenal insufficiency - a worldwide patient survey. BMC Endocr Disord. 2012;12:8.

38. Castinetti F, Sahnoun M, Albarel F, Morange I, Philippon M, Conte-Devolx B, et al. An observational study on adrenal insufficiency in a French tertiary centre: Real life versus theory. Ann Endocrinol (Paris). 2015;76(1):1-8.

39. Ferreira L, Silva J, Garrido S, Bello C, Oliveira D, Simoes H, et al. Primary adrenal insufficiency in adult population: a Portuguese Multicentre Study by the Adrenal Tumours Study Group. Endocr Connect. 2017;6(8):935-42.

40. Linder BL, Esteban NV, Yergey AL, Winterer JC, Loriaux DL, Cassorla F. Cortisol production rate in childhood and adolescence. J Pediatr. 1990;117(6):892-6.

41. Esteban NV, Loughlin T, Yergey AL, Zawadzki JK, Booth JD, Winterer JC, et al. Daily cortisol production rate in man determined by stable isotope dilution/mass spectrometry. J Clin Endocrinol Metab. 1991;72(1):39-45.

42. Kerrigan JR, Veldhuis JD, Leyo SA, Iranmanesh A, Rogol AD. Estimation of daily cortisol production and clearance rates in normal pubertal males by deconvolution analysis. J Clin Endocrinol Metab. 1993;76(6):1505-10.

43. Purnell JQ, Brandon DD, Isabelle LM, Loriaux DL, Samuels MH. Association of 24-hour cortisol production rates, cortisol-binding globulin, and plasma-free cortisol levels with body composition, leptin levels, and aging in adult men and women. J Clin Endocrinol Metab. 2004;89(1):281-7.

44. Filipsson H, Monson JP, Koltowska-Haggstrom M, Mattsson A, Johannsson G. The impact of glucocorticoid replacement regimens on metabolic outcome and comorbidity in hypopituitary patients. J Clin Endocrinol Metab. 2006;91(10):3954-61.

45. Sherlock M, Reulen RC, Alonso AA, Ayuk J, Clayton RN, Sheppard MC, et al. ACTH deficiency, higher doses of hydrocortisone replacement, and radiotherapy are independent predictors of mortality in patients with acromegaly. J Clin Endocrinol Metab. 2009;94(11):4216-23.

46. Zueger T, Kirchner P, Herren C, Fischli S, Zwahlen M, Christ E, et al. Glucocorticoid replacement and mortality in patients with nonfunctioning pituitary adenoma. J Clin Endocrinol Metab. 2012;97(10):E1938-42.

47. Dalin F, Nordling Eriksson G, Dahlqvist P, Hallgren A, Wahlberg J, Ekwall O, et al. Clinical and Immunological Characteristics of Autoimmune Addison Disease: A Nationwide Swedish Multicenter Study. J Clin Endocrinol Metab. 2017;102(2):379-89.

48. O'Reilly MW, Reulen RC, Gupta S, Thompson CA, Dineen R, Goulden EL, et al. ACTH and gonadotropin deficiencies predict mortality in patients treated for nonfunctioning pituitary adenoma: long-term follow-up of 519 patients in two large European centres. Clin Endocrinol (Oxf). 2016;85(5):748-56.

49. Hammarstrand C, Ragnarsson O, Hallen T, Andersson E, Skoglund T, Nilsson AG, et al. Higher glucocorticoid replacement doses are associated with increased mortality in patients with pituitary adenoma. Eur J Endocrinol. 2017;177(3):251-6.

50. DeVile CJ, Stanhope R. Hydrocortisone replacement therapy in children and adolescents with hypopituitarism. Clin Endocrinol (Oxf). 1997;47(1):37-41.

51. Howlett TA. An assessment of optimal hydrocortisone replacement therapy. Clin Endocrinol (Oxf). 1997;46(3):263-8.

52. Simon N, Castinetti F, Ouliac F, Lesavre N, Brue T, Oliver C. Pharmacokinetic evidence for suboptimal treatment of adrenal insufficiency with currently available hydrocortisone tablets. Clin Pharmacokinet. 2010;49(7):455-63.

53. Dineen R, Stewart PM, Sherlock M. Factors impacting on the action of glucocorticoids in patients receiving glucocorticoid therapy. Clin Endocrinol (Oxf). 2019;90(1):3-14.

54. Toogood AA, Taylor NF, Shalet SM, Monson JP. Modulation of cortisol metabolism by low-dose growth hormone replacement in elderly hypopituitary patients. J Clin Endocrinol Metab. 2000;85(4):1727-30.

55. Weaver JU, Thaventhiran L, Noonan K, Burrin JM, Taylor NF, Norman MR, et al. The effect of growth hormone replacement on cortisol metabolism and glucocorticoid sensitivity in hypopituitary adults. Clin Endocrinol (Oxf). 1994;41(5):639-48.

56. Moore JS, Monson JP, Kaltsas G, Putignano P, Wood PJ, Sheppard MC, et al. Modulation of 11beta-hydroxysteroid dehydrogenase isozymes by growth hormone and insulin-like growth factor: in vivo and in vitro studies. J Clin Endocrinol Metab. 1999;84(11):4172-7.

57. Giavoli C, Libe R, Corbetta S, Ferrante E, Lania A, Arosio M, et al. Effect of recombinant human growth hormone (GH) replacement on the hypothalamic-pituitary-adrenal axis in adult GH-deficient patients. J Clin Endocrinol Metab. 2004;89(11):5397-401.

58. Iranmanesh A, Lizarralde G, Johnson ML, Veldhuis JD. Dynamics of 24-hour endogenous cortisol secretion and clearance in primary hypothyroidism assessed before and after partial thyroid hormone replacement. J Clin Endocrinol Metab. 1990;70(1):155-61.

59. Kang MS, Sandhu CS, Singh N, Evans T. Initiation of levothyroxine in a patient with hypothyroidism inducing adrenal crisis requiring VA ECMO: a tale of preventable disaster. BMJ Case Rep. 2019;12(8).

60. Fonseca V, Brown R, Hochhauser D, Ginsburg J, Havard CW. Acute adrenal crisis precipitated by thyroxine. Br Med J (Clin Res Ed). 1986;292(6529):1185-6.

61. Shaikh MG, Lewis P, Kirk JM. Thyroxine unmasks Addison's disease. Acta Paediatr. 2004;93(12):1663-5.

62. Sandberg AA, Slaunwhite WR, Jr. Transcortin: a corticosteroid-binding protein of plasma. II. Levels in various conditions and the effects of estrogens. J Clin Invest. 1959;38(8):1290-7.

63. Musa BU, Seal US, Doe RP. Elevation of certain plasma proteins in man following estrogen administration: a dose-response relationship. J Clin Endocrinol Metab. 1965;25(9):1163-6.

64. Qureshi AC, Bahri A, Breen LA, Barnes SC, Powrie JK, Thomas SM, et al. The influence of the route of oestrogen administration on serum levels of cortisol-binding globulin and total cortisol. Clin Endocrinol (Oxf). 2007;66(5):632-5.

65. Shifren JL, Desindes S, McIlwain M, Doros G, Mazer NA. A randomized, open-label, crossover study comparing the effects of oral versus transdermal estrogen therapy on serum androgens, thyroid hormones, and adrenal hormones in naturally menopausal women. Menopause. 2007;14(6):985-94.

66. Sherlock M, Behan LA, Hannon MJ, Alonso AA, Thompson CJ, Murray RD, et al. The modulation of corticosteroid metabolism by hydrocortisone therapy in patients with hypopituitarism increases tissue glucocorticoid exposure. Eur J Endocrinol. 2015;173(5):583-93.

67. Mah PM, Jenkins RC, Rostami-Hodjegan A, Newell-Price J, Doane A, Ibbotson V, et al. Weight-related dosing, timing and monitoring hydrocortisone replacement therapy in patients with adrenal insufficiency. Clin Endocrinol (Oxf). 2004;61(3):367-75.

68. Lovas K, Loge JH, Husebye ES. Subjective health status in Norwegian patients with Addison's disease. Clin Endocrinol (Oxf). 2002;56(5):581-8.

69. Hahner S, Loeffler M, Fassnacht M, Weismann D, Koschker AC, Quinkler M, et al. Impaired subjective health status in 256 patients with adrenal insufficiency on standard therapy based on cross-sectional analysis. J Clin Endocrinol Metab. 2007;92(10):3912-22.

70. Lovas K, Husebye ES, Holsten F, Bjorvatn B. Sleep disturbances in patients with Addison's disease. Eur J Endocrinol. 2003;148(4):449-56.

71. Thomsen AF, Kvist TK, Andersen PK, Kessing LV. The risk of affective disorders in patients with adrenocortical insufficiency. Psychoneuroendocrinology. 2006;31(5):614-22.

72. Dunlop D. Eighty-Six Cases of Addison's Disease. Br Med J. 1963;2(5362):887-91.

73. Bergthorsdottir R, Leonsson-Zachrisson M, Oden A, Johannsson G. Premature mortality in patients with Addison's disease: a population-based study. J Clin Endocrinol Metab. 2006;91(12):4849-53.

74. Bensing S, Brandt L, Tabaroj F, Sjoberg O, Nilsson B, Ekbom A, et al. Increased death risk and altered cancer incidence pattern in patients with isolated or combined autoimmune primary adrenocortical insufficiency. Clin Endocrinol (Oxf). 2008;69(5):697-704.

75. Chantzichristos D, Persson A, Eliasson B, Miftaraj M, Franzen S, Bergthorsdottir R, et al. Mortality in patients with diabetes mellitus and Addison's disease: a nationwide, matched, observational cohort study. Eur J Endocrinol. 2017;176(1):31-9.

76. Bates AS, Van't Hoff W, Jones PJ, Clayton RN. The effect of hypopituitarism on life expectancy. J Clin Endocrinol Metab. 1996;81(3):1169-72.

77. Bulow B, Hagmar L, Mikoczy Z, Nordstrom CH, Erfurth EM. Increased cerebrovascular mortality in patients with hypopituitarism. Clin Endocrinol (Oxf). 1997;46(1):75-81.

78. Tomlinson JW, Holden N, Hills RK, Wheatley K, Clayton RN, Bates AS, et al. Association between premature mortality and hypopituitarism. West Midlands Prospective Hypopituitary Study Group. Lancet. 2001;357(9254):425-31.

79. Svensson J, Bengtsson BA, Rosen T, Oden A, Johannsson G. Malignant disease and cardiovascular morbidity in hypopituitary adults with or without growth hormone replacement therapy. J Clin Endocrinol Metab. 2004;89(7):3306-12.

80. Gaillard RC, Mattsson AF, Akerblad AC, Bengtsson BA, Cara J, Feldt-Rasmussen U, et al. Overall and cause-specific mortality in GH-deficient adults on GH replacement. Eur J Endocrinol. 2012;166(6):1069-77.

81. Burman P, Mattsson AF, Johannsson G, Hoybye C, Holmer H, Dahlqvist P, et al. Deaths among adult patients with hypopituitarism: hypocortisolism during acute stress, and de novo malignant brain tumors contribute to an increased mortality. J Clin Endocrinol Metab. 2013;98(4):1466-75.

82. Ntali G, Capatina C, Fazal-Sanderson V, Byrne JV, Cudlip S, Grossman AB, et al. Mortality in patients with non-functioning pituitary adenoma is increased: systematic analysis of 546 cases with long follow-up. Eur J Endocrinol. 2016;174(2):137-45.

83. Goldman DA, Brender JD. Are standardized mortality ratios valid for public health data analysis? Stat Med. 2000;19(8):1081-8.

84. Naing NN. Easy way to learn standardization : direct and indirect methods. Malays J Med Sci. 2000;7(1):10-5.

85. Bates AS, Bullivant B, Sheppard MC, Stewart PM. Life expectancy following surgery for pituitary tumours. Clin Endocrinol (Oxf). 1999;50(3):315-9.

86. Mills JL, Schonberger LB, Wysowski DK, Brown P, Durako SJ, Cox C, et al. Long-term mortality in the United States cohort of pituitary-derived growth hormone recipients. J Pediatr. 2004;144(4):430-6.

87. Lindholm J, Nielsen EH, Bjerre P, Christiansen JS, Hagen C, Juul S, et al. Hypopituitarism and mortality in pituitary adenoma. Clin Endocrinol (Oxf). 2006;65(1):51-8.

88. Nielsen E, Lindholm J, Laurberg P, Bjerre P, Christiansen J, Hagen C, et al. Nonfunctioning pituitary adenoma: incidence, causes of death and quality of life in relation to pituitary function. The Official Journal of the Pituitary Society. 2007;10(1):67-73.

89. van Bunderen CC, van Nieuwpoort IC, Arwert LI, Heymans MW, Franken AA, Koppeschaar HP, et al. Does growth hormone replacement therapy reduce mortality in adults with growth hormone deficiency? Data from the Dutch National Registry of Growth Hormone Treatment in adults. J Clin Endocrinol Metab. 2011;96(10):3151-9.

90. Olsson DS, Nilsson AG, Bryngelsson IL, Trimpou P, Johannsson G, Andersson E. Excess Mortality in Women and Young Adults With Nonfunctioning Pituitary Adenoma: A Swedish Nationwide Study. J Clin Endocrinol Metab. 2015;100(7):2651-8.

91. Quinkler M, Ekman B, Zhang P, Isidori AM, Murray RD, Investigators E-A. Mortality data from the European Adrenal Insufficiency Registry-Patient characterization and associations. Clin Endocrinol (Oxf). 2018;89(1):30-5.

92. Brada M, Ashley S, Ford D, Traish D, Burchell L, Rajan B. Cerebrovascular mortality in patients with pituitary adenoma. Clin Endocrinol (Oxf). 2002;57(6):713-7.

93. Olsson DS, Bryngelsson IL, Ragnarsson O. Time trends of mortality in patients with non-functioning pituitary adenoma: a Swedish nationwide study. Pituitary. 2017;20(2):218-24.

94. Nielsen EH, Lindholm J, Laurberg P. Excess mortality in women with pituitary disease: a meta-analysis. Clin Endocrinol (Oxf). 2007;67(5):693-7.

95. Gibney J, Johannsson G, Leung KC, Ho KK. Comparison of the metabolic effects of raloxifene and oral estrogen in postmenopausal and growth hormone-deficient women. J Clin Endocrinol Metab. 2005;90(7):3897-903.

96. Kaiser U, Ho KKY. Pituitary Physiology and Diagnostic Evaluation. In: Melmed Se, Polonsky KSe, Larsen PRe, Kronenberg He, editors. Williams textbook of endocrinology. Thirteenth ed. Philadelphia, PA: Elsevier; 2016. p. 176-231.

97. Mah PM, Webster J, Jonsson P, Feldt-Rasmussen U, Koltowska-Haggstrom M, Ross RJ. Estrogen replacement in women of fertile years with hypopituitarism. J Clin Endocrinol Metab. 2005;90(11):5964-9.

98. O'Sullivan AJ, Crampton LJ, Freund J, Ho KK. The route of estrogen replacement therapy confers divergent effects on substrate oxidation and body composition in postmenopausal women. J Clin Invest. 1998;102(5):1035-40.

99. Gutierrez LP, Koltowska-Haggstrom M, Jonsson PJ, Mattsson AF, Svensson D, Westberg B, et al. Registries as a tool in evidence-based medicine: example of KIMS (Pfizer International Metabolic Database). Pharmacoepidemiol Drug Saf. 2008;17(1):90-102.

100. Skov J, Sundstrom A, Ludvigsson JF, Kampe O, Bensing S. Sex-Specific Risk of Cardiovascular Disease in Autoimmune Addison Disease-A Population-Based Cohort Study. J Clin Endocrinol Metab. 2019;104(6):2031-40.

101. Fardet L, Petersen I, Nazareth I. Common Infections in Patients Prescribed Systemic Glucocorticoids in Primary Care: A Population-Based Cohort Study. PLoS Med. 2016;13(5):e1002024.

102. Puar TH, Stikkelbroeck NM, Smans LC, Zelissen PM, Hermus AR. Adrenal Crisis: Still a Deadly Event in the 21st Century. Am J Med. 2016;129(3):339 e1-9.

103. Hahner S, Spinnler C, Fassnacht M, Burger-Stritt S, Lang K, Milovanovic D, et al. High incidence of adrenal crisis in educated patients with chronic adrenal insufficiency: a prospective study. J Clin Endocrinol Metab. 2015;100(2):407-16.

104. Hahner S, Loeffler M, Bleicken B, Drechsler C, Milovanovic D, Fassnacht M, et al. Epidemiology of adrenal crisis in chronic adrenal insufficiency: the need for new prevention strategies. Eur J Endocrinol. 2010;162(3):597-602.

105. Hahner S. Acute adrenal crisis and mortality in adrenal insufficiency: Still a concern in 2018! Ann Endocrinol (Paris). 2018;79(3):164-6.

106. Rushworth RL, Torpy DJ, Falhammar H. Adrenal crises: perspectives and research directions. Endocrine. 2017;55(2):336-45.

107. Sherlock M, Gittoes NJ, Arlt W. Adrenal crisis causing critical illness related reversible myocardial dysfunction. Clin Endocrinol (Oxf). 2008;68(4):667-9.

108. Ukita C, Miyazaki H, Toyoda N, Kosaki A, Nishikawa M, Iwasaka T. Takotsubo cardiomyopathy during acute adrenal crisis due to isolated adrenocorticotropin deficiency. Intern Med. 2009;48(5):347-52.

109. Shimizu M, Monguchi T, Takano T, Miwa Y. Isolated ACTH deficiency presenting with severe myocardial dysfunction. J Cardiol Cases. 2011;4(1):e26-e30.

110. Falhammar H, Frisen L, Norrby C, Hirschberg AL, Almqvist C, Nordenskjold A, et al. Increased mortality in patients with congenital adrenal hyperplasia due to 21-hydroxylase deficiency. J Clin Endocrinol Metab. 2014;99(12):E2715-21.

111. Omori K, Nomura K, Shimizu S, Omori N, Takano K. Risk factors for adrenal crisis in patients with adrenal insufficiency. Endocr J. 2003;50(6):745-52.

112. Smans LC, Van der Valk ES, Hermus AR, Zelissen PM. Incidence of adrenal crisis in patients with adrenal insufficiency. Clin Endocrinol (Oxf). 2016;84(1):17-22.

113. Notter A, Jenni S, Christ E. Evaluation of the frequency of adrenal crises and preventive measures in patients with primary and secondary adrenal insufficiency in Switzerland. Swiss Med Wkly. 2018;148:w14586.

114. Ono Y, Ono S, Yasunaga H, Matsui H, Fushimi K, Tanaka Y. Clinical features and practice patterns of treatment for adrenal crisis: a nationwide cross-sectional study in Japan. Eur J Endocrinol. 2017;176(3):329-37.

115. Braatvedt GD, Newrick PG, Corrall RJ. Patients' self administration of hydrocortisone. BMJ. 1990;301(6764):1312.

116. Nagesser SK, van Seters AP, Kievit J, Hermans J, Krans HM, van de Velde CJ. Long-term results of total adrenalectomy for Cushing's disease. World J Surg. 2000;24(1):108-13.

117. Thompson SK, Hayman AV, Ludlam WH, Deveney CW, Loriaux DL, Sheppard BC. Improved quality of life after bilateral laparoscopic adrenalectomy for Cushing's disease: a 10-year experience. Ann Surg. 2007;245(5):790-4.

118. White K, Arlt W. Adrenal crisis in treated Addison's disease: a predictable but under-managed event. Eur J Endocrinol. 2010;162(1):115-20.

119. Reisch N, Willige M, Kohn D, Schwarz HP, Allolio B, Reincke M, et al. Frequency and causes of adrenal crises over lifetime in patients with 21-hydroxylase deficiency. Eur J Endocrinol. 2012;167(1):35-42.

120. Ritzel K, Beuschlein F, Mickisch A, Osswald A, Schneider HJ, Schopohl J, et al. Clinical review: Outcome of bilateral adrenalectomy in Cushing's syndrome: a systematic review. J Clin Endocrinol Metab. 2013;98(10):3939-48.

121. Etxabe J, Vazquez JA. Morbidity and mortality in Cushing's disease: an epidemiological approach. Clin Endocrinol (Oxf). 1994;40(4):479-84.

122. Clayton RN, Raskauskiene D, Reulen RC, Jones PW. Mortality and morbidity in Cushing's disease over 50 years in Stoke-on-Trent, UK: audit and meta-analysis of literature. J Clin Endocrinol Metab. 2011;96(3):632-42.

123. Vogelzangs N, Beekman AT, Milaneschi Y, Bandinelli S, Ferrucci L, Penninx BW. Urinary cortisol and six-year risk of all-cause and cardiovascular mortality. J Clin Endocrinol Metab. 2010;95(11):4959-64.

124. Ross IL, Bergthorsdottir R, Levitt NS, Schatz DA, Johannsson G, Marais AD. Increased cardiovascular risk in South African patients with Addison's disease. Horm Metab Res. 2013;45(12):905-10.

125. Stewart PM, Biller BM, Marelli C, Gunnarsson C, Ryan MP, Johannsson G. Exploring Inpatient Hospitalizations and Morbidity in Patients With Adrenal Insufficiency. J Clin Endocrinol Metab. 2016;101(12):4843-50.

126. Giordano R, Marzotti S, Balbo M, Romagnoli S, Marinazzo E, Berardelli R, et al. Metabolic and cardiovascular profile in patients with Addison's disease under conventional glucocorticoid replacement. J Endocrinol Invest. 2009;32(11):917-23.

127. Markussis V, Beshyah SA, Fisher C, Sharp P, Nicolaides AN, Johnston DG. Detection of premature atherosclerosis by high-resolution ultrasonography in symptom-free hypopituitary adults. Lancet. 1992;340(8829):1188-92.

128. Erfurth EM, Bulow B, Eskilsson J, Hagmar L. High incidence of cardiovascular disease and increased prevalence of cardiovascular risk factors in women with hypopituitarism not receiving growth hormone treatment: preliminary results. Growth Horm IGF Res. 1999;9 Suppl A:21-4.

129. Holmer H, Svensson J, Rylander L, Johannsson G, Rosen T, Bengtsson BA, et al. Nonfatal stroke, cardiac disease, and diabetes mellitus in hypopituitary patients on hormone replacement including growth hormone. J Clin Endocrinol Metab. 2007;92(9):3560-7.

130. Olsson DS, Bryngelsson IL, Ragnarsson O. Higher incidence of morbidity in women than men with non-functioning pituitary adenoma: a Swedish nationwide study. Eur J Endocrinol. 2016;175(1):55-61.

131. Bergthorsdottir R, Ragnarsson O, Skrtic S, Glad CAM, Nilsson S, Ross IL, et al. Visceral Fat and Novel Biomarkers of Cardiovascular Disease in Patients With Addison's Disease: A Case-Control Study. J Clin Endocrinol Metab. 2017;102(11):4264-72.

132. Bjornsdottir S, Sundstrom A, Ludvigsson JF, Blomqvist P, Kampe O, Bensing S. Drug prescription patterns in patients with Addison's disease: a Swedish population-based cohort study. J Clin Endocrinol Metab. 2013;98(5):2009-18.

133. Elhadd TA, Abdu TA, Oxtoby J, Kennedy G, McLaren M, Neary R, et al. Biochemical and biophysical markers of endothelial dysfunction in adults with hypopituitarism and severe GH deficiency. J Clin Endocrinol Metab. 2001;86(9):4223-32.

134. Leelarathna L, Breen L, Powrie JK, Thomas SM, Guzder R, McGowan B, et al. Co-morbidities, management and clinical outcome of auto-immune Addison's disease. Endocrine. 2010;38(1):113-7.

135. Quinkler M, Ekman B, Marelli C, Uddin S, Zelissen P, Murray RD, et al. Prednisolone is associated with a worse lipid profile than hydrocortisone in patients with adrenal insufficiency. Endocr Connect. 2017;6(1):1-8.

136. al-Shoumer KA, Cox KH, Hughes CL, Richmond W, Johnston DG. Fasting and postprandial lipid abnormalities in hypopituitary women receiving conventional replacement therapy. J Clin Endocrinol Metab. 1997;82(8):2653-9.

137. Abdu TA, Neary R, Elhadd TA, Akber M, Clayton RN. Coronary risk in growth hormone deficient hypopituitary adults: increased predicted risk is due largely to lipid profile abnormalities. Clin Endocrinol (Oxf). 2001;55(2):209-16.

138. Sesmilo G, Miller KK, Hayden D, Klibanski A. Inflammatory cardiovascular risk markers in women with hypopituitarism. J Clin Endocrinol Metab. 2001;86(12):5774-81.

139. Bulow B, Hagmar L, Eskilsson J, Erfurth EM. Hypopituitary females have a high incidence of cardiovascular morbidity and an increased prevalence of cardiovascular risk factors. J Clin Endocrinol Metab. 2000;85(2):574-84.

140. Markussis V, Beshyah SA, Fisher C, Parker KH, Nicolaides AN, Johnston DG. Abnormal carotid arterial wall dynamics in symptom-free hypopituitary adults. Eur J Endocrinol. 1997;136(2):157-64.

141. Brada M, Burchell L, Ashley S, Traish D. The incidence of cerebrovascular accidents in patients with pituitary adenoma. Int J Radiat Oncol Biol Phys. 1999;45(3):693-8.

142. Morris B, Partap S, Yeom K, Gibbs IC, Fisher PG, King AA. Cerebrovascular disease in childhood cancer survivors: A Children's Oncology Group Report. Neurology. 2009;73(22):1906-13.

143. The Clinical Practice Research Datalink. *The Clinical Practice Research Datalink (CPRD)* 06/01/2020 22nd January 2020. Available from: https://www.cprd.com/. [Accessed 22nd January 2020]

144. Herrett E, Gallagher AM, Bhaskaran K, Forbes H, Mathur R, van Staa T, et al. Data Resource Profile: Clinical Practice Research Datalink (CPRD). Int J Epidemiol. 2015;44(3):827-36.

145. The Clinical Practice Research Datalink. *The Clinical Practice Research Datalink (CPRD)*. Available from: https://www.cprd.com/. [Accessed 22nd January 2020]

146. Medicines and Healthcare products Regulatory Agency. CPRD GOLD e-learning course. Available from: http://learning.mhra.gov.uk/mhra/index.jsp. [Accessed 6th July 2018]

147. Herrett E, Shah A, Boggon R, Denaxas S, Smeeth L, van Staa T, et al. Completeness and diagnostic validity of recording acute myocardial infarction events in primary care, hospital care, disease registry, and national mortality records: cohort study. British Medical Journal. 2013;346(7909):14.

148. Gallagher AM, Dedman D, Padmanabhan S, Leufkens HGM, de Vries F. The accuracy of date of death recording in the Clinical Practice Research Datalink GOLD database in England compared with the Office for National Statistics death registrations. Pharmacoepidemiol Drug Saf. 2019;28(5):563-9.

149. NHS Digital. Quality and Outcomes Framework (QOF), enhanced services and core contract extraction specifications (business rules). Available from: https://digital.nhs.uk/data-and-information/data-collections-and-data-sets/data-collections/quality-and-outcomes-framework-qof. [Accessed 23rd January 2020]

150. Padmanabhan S, Carty L, Cameron E, Ghosh RE, Williams R, Strongman H. Approach to record linkage of primary care data from Clinical Practice Research Datalink to other health-related patient data: overview and implications. Eur J Epidemiol. 2019;34(1):91-9.

151. The Clinical Practice Research Datalink. *CPRD linked data*. Available from: https://cprd.com/linked-data. [Accessed 2nd February 2020]

152. NHS Digital. Hospital Episode Statistics Data Dictionary. Available from: https://digital.nhs.uk/data-and-information/data-tools-and-services/data-services/hospital-episode-statistics/hospital-episode-statistics-data-dictionary. [Accessed 2nd February 2019]

153. HM Passport Office. Guidance for doctors completing medical certificates of cause of death (MCCD) in England and Wales updated 25th September 2018. Available from: https://www.gov.uk/government/publications/guidance-notes-for-completing-a-medical-certificate-of-cause-of-death. [Accessed 6th February 2020]

154. Office for National Statistics. *User guide to mortality statistics*. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/methodologies/userguidetomortalitystatisticsjuly2017#cause-of-death-coding. [Accessed 10th February 2020]

155. British Heart Foundation. Cardiovascular Disease Statistics 2018. Available from: https://www.bhf.org.uk/research/heart-statistics/heart-statistics-publications/cardiovascular-disease-statistics-2018. [Accessed 3rd March 2018]

156. Officie for National Statistics. Deaths registered in England and Wales: 2017. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/bulletins/deathsregistrationsummarytables/2017#age-standardised-mortality-rates-continued-to-decrease-in-2017. [Accessed 10th February 2020]

157. Mario Cleves S. Analysis of multiple failure-time survival data. Available from: https://www.stata.com/support/faqs/statistics/multiple-failure-time-data/. [Accessed 23rd January 2019]

158. Pappachan JM, Raskauskiene D, Kutty VR, Clayton RN. Excess mortality associated with hypopituitarism in adults: a meta-analysis of observational studies. J Clin Endocrinol Metab. 2015;100(4):1405-11.

159. Jasim S, Alahdab F, Ahmed AT, Tamhane S, Prokop LJ, Nippoldt TB, et al. Mortality in adults with hypopituitarism: a systematic review and meta-analysis. Endocrine. 2017;56(1):33-42.

160. Sherlock M, Ayuk J, Tomlinson JW, Toogood AA, Aragon-Alonso A, Sheppard MC, et al. Mortality in patients with pituitary disease. Endocr Rev. 2010;31(3):301-42.

161. Goldstein BA, Bhavsar NA, Phelan M, Pencina MJ. Controlling for Informed Presence Bias Due to the Number of Health Encounters in an Electronic Health Record. Am J Epidemiol. 2016;184(11):847-55.

162. Frey N, Bircher A, Bodmer M, Jick SS, Meier CR, Spoendlin J. Validation of Stevens–Johnson syndrome or toxic epidermal necrolysis diagnoses in the Clinical Practice Research Datalink. Pharmacoepidemiology and Drug Safety. 2017;26(4):429-36.

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Not applicable

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Chapter 6: Discussion and Conclusion

Not applicable

Suppl. Table 2.1: Medical codes, Read codes, and Read terms for inclusion of adrenal insufficiency classified into three groups: Primary, Secondary, and Unspecified adrenal insufficiency

Medical code	Read code	Read term (Clinical terminology)
Primary adrenal insufficiency		
35760	A176.00	Tuberculosis of adrenal glands - Addison's disease
69198	F395000	Myopathy due to Addison's disease
4481	C154100	Addison's disease
Secondary adrenal insufficiency		
50334	B920000	Neoplasm of uncertain behaviour of pituitary gland
48590	C132000	Idiopathic panhypopituitarism
50958	C137.11	Iatrogenic hypopituitarism
43908	C134z11	Anterior pituitary hormone deficiency NEC
56983	C137.00	Iatrogenic pituitary disorders
101679	7102400	Operation on pituitary stalk
8551	710..12	Pituitary gland operations
57797	PK24000	Aberrant pituitary gland
53569	7100y00	Other specified excision of pituitary gland
44873	C132300	Postinfective panhypopituitarism
40070	7101100	Implantation of radioactive substance into pituitary gland
9895	C134.00	Other anterior pituitary disorder
5026	C132.00	Panhypopituitarism
93883	710y.00	Pituitary gland or pineal gland operations OS
49056	7100z00	Excision of pituitary gland NOS
50514	7102200	Decompression of pituitary gland
4365	7102z00	Other operation on pituitary gland NOS
70695	C132200	Postinfarction panhypopituitarism
105672	C137000	Hormone-induced hypopituitarism
67154	C132y00	Other specified panhypopituitarism
42685	B920.00	Neop uncertain behaviour pituitary and craniopharyngeal duct
72267	7101000	Cryotherapy to pituitary gland
8552	C132.11	Hypopituitarism NOS
73931	Cyu4400	[X]Other disorders of pituitary gland
20287	C133.00	Pituitary dwarfism
68461	7102300	Exploration of pituitary gland
44881	C137100	Post-hypophysectomy hypopituitarism
105321	C13A.00	Pituitary apoplexy
12449	C13z.00	Pituitary disorders NOS
26120	BB5V.00	[M]Pituitary adenomas and carcinomas
97846	C137111	Surgically-induced hypopituitarism
34459	C137z00	Iatrogenic pituitary disorder NOS
69903	C133y00	Other specified pituitary dwarfism
34261	7102000	Excision of lesion of pituitary gland
73009	7101	Destruction of pituitary gland

93629	710z.00	Pituitary gland and pineal gland operations NOS
58596	7102y00	Other specified other operation on pituitary gland
20267	B7H2000	Benign neoplasm of pituitary gland
57422	BB5Vz00	[M]Pituitary adenoma or carcinoma NOS
24418	C13..00	Disorders of pituitary gland and its hypothalamic control
100348	7101200	Injection of destructive substance into pituitary gland NEC
71886	B7H2z00	Benign neoplasm of pituitary and craniopharyngeal duct NOS
39009	710..00	Pituitary gland and pineal gland operations
52399	7102	Other operations on pituitary gland
34406	7102100	Biopsy of lesion of pituitary gland
33653	C132z00	Panhypopituitarism NOS
20299	C13yz00	Other pituitary disorders + diencephalohypophyseal synd NOS
50513	F4H5000	Disorder of optic chiasm due to pituitary disorder
53993	C13y000	Abscess of pituitary
94371	B920z00	Neop uncertain behaviour pituitary and craniopharyngeal NOS
61409	C133z00	Pituitary dwarfism NOS
50190	7100	Excision of pituitary gland
5706	B7H2.00	Benign neoplasm of pituitary gland and craniopharyngeal duct
70576	PK24z00	Anomaly of pituitary gland NOS
101601	C132100	Post-birth injury panhypopituitarism
111629	PK24100	Congenital absence of pituitary gland
15488	C134z00	Other anterior pituitary disorder NOS
44186	C13y.00	Other pituitary disorders + diencephalohypophyseal syndromes
44247	C137200	Post-radiotherapy hypopituitarism
32424	PK24.00	Anomalies of pituitary gland
8946	7N11000	[SO]Pituitary gland
2321	B7H2.11	Pituitary adenoma
28178	BBa0.00	[M]Craniopharyngioma
21279	C132.12	Sheehan's syndrome
5707	BB5y400	[M]Prolactinoma
38315	4486100	Pituitary function test abnormal
52426	C134000	Prolactin deficiency
16004	C134011	Hypoprolactinaemia
Unspecified adrenal insufficiency (Unknown type)		
12396	C154z00	Corticoadrenal insufficiency NOS
20786	C154z12	Adrenal insufficiency NEC
21539	C154000	Acute adrenal insufficiency
3113	C154.00	Corticoadrenal insufficiency
42873	C154012	Adrenal crisis
12227	C154600	Addisonian crisis
4042	C154011	Addisonian crisis

Suppl. Table 2.2: Product codes and product names for glucocorticoid usage

Product code	Product name
3418	Hydrocortisone 10mg tablets
4535	Hydrocortisone 20mg tablets
14076	Hydrocortisone 5mg/5ml Oral solution
15471	HYDROCORTISONE 25 MG TAB
17263	HYDROCORTISONE SODIUM PHOSPHATE 5 MG SOL
22894	HYDROCORTISONE 4 MG PAS
27720	HYDROCORTISONE
38022	Hydrocortisone 10mg/5ml oral suspension
38054	Hydrocortisone Tablet
51722	Hydrocortisone 5mg/5ml oral suspension
51824	Hydrocortisone 5mg/5ml oral suspension sugar free
51849	Hydrocortisone 1mg/5ml oral suspension
51871	Hydrocortisone 2mg capsules
51872	Hydrocortisone 2.5mg capsules
52053	Hydrocortisone 3mg/5ml oral suspension
53953	Hydrocortisone 5mg modified-release tablets
54794	Hydrocortisone 20mg modified-release tablets
57931	Hydrocortisone 20mg tablets (Teva UK Ltd)
63138	Hydrocortisone 5mg/5ml oral solution
64059	Hydrocortisone 2.5mg/5ml oral suspension
64787	Hydrocortisone 10mg tablets (Almus Pharmaceuticals Ltd)
65984	Hydrocortisone 10mg tablets (Actavis UK Ltd)
66327	Hydrocortisone 20mg tablets (Actavis UK Ltd)
66666	Hydrocortisone 10mg tablets (Teva UK Ltd)
53705	Cortisone acetate 5mg Capsule (Martindale Pharmaceuticals Ltd)
33639	CORTISONE ACETATE MSD 25 MG TAB
23788	CORTISONE ACETATE 2.5 MG TAB
36686	CORTISONE ACETATE MSD 5 MG TAB
10574	Cortisone acetate 5mg tablets
60421	Prednisolone 5mg tablets (Strides Shasun (UK) Ltd)
20670	PREDNISOLONE E/C
7584	PREDNISOLONE 4 MG TAB
13522	PREDNISOLONE 2 MG TAB
24716	PREDNISOLONE E/C
2390	PREDNISOLONE E/C 1 MG TAB
66914	Prednisolone 1mg gastro-resistant tablets
34660	Prednisolone 1mg tablets (Kent Pharmaceuticals Ltd)
41515	Prednisolone 5mg tablets (Teva UK Ltd)
32803	Prednisolone 5mg gastro-resistant tablets (Actavis UK Ltd)
34393	Prednisolone 5mg gastro-resistant tablets (Teva UK Ltd)

58987	Prednisolone 5mg gastro-resistant tablets (Phoenix Healthcare Distribution Ltd)
34631	Prednisolone 1mg Tablet (Co-Pharma Ltd)
34748	Prednisolone 1mg tablets (Teva UK Ltd)
63214	Prednisolone 5mg soluble tablets (Alliance Healthcare (Distribution) Ltd)
34914	Prednisolone 1mg Tablet (Celltech Pharma Europe Ltd)
34978	Prednisolone 1mg tablets (Wockhardt UK Ltd)
2368	Prednisolone 2.5mg tablet
578	Prednisolone 1mg tablets
28376	Prednisolone 2.5mg Gastro-resistant tablet (Biorex Laboratories Ltd)
34452	Prednisolone 1mg tablets (A A H Pharmaceuticals Ltd)
34781	Prednisolone 5mg tablets (Kent Pharmaceuticals Ltd)
44	Prednisolone 5mg gastro-resistant tablets
45302	Prednisolone 5mg Tablet (Biorex Laboratories Ltd)
31532	Prednisolone 5mg gastro-resistant tablets (A A H Pharmaceuticals Ltd)
61689	Prednisolone 5mg soluble tablets (A A H Pharmaceuticals Ltd)
61162	Prednisolone 5mg tablets (Waymade Healthcare Plc)
67107	Prednisolone 5mg gastro-resistant tablets (Alliance Pharmaceuticals Ltd)
47142	Prednisolone 5mg Soluble tablet (Amdipharm Plc)
21417	Prednisolone 5mg tablets (A A H Pharmaceuticals Ltd)
34404	Prednisolone 1mg tablets (Actavis UK Ltd)
19141	Prednisolone 5mg soluble tablets (AMCo)
55480	Prednisolone 2.5mg gastro-resistant tablets (Alliance Pharmaceuticals Ltd)
59912	Prednisolone 5mg gastro-resistant tablets (Waymade Healthcare Plc)
51753	Prednisolone 1mg tablets (Strides Shasun (UK) Ltd)
34109	Prednisolone 5 mg gastro-resistant tablet
66550	Prednisolone 5mg gastro-resistant tablets (Alliance Healthcare (Distribution) Ltd)
58384	Prednisolone 1mg tablets (Almus Pharmaceuticals Ltd)
33691	Prednisolone 5mg Gastro-resistant tablet (Biorex Laboratories Ltd)
56891	Prednisolone 1mg tablets (Waymade Healthcare Plc)
95	Prednisolone 5mg tablets
61132	Prednisolone 1mg tablets (Boston Healthcare Ltd)
33988	Prednisolone 5mg Tablet (Co-Pharma Ltd)
63066	Prednisolone 2.5mg tablets
28375	Prednisolone 2.5mg gastro-resistant tablets (A A H Pharmaceuticals Ltd)
32835	Prednisolone 5mg tablets (Wockhardt UK Ltd)
955	Prednisolone 5mg soluble tablets
34461	Prednisolone 2.5mg gastro-resistant tablets (Actavis UK Ltd)
557	Prednisolone 2.5mg gastro-resistant tablets
58000	Prednisolone 5mg tablets (Almus Pharmaceuticals Ltd)
58369	Prednisolone 5mg tablets (Boston Healthcare Ltd)
29333	Prednisolone 5mg tablets (Actavis UK Ltd)
33990	Prednisolone 5mg Tablet (IVAX Pharmaceuticals UK Ltd)
2044	PREDNISONE 2.5 MG TAB
44723	Prednisone 5mg modified-release tablets

44380	Prednisone 1mg modified-release tablets
43544	Prednisone 5mg Tablet (Knoll Ltd)
62656	Prednisone 5mg Tablet (Hillcross Pharmaceuticals Ltd)
46711	Prednisone 2mg modified-release tablets
3557	Prednisone 1mg tablets
2949	Prednisone 5mg tablets

Suppl. Table 2.3: Medical codes, Read codes, and Read terms used for diseases that were excluded from the study

Medical code	Read code	Read term (Clinical terminology)
65120	C150300	Ectopic ACTH secretion causing Cushing's syndrome
65754	C150500	Alcohol-induced pseudo-Cushing's syndrome
53682	C150200	Pituitary dependent Cushing's syndrome
60534	C150z00	Cushing's syndrome NOS
95807	Cyu4500	[X]Other Cushing's syndrome
17604	C150.00	Cushing's syndrome
18382	C150111	Drug-induced Cushings syndrome
60690	F395100	Myopathy due to Cushing's syndrome
20275	C150100	Iatrogenic Cushing's syndrome
4404	2226.11	O/E - cushingoid facies
70967	C150000	Idiopathic Cushing's syndrome
67628	C130.00	Gigantism and acromegaly
5316	C130200	Acromegaly
25850	C130100	Gigantism
18250	C152812	Congenital adrenal hyperplasia NEC
70360	C152912	Precocious puberty with adrenal hyperplasia
8550	B542000	Malignant neoplasm of pituitary gland
59718	B542z00	Malig neop pituitary gland or craniopharyngeal duct NOS
59823	B542.00	Malignant neoplasm pituitary gland and craniopharyngeal duct
45909	B8yy300	Carcinoma in situ of pituitary gland
36401	B587.00	Secondary malignant neoplasm of adrenal gland

Supplementary Material 2.4: The Study Protocol

as approved by the Independent Scientific Advisory Committee for MHRA Database Research (ISAC) on 27th July 2018

Protocol number 18_179

Applicants must complete all sections listed below

Sections which do not apply should be completed as '*Not Applicable*'

A. Study Title[§]

[§]*Please note: This information will be published on CPRD's website as part of its transparency policy*

A study of cardiovascular mortality and morbidity of patients with adrenal insufficiency.

B. Lay Summary (Max. 200 words)[§]

[§]*Please note: This information will be published on CPRD's website as part of its transparency policy*

Adrenal insufficiency occurs when there is hypothalamic-pituitary-adrenal dysfunction and the adrenal glands cannot produce sufficient glucocorticoids. This lack of glucocorticoids can be due to adrenal gland failure (primary adrenal insufficiency) or hypothalamic-pituitary failure (secondary adrenal insufficiency). Without steroid (glucocorticoid) replacement, adrenal insufficiency can lead to premature death. However, many observational studies have shown that, even with steroid therapy, adrenal insufficiency is associated with higher mortality than in the general population and there is evidence that cardiovascular mortality contributes to this.

Steroid overdose may be a factor in this heightened cardiovascular mortality. Over the past few decades, steroids have traditionally been prescribed at supra-physiological doses. In current care for adrenal insufficiency, lower steroid dosages and cardio-protective agents such as statins and antihypertensive medications are increasingly being used. All could help mitigate the cardiovascular event risk associated with treated adrenal insufficiency. The current cardiovascular mortality and morbidity among these patients may therefore be lower than observed under previous treatment regimens.

This observational study will examine the overall and cardiovascular morbidity and mortality of adrenal insufficiency patients. We hypothesise that the cardiovascular mortality and morbidity of these patients is now similar to that of the general population.

C. Technical Summary (Max. 200 words)[§]

[§]*Please note: This information will be published on CPRD's website as part of its transparency policy*

A retrospective cohort study is planned. The study population comprises patients diagnosed with Addison's disease, hypopituitarism, and/or adrenal insufficiency – as per the Clinical Practice Research Datalink record - between 1st January 1987 and 31st December 2017. Outcomes of interest are risks of cardiovascular mortality, all-cause mortality, cardiovascular morbidity (myocardial infarction, ischaemic heart disease, congestive heart failure, atrial fibrillation, cerebrovascular disease, and peripheral arterial diseases), and adrenal crisis, all of which will be derived from primary care code lists, Hospital Episode Statistics and Office for National Statistics mortality information. The primary aim is to compare the cardiovascular event rate in adrenal insufficiency patients with that in a background population.

A further aim is to compare the all-cause mortality rate in adrenal insufficiency patients with that in the general population and to describe other causes of deaths in adrenal insufficiency patients. The observed rate of cardiovascular events in adrenal insufficiency patients will be compared with the expected rate, as observed in the CPRD general population, with age and sex standardization, and derivation of the standardised incidence ratio (SIR). Factors associated with cardiovascular mortality and morbidity will be evaluated using a multivariate Cox regression model. The hazard ratio with 95% confidence interval will be adjusted by age of onset, sex, and period of follow-up.

D. Objectives, Specific Aims and Rationale

(i) Research Objectives

We will estimate risks of all-cause and cardiovascular mortality and morbidity (myocardial infarction, ischaemic heart disease, congestive heart failure, atrial fibrillation, cerebrovascular disease, and peripheral arterial diseases) among patients with primary and secondary adrenal insufficiency.

Applicants must complete all sections listed below

Sections which do not apply should be completed as '*Not Applicable*'

(ii) Specific Aims

(a) Primarily, to compare cardiovascular event rates between patients with adrenal insufficiency and the general population and secondarily:

(b) To compare all-cause mortality rates of patients with adrenal insufficiency with the general population.

(c) To describe the major causes of death among patients with adrenal insufficiency.

(d) To compare the prevalence of cardiovascular morbidity (myocardial infarction, ischaemic heart disease, congestive heart failure, atrial fibrillation, cerebrovascular disease, and peripheral arterial diseases) in adrenal insufficiency patients with rates in the general population.

(iii) Rationale

Recent cardiovascular morbidity and mortality rates among adrenal insufficiency patients in the UK have not been described. We hypothesise that, due to changes in clinical practice such as reductions in steroid replacement dose and use of cardio-protective agents, cardiovascular mortality and morbidity should no longer be elevated compared with the general population.

E. Study Background

Glucocorticoids play a major role in maintaining normal blood glucose levels and normal hemodynamics (3, 4). These actions are essential for life and a higher level of glucocorticoids is needed during acute stress. Adrenal insufficiency is the state in which the adrenal cortex is unable to produce sufficient glucocorticoids. This defect can originate in the adrenal glands (primary adrenal failure, PAF) or in the hypothalamus or pituitary gland (secondary hypothalamic-pituitary-adrenal axis failure, SAF). PAF patients often have severe glucocorticoid deficiency while some SAF patients may have a milder defect, only obvious under stress. These two entities of adrenal insufficiency have unique characteristics. Apart from glucocorticoid deficiency, PAF patients may lack mineralocorticoids which are important for salt-water and blood-pressure control (3, 15). SAF can, however, be accompanied by other pituitary hormone deficiencies such as growth hormone, gonadotropins, thyrotropin, or vasopressin and in these cases, SAF can be classified as hypopituitarism (3, 21).

Before synthetic glucocorticoid was available, most adrenal insufficiency patients died within two years of diagnosis (72) and, after glucocorticoid became widely available, their survival rate was expected to be normal (72). However, many subsequent population-based studies have demonstrated that, despite glucocorticoid therapy, patients' life expectancy remained significantly reduced (73, 74, 158, 159). The overall mortality of hypopituitarism patients compared with the age and sex-matched general population or the standardised mortality ratio (SMR) has been reported between 0.88 and 3.80 (49, 76-81, 87, 89, 90). Studies of PAF patients have established SMRs of 1.15 to 2.70 (19, 74).

There are a number of factors associated with increased mortality in hypopituitarism patients. Female patients or those with younger age of onset have higher SMRs (76-81, 87, 89, 90). Patients with craniopharyngioma have the highest SMR compared with other diagnoses (78, 80, 89). Therapeutic methods for pituitary disorders could also affect the mortality. Craniotomy or multiple surgeries or cranial irradiation are associated with increased SMRs compared with trans-sphenoidal surgery (78, 80, 81, 90). Concomitant hormonal deficiencies and their treatments could be associated with increased mortality. Untreated hypogonadism is associated with higher SMRs than eugonadism or treated hypogonadism (48, 77, 78) especially in women (87). Some studies, however, found that hypogonadism was not associated with increased SMRs (76, 81). Growth hormone deficiency without replacement therapy could also be associated with decreased survival (48, 79-81, 89). Nevertheless, Lindholm et al. reported that growth hormone treatment did not affect the mortality rate in suprasellar pituitary adenoma patients (87). Treating hypothyroidism with less than 100 microgram daily dose of levothyroxine was found to increase mortality compared with higher doses in a tertiary care-based study (48). Additionally, hypopituitarism patients with diabetes insipidus have higher SMRs compared with those without (78, 80, 81, 90).

The mortality rates of PAF are similar between sexes (19, 73, 74). The SMRs are increased in younger-onset PAF patients (19, 74). Ericson et al. found the SMR significantly raised in male patients aged under 40 years compared with age-matched females (19). The mortality rates of PAF patients also significantly increase when coexisting with type-1 autoimmune polyglandular syndrome (74). Concomitant diabetes could affect the mortality rate in PAF patients (73).

Chronic excess glucocorticoid use may contribute to the increased mortality of adrenal insufficiency patients. Over-dosaging has traditionally been practised and this can increase insulin resistance, glucose intolerance, hypertension, and dyslipidaemia. All are associated with cardiovascular morbidity and mortality. Hydrocortisone at more than 25 mg per day dose was first reported to increase mortality in acromegaly

patients (45). Later studies of patients with non-functioning pituitary adenoma demonstrated that patients commencing hydrocortisone at a dose of over than 30 mg per day have significantly increased mortality compared with those using lower doses (46, 48). Recently, Hammarstrand et al. found that even a hydrocortisone dose of more than 20 mg per day could still be associated with the increased mortality of pituitary adenoma patients (49). There are no clinical data for PAF patients to support an effect of excess steroid doses on mortality but it would theoretically resemble SAF.

With increasing reports of increased mortality in patients commencing excess steroid, there is now a tendency to prescribe lower steroid doses in current adrenal insufficiency care. Cardio-protective agents such as statins and antihypertensive drugs are also increasingly prescribed. Cardiovascular morbidity and mortality in adrenal insufficiency patients are therefore presumed to be approximately normal. In a Swedish cohort, there was a decreased SMR in female patients with non-functioning pituitary adenoma who were diagnosed during 2007-2011 compared with those diagnosed before 2006 (93). However, data on the prevalence and treatment of pituitary hormone deficiencies that could contribute to the change in mortality was unavailable in that study (93).

Apart from receiving an appropriate steroid replacement dose, it is important that patients should be informed to increase their daily steroid doses during stress. Failure to adjust steroid doses appropriately or change to an injection form of glucocorticoids when faced with intercurrent illness can lead to adrenal crisis and unexpected deaths (102). Adrenal crisis was one of the major causes of death in a population-based study in PAF patients (19). The prevalence of adrenal crisis was also believed to be underestimated in the reports of infection-related deaths of PAF and SAF patients (19, 81). In order to prevent an adrenal crisis, patient education on steroid adjustment is essential for treating adrenal insufficiency patients.

This study aims to investigate cardiovascular mortality and morbidity in adrenal insufficiency patients and to establish causes of death including adrenal crisis. To the best of our knowledge, this is the first study using CPRD datalink to attain mortality and morbidity data of patients with adrenal insufficiency.

F. Study Type

This study is primarily a descriptive study as it aims to focus mainly on identifying patterns or trends in cardiovascular mortality and morbidity occurrence over time.

G. Study Design

The study design is a retrospective cohort. Participants are patients diagnosed with adrenal insufficiency. All participants will be followed-up from the 1st January 1987 or the date of first mention of adrenal insufficiency to the death date or the earliest date of transfer out or last collection date or the 31st December 2017. The occurrence of death and cardiovascular diseases, as well as their associated factors, will be examined.

H. Feasibility counts

The CPRD data has been accessed to estimate the number of participants for this study. To attain an appropriate study population, medical codes of diagnoses of adrenal insufficiency, pituitary disorders, Addison's disease, and adrenal crisis, as well as pituitary function test abnormalities, are used as inclusion criteria (see medical code list in Annex 1). All included participants must have received oral forms of any of hydrocortisone or cortisone acetate or prednisolone or prednisone (see product code list in Annex 2). Patients who have been, at any time, diagnosed with Cushing syndrome or Acromegaly or Gigantism or Congenital adrenal hyperplasia are excluded from the study (see medical code list for exclusion criteria in Annex 3). Our assessment of study feasibility has identified 8,043 eligible participants in the CPRD between the 1st January 1987 and 31st December 2017.

I. Sample size considerations

According to previous studies, the cardiovascular disease standardised mortality ratios (SMRs) of patients with adrenal insufficiency have been estimated to be between 0.83 and 3.39 (19, 73, 77, 78, 80, 81, 89, 90). Our study hypothesis is that, due to lower glucocorticoid replacement doses and cardiovascular protective agents having been increasingly prescribed to adrenal insufficiency patients in recent years, the cardiovascular mortality and morbidity risk of adrenal insufficiency patients should not differ from that of the general population. We consider a standardised incidence ratio (SIR) of cardiovascular morbidity and mortality of less than 1.14 will represent a clinically important reduction in risk relative to earlier published estimates. We would, therefore, expect to be able to demonstrate as significant at $p<0.05$ and with 80% power, a ratio of 1.14 or more.

Applicants must complete all sections listed below

Sections which do not apply should be completed as '*Not Applicable*'

From cardiovascular disease statistics published by the British Heart Foundation, the prevalence of cardiovascular morbidities in 2011 for men and women in England of age range of 45-64 years is currently 14.6% and 8.4%, respectively (155). Therefore, the cardiovascular prevalence for both genders is 11.5% with a fractional prevalence of 0.1150. Given a SIR of 1.14, the risk will increase to a fractional prevalence of cardiovascular diseases of 0.1311. To demonstrate the difference between these two fractional prevalences of cardiovascular disease as significant at $p<0.05$ and 80% power, 3,657 adrenal insufficiency patients would need to be compared with 36,570 age and gender-equivalent controls. These numbers are well within the numbers identified in our feasibility assessment.

We understand that approximately 70% of CPRD GP practices based in England have currently contributed to the linkage scheme. Study patients who have the HES/ONS data will therefore be approximately 4,458 or 55% of total eligible CPRD patients. This number is, nevertheless, still sufficient for testing our primary hypothesis with adequate power.

J. Data Linkage Required (if applicable):§

§*Please note that the data linkage/s requested in research protocols will be published by the CPRD as part of its transparency policy*

The ONS Death Registration data are required to provide the specific causes of death and the date of death (144). Data from HES Admitted Patient Care are also required to identify non-fatal cardiovascular events and adrenal crises during hospital admissions. These events might be under-recorded in the CPRD GOLD since definite diagnoses were made in secondary care settings. A cohort study in England has indicated that 17% of non-fatal myocardial infarction patients who were not recorded in the CPRD could be identified in the HES (147). A study to validate CPRD diagnostic accuracy has shown that a positive predictive value for the diagnosis of Stevens-Johnson syndrome/ Toxic epidermal necrolysis was 0.79 (95%CI, 0.71-0.86), compared with hospital referral records (162). The HES/ONS data linkage can therefore improve diagnostic validation.

K. Study population

All patients at age below 100 years with any diagnoses of adrenal insufficiency, pituitary disorders, Addison's disease, and adrenal crisis, as well as those with pituitary hormone deficiency, who have had their data entered on the CPRD between the 1st January 1987 and 31st December 2017, are eligible (see Medical code list in Annex 1).

For the above populations, the following additional inclusion criteria will be applied:

- Having been prescribed oral forms of any of hydrocortisone, cortisone acetate, prednisolone, or prednisone (see Product code list in Annex 2) within 3 months after the first mention of adrenal insufficiency or pituitary disorders or pituitary hormone deficiency or Addison's disease or adrenal crisis.
- A minimum follow-up period for this study cohort of 1 month.

For each of the above populations, the following exclusion criteria will be applied:

- Being diagnosed, at any time, with Cushing syndrome or Acromegaly or Gigantism or Congenital adrenal hyperplasia (see Medical code list in Annex 3)
- Being diagnosed, at any time, with malignant neoplasm of the pituitary gland or adrenal glands (see Medical code list in Annex 3)

The cohort entry date (the index date) for each participant is the date-of-first-diagnosis of adrenal insufficiency or the 1st January 1987 for those diagnosed earlier. Baseline data will be obtained on the index date when all inclusion and exclusion criteria are fulfilled. The end of follow-up date is the date of death or the earliest date of transfer out or last collection date or the 31st December 2017. A primary outcome is the first occurrence of cardiovascular mortality and morbidity during the study period.

L. Selection of comparison group(s) or controls

Patients in the CPRD who have not met inclusion criteria for the adrenal insufficiency study population represent a suitable control population. Control patients from the CPRD population will be randomly sampled in a ratio of 10:1 according to gender and the strata of 10-year ranges for the year of birth of the study population. There would be 80,480 age, gender, and practice- matched patients eligible for controls. The date of first entry in our study for the controls (the control index date) will also be matched with the index date of their corresponding study patients. Baseline data of the controls will be obtained on the control index date.

M. Exposures, Health Outcomes§ and Covariates

Applicants must complete all sections listed below

Sections which do not apply should be completed as '*Not Applicable*'

§*Please note: Summary information on health outcomes (as included on the ISAC application form above)will be published on CPRD's website as part of its transparency policy*

Exposures

The exposure of interest is record of a Read code for adrenal insufficiency, as listed in Annex 1, and documented in the patient clinical or referral record.

Health outcomes

The outcome of interest is cardiovascular event, which can include: ischaemic heart disease, myocardial infarction, angina, coronary artery intervention, congestive cardiac failure, atrial fibrillation, ischaemic stroke, non-traumatic intracerebral haemorrhage, and peripheral arterial diseases (see ICD10 and ICD9 code list in Annex 4 and Annex 5). These circulatory system codes are based on all cardiovascular diseases codes published by the British Heart Foundation (26) and a code of diseases from the central nervous system for transient cerebral ischaemic attack. Cardiovascular events will be obtained from the CPRD GOLD and the linkage system (HES and ONS). Secondary outcomes are all-cause mortality and other causes of death.

Covariates

Potential confounding factors and effect modifiers of the prevalence of cardiovascular diseases and cardiovascular-related deaths are demonstrated in table 1.

Table 1: Risk factors of the cardiovascular events

Risk factor	**Definition**	
Current age	-	
Duration of follow-up	Period of follow-up in the study cohort.	
Gender	-	
Body mass index	see Read code list for body mass index in Annex 6	
Smoking status	see Read code list for smoking status in Annex 7	
Diagnosis of diabetes at baseline	Participants were diagnosed as diabetes before or at the index date. (see a Read code list in Annex 8)	
Diagnosis of hypertension at baseline	Participants were diagnosed as hypertension before or at the index date. (see a Read code list in Annex 9)	
Diagnosis of dyslipidaemia at baseline	Participants were received any lipid-lowering drugs before or at the index date. (see a Product code list in Annex 10)	
Previous cardiovascular diseases	Participants were diagnosed as cardiovascular diseases before or at the index date. (see a Read code list in Annex 11)	
Statin use	Participants were received statins at any time during the study period. (see a Product code list in Annex 12)	
Anti-hypertensive agent use	Participants were received anti-hypertensive agents at any time during the study period. (see a Product code list in Annex 13)	

Applicants must complete all sections listed below

Sections which do not apply should be completed as '*Not Applicable*'

According to previous studies, various factors relating to adrenal insufficiency presentation and treatment could modify the increased mortality risk in adrenal insufficiency and/or hypopituitarism patients. These factors are listed as covariates in table 2.

Table 2: Covariates that may affect overall mortality in study patients

Risk factor	Reference	Availability in the CPRD data	
Age at diagnosis	(19, 74, 76-78, 80, 81, 89, 90)	Complete	
Gender	(19, 76-81, 87, 89, 90, 94, 158, 159)	Complete	
Causes of adrenal insufficiency/ hypopituitarism: craniopharyngioma, autoimmune polyglandular syndrome	(74, 78, 80, 89)	Fair, data from HES are required to increase accuracy of diagnosis.	
Diabetes as a comorbidity	(73)	Complete	
Using anti-hypertensive agent	(80)	Complete	
Type of pituitary surgery: Trans-sphenoidal surgery, Craniotomy	(78, 80, 81)	Good, data from HES are required to increase accuracy of diagnosis.	
Cranial irradiation	(78, 80, 89, 90)	Good, data from HES are required to increase accuracy of diagnosis.	
Untreated hypogonadism	(48, 76, 78, 87)	Fair, data from clinical, test, and therapy files	
Untreated growth hormone deficiency	(78-81, 89, 158)	Fair, data from clinical, test, and therapy files	
Inappropriate dose of thyroid replacement therapy	(48)	Good, data from clinical, test, and therapy files	
Concomitant diabetes insipidus	(78, 80, 81, 90)	Good, data from clinical, test, and therapy files	

N. Data/ Statistical Analysis

Primary outcome

Our primary outcome is the standardised incidence ratio (SIR) of cardiovascular events and deaths from cardiovascular diseases. The SIR with 95% confidence interval (95% CI) will be estimated by comparing the observed number of cardiovascular events and cardiovascular-related deaths of adrenal insufficiency patients (the study population) with the expected number of these events in our age, gender, practice, and the index date-matched control population sample.

Secondary outcomes

We aim to compare the overall mortality rate of the study population with that of the control population. The outcome will be demonstrated as the standardised mortality ratio (SMR) with 95% CI. The prevalence of other specified causes of death and adrenal crisis will be described. Cardiovascular morbidity will also be compared between the study and control populations.

A number of factors may influence cardiovascular disease risk (Table 1) and may differ between study and control populations. These potential confounders of cardiovascular mortality and morbidity will be addressed in multivariable Cox proportional hazards regression models.

Applicants must complete all sections listed below

Sections which do not apply should be completed as '*Not Applicable*'

O. Plan for addressing confounding

Matching of cases and controls will be according to age-range, gender, practice, and the index date. In addition, these and other potential confounding covariates that can affect the difference in cardiovascular risks will also be included in the adjusted model (see table 1 in section M. for details of confounding factors).

P. Plans for addressing missing data

At this stage, we are adjusting age and gender to obtain the standardised incidence ratio for cardiovascular diseases. Age, gender, and cardiovascular disease incidence are well recorded in the CPRD and its linkage. There is no a priori reason to suspect that recording would be different between study patients and controls.

Q. Patient or user group involvement (if applicable)

No patient or user group are involved in this study.

R. Plans for disseminating and communicating study results, including the presence or absence of any restrictions on the extent and timing of publication

This study will be presented at institutional meetings as well as national/international scientific conferences. Study results will be disseminated and published in medical journals. These publications will follow the principles outlined in the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) and any other relevant guidelines in the Enhancing the Quality and Transparency of health research (EQUATOR) network.

S. Limitations of the study design, data sources, and analytic methods

Adrenal insufficiency is relatively rare and requires special investigations as well as experienced interpretation for diagnosis. The diagnosis, based on laboratory results at the time of diagnosis, has usually been established in hospital settings. Diagnostic data may not be available in primary care data sources. The number of adrenal insufficiency patients could therefore be underestimated when using this data source. We then use the code diagnoses of pituitary disorders and pituitary hormone deficiency to include participants who probably have had secondary adrenal insufficiency. However, not all patients with these disorders may have had adrenal insufficiency. More specifically, some patients may have a pituitary disorder while preserving hypothalamic-pituitary-adrenal axis function. To minimise this misclassification, we have added an inclusion criterion of receiving glucocorticoids as hormonal replacement therapy. These medications must be prescribed simultaneously with the first mention of the above diagnoses.

Some patients with a Read code for adrenal insufficiency may have adrenal insufficiency following prolonged using of exogenous steroid taken for other reasons. However, these patients are not a population of interest in our study. To minimise this misclassification, we will exclude patients who have taken glucocorticoids at higher doses than the usual dose for treating adrenal insufficiency patients.

Further limitations relate to the differentiation and categorisation of the data available, for example cigarette smoking may only be recorded as 'current smoker' or 'ex-smoker' or 'non-smoker' with no discrimination of numbers of cigarettes smoked per day.

T. References

List of Appendices *(Submit all appendices as separate documents to this application)*

A list of Appendices is demonstrated in the attached file.

Suppl. Table 2.5: Medical codes, Read codes, and Read terms for cardiovascular events

Medical code	Read code	Read term (Clinical terminology)
504	G65..00	Transient cerebral ischaemia
569	G64..12	Infarction - cerebral
1298	G66..11	CVA unspecified
1433	G65..12	Transient ischaemic attack
1469	G66..00	Stroke and cerebrovascular accident unspecified
1895	G65z.00	Transient cerebral ischaemia NOS
3149	G64z.00	Cerebral infarction NOS
4152	G631.12	Thrombosis, carotid artery
4240	G631.00	Carotid artery occlusion
5185	G64z111	Lateral medullary syndrome
5363	G64..11	CVA - cerebral artery occlusion
5602	G64z.12	Cerebellar infarction
5871	14A7.12	H/O: stroke
6116	G66..13	CVA - Cerebrovascular accident unspecified
6155	G64..13	Stroke due to cerebral arterial occlusion
6228	G68X.00	Sequelae of stroke,not specfd as h'morrhage or infarction
6253	G66..12	Stroke unspecified
6305	14A7.11	H/O: CVA
7138	ZV12512	[V]Personal history of cerebrovascular accident (CVA)
7780	G667.00	Left sided CVA
8443	G663.00	Brain stem stroke syndrome
8837	G64..00	Cerebral arterial occlusion
9985	G64z200	Left sided cerebral infarction
10504	G64z300	Right sided cerebral infarction
12833	G668.00	Right sided CVA
13567	14AB.00	H/O: TIA
15252	G64z.11	Brainstem infarction NOS
15788	G65zz00	Transient cerebral ischaemia NOS
16517	G640.00	Cerebral thrombosis
17322	G664.00	Cerebellar stroke syndrome
18689	G660.00	Middle cerebral artery syndrome
19260	G662.00	Posterior cerebral artery syndrome
19280	G661.00	Anterior cerebral artery syndrome
19348	ZV12511	[V]Personal history of stroke
19354	G65y.00	Other transient cerebral ischaemia
23671	G63y000	Cerebral infarct due to thrombosis of precerebral arteries
25615	G64z000	Brainstem infarction
26424	G64z400	Infarction of basal ganglia
32447	G630.00	Basilar artery occlusion
33499	G665.00	Pure motor lacunar syndrome
33543	G6X..00	Cerebrl infarctn due/unspcf occlusn or sten/cerebrl artrs
34135	14A7.00	H/O: CVA/stroke

36717	G640000	Cerebral infarction due to thrombosis of cerebral arteries
39344	G676000	Cereb infarct due cerebral venous thrombosis, nonpyogenic
39403	G683.00	Sequelae of cerebral infarction
40758	G6W..00	Cereb infarct due unsp occlus/stenos precerebr arteries
40847	G632.00	Vertebral artery occlusion
44765	G653.00	Carotid artery syndrome hemispheric
45781	G63..00	Precerebral arterial occlusion
47642	G64z100	Wallenberg syndrome
50594	G654.00	Multiple and bilateral precerebral artery syndromes
51326	G63y.00	Other precerebral artery occlusion
51759	G677000	Occlusion and stenosis of middle cerebral artery
51767	G666.00	Pure sensory lacunar syndrome
53745	Gyu6400	[X]Other cerebral infarction
55351	7P24200	Delivery of rehabilitation for stroke
57495	G63..11	Infarction - precerebral
57527	G677100	Occlusion and stenosis of anterior cerebral artery
63746	Fyu5500	[X]Other transnt cerebral ischaemic attacks+related syndroms
65770	G677200	Occlusion and stenosis of posterior cerebral artery
66873	14AK.00	H/O: Stroke in last year
71585	G63z.00	Precerebral artery occlusion NOS
90572	Gyu6500	[X]Occlusion and stenosis of other precerebral arteries
91627	Gyu6300	[X]Cerebrl infarctn due/unspcf occlusn or sten/cerebrl artrs
92036	Gyu6600	[X]Occlusion and stenosis of other cerebral arteries
94482	Gyu6G00	[X]Cereb infarct due unsp occlus/stenos precerebr arteries
98642	G633.00	Multiple and bilateral precerebral arterial occlusion
101251	ZV12D00	[V]Personal history of transient ischaemic attack
105202	14AB000	H/O amaurosis fugax
105520	8Hd6.00	Admission to stroke unit
105738	G657.00	Carotid territory transient ischaemic attack
241	G30..00	Acute myocardial infarction
1204	G30..14	Heart attack
1431	G311.13	Unstable angina
1677	G30..15	MI - acute myocardial infarction
1678	G308.00	Inferior myocardial infarction NOS
2155	G341000	Ventricular cardiac aneurysm
2491	G30..12	Coronary thrombosis
3704	G307.00	Acute subendocardial infarction
4017	G32..00	Old myocardial infarction
5387	G301.00	Other specified anterior myocardial infarction
6331	G341.00	Aneurysm of heart
7320	G343.00	Ischaemic cardiomyopathy
7347	G311100	Unstable angina
8935	G302.00	Acute inferolateral infarction
9276	G31y000	Acute coronary insufficiency

9413	G31y.00	Other acute and subacute ischaemic heart disease
9507	G307000	Acute non-Q wave infarction
9555	G33z500	Post infarct angina
10562	G307100	Acute non-ST segment elevation myocardial infarction
11983	G311500	Acute coronary syndrome
12139	G300.00	Acute anterolateral infarction
12229	G30X000	Acute ST segment elevation myocardial infarction
13566	G30..11	Attack - heart
14658	G30z.00	Acute myocardial infarction NOS
14897	G301z00	Anterior myocardial infarction NOS
14898	G305.00	Lateral myocardial infarction NOS
16408	G32..11	Healed myocardial infarction
17307	G311200	Angina at rest
17464	G32..12	Personal history of myocardial infarction
17689	G30..17	Silent myocardial infarction
17872	G301100	Acute anteroseptal infarction
18118	G311400	Worsening angina
18842	G35..00	Subsequent myocardial infarction
19655	G311.14	Angina at rest
23579	G310.00	Postmyocardial infarction syndrome
23708	G361.00	Atrial septal defect/curr comp folow acut myocardal infarct
23892	G304.00	Posterior myocardial infarction NOS
24126	G360.00	Haemopericardium/current comp folow acut myocard infarct
27484	G341.11	Cardiac aneurysm
28736	G30y000	Acute atrial infarction
29300	662K300	Angina control - worsening
29421	G344.00	Silent myocardial ischaemia
29553	G366.00	Thrombosis atrium,auric append&vent/curr comp foll acute MI
29643	G303.00	Acute inferoposterior infarction
29758	G30X.00	Acute transmural myocardial infarction of unspecif site
30330	G309.00	Acute Q-wave infarct
30421	G30..13	Cardiac rupture following myocardial infarction (MI)
32272	G38..00	Postoperative myocardial infarction
32854	G30B.00	Acute posterolateral myocardial infarction
33650	7929100	Percut transluminal coronary thrombolysis with streptokinase
34803	G30y.00	Other acute myocardial infarction
36423	G36..00	Certain current complication follow acute myocardial infarct
36523	G311.00	Preinfarction syndrome
37657	G362.00	Ventric septal defect/curr comp fol acut myocardal infarctn
38609	G351.00	Subsequent myocardial infarction of inferior wall
40399	14A4.00	H/O: myocardial infarct >60
40429	G301000	Acute anteroapical infarction
40996	7929111	Percut translum coronary thrombolytic therapy- streptokinase
41221	G30y200	Acute septal infarction

41677	G341z00	Aneurysm of heart NOS
41835	G384.00	Postoperative subendocardial myocardial infarction
46017	G30yz00	Other acute myocardial infarction NOS
46112	G380.00	Postoperative transmural myocardial infarction anterior wall
46166	G35X.00	Subsequent myocardial infarction of unspecified site
46276	G381.00	Postoperative transmural myocardial infarction inferior wall
50372	14AH.00	H/O: Myocardial infarction in last year
54251	G311z00	Preinfarction syndrome NOS
59189	G363.00	Ruptur cardiac wall w'out haemopericard/cur comp fol ac MI
59940	G364.00	Ruptur chordae tendinae/curr comp fol acute myocard infarct
62626	G30y100	Acute papillary muscle infarction
63467	G306.00	True posterior myocardial infarction
67087	G341100	Other cardiac wall aneurysm
68357	G31y100	Microinfarction of heart
68748	G38z.00	Postoperative myocardial infarction, unspecified
69474	G365.00	Rupture papillary muscle/curr comp fol acute myocard infarct
72562	G353.00	Subsequent myocardial infarction of other sites
96838	Gyu3400	[X]Acute transmural myocardial infarction of unspecif site
99991	Gyu3600	[X]Subsequent myocardial infarction of unspecified site
100139	14AT.00	History of myocardial infarction
105216	14AW.00	H/O acute coronary syndrome
105250	G341111	Mural cardiac aneurysm
106812	G383.00	Postoperative transmural myocardial infarction unspec site
107406	7.92E+02	Emergency percutaneous coronary intervention
2156	G631.11	Stenosis, carotid artery
2652	G634.00	Carotid artery stenosis
2654	7A20400	Endarterectomy of carotid artery NEC
5904	792..00	Coronary artery operations
10603	792z.00	Coronary artery operations NOS
12733	7A20311	Carotid endarterectomy and patch
29973	7A22000	Percutaneous transluminal angioplasty of carotid artery
31704	G677.00	Occlusion/stenosis cerebral arts not result cerebral infarct
47580	7A22300	Percutaneous transluminal insertion stent carotid artery
55074	7A28200	Percutaneous transluminal angioplasty of vertebral artery
63830	G63..12	Stenosis of precerebral arteries
68069	7A22200	Endovascular repair of carotid artery
240	G3...00	Ischaemic heart disease
732	7928z00	Transluminal balloon angioplasty of coronary artery NOS
1344	G340.12	Coronary artery disease
1414	G33z300	Angina on effort
1430	G33..00	Angina pectoris
1655	G340.11	Triple vessel disease of the heart
1676	G3z..00	Ischaemic heart disease NOS
1792	G3...13	IHD - Ischaemic heart disease

2901	7928	Transluminal balloon angioplasty of coronary artery
3159	792Dy00	Other specified other bypass of coronary artery
3999	G340000	Single coronary vessel disease
4656	G311.11	Crescendo angina
5254	G340100	Double coronary vessel disease
5413	G340.00	Coronary atherosclerosis
5703	7928.11	Percutaneous balloon coronary angioplasty
5744	7927500	Open angioplasty of coronary artery
6182	7929y00	Other therapeutic transluminal op on coronary artery OS
6336	14A5.00	H/O: angina pectoris
7134	7921.11	Other autograft bypass of coronary artery
7137	7920y00	Saphenous vein graft replacement of coronary artery OS
7442	7920200	Saphenous vein graft replacement of three coronary arteries
7609	7921z00	Other autograft replacement of coronary artery NOS
7634	7920100	Saphenous vein graft replacement of two coronary arteries
8312	7920.11	Saphenous vein graft bypass of coronary artery
8679	7920000	Saphenous vein graft replacement of one coronary artery
8942	7929400	Insertion of coronary artery stent
9414	7921	Other autograft replacement of coronary artery
10209	7921200	Autograft replacement of three coronary arteries NEC
11610	7920300	Saphenous vein graft replacement of four+ coronary arteries
12804	G33z700	Stable angina
13185	662K.00	Angina control
13571	G30..16	Thrombosis - coronary
14782	662K200	Angina control - improving
15349	662Kz00	Angina control NOS
15373	662K100	Angina control - poor
15754	G34z.00	Other chronic ischaemic heart disease NOS
18249	7920	Saphenous vein graft replacement of coronary artery
18670	7928000	Percut transluminal balloon angioplasty one coronary artery
18889	G34z000	Asymptomatic coronary heart disease
19046	7929300	Rotary blade coronary angioplasty
19164	7927100	Repair of aneurysm of coronary artery
19193	7923z00	Prosthetic replacement of coronary artery NOS
19402	7923	Prosthetic replacement of coronary artery
19413	7921100	Autograft replacement of two coronary arteries NEC
19542	662K000	Angina control - good
20416	G3...12	Atherosclerotic heart disease
21844	G31y300	Transient myocardial ischaemia
22020	792B000	Endarterectomy of coronary artery NEC
22383	G3y..00	Other specified ischaemic heart disease
22647	7925311	LIMA single anastomosis
22828	7929000	Percutaneous transluminal laser coronary angioplasty
23078	G34y100	Chronic myocardial ischaemia

24540	G34y000	Chronic coronary insufficiency
24783	G3...11	Arteriosclerotic heart disease
24888	7929	Other therapeutic transluminal operations on coronary artery
25842	G33z.00	Angina pectoris NOS
26863	G33z600	New onset angina
27951	G31..00	Other acute and subacute ischaemic heart disease
27977	G31yz00	Other acute and subacute ischaemic heart disease NOS
28138	G34..00	Other chronic ischaemic heart disease
28554	G33zz00	Angina pectoris NOS
28837	7925.11	Creation of bypass from mammary artery to coronary artery
30963	1J61.00	Suspected ischaemic heart disease
31519	7925100	Double implant of mammary arteries into coronary arteries
31540	7924200	Revision of bypass for three coronary arteries
31556	7922	Allograft replacement of coronary artery
31571	792y.00	Other specified operations on coronary artery
31679	7929z00	Other therapeutic transluminal op on coronary artery NOS
32651	7922.11	Allograft bypass of coronary artery
33461	7924	Revision of bypass for coronary artery
33471	792Dz00	Other bypass of coronary artery NOS
33620	792B.00	Repair of coronary artery NEC
33718	7925000	Double anastomosis of mammary arteries to coronary arteries
33735	7928100	Percut translum balloon angioplasty mult coronary arteries
34328	G311300	Refractory angina
34633	G34y.00	Other specified chronic ischaemic heart disease
34963	792D.00	Other bypass of coronary artery
34965	792A.00	Diagnostic transluminal operations on coronary artery
35713	G34yz00	Other specified chronic ischaemic heart disease NOS
36011	7923.11	Prosthetic bypass of coronary artery
36609	G342.00	Atherosclerotic cardiovascular disease
37682	7925	Connection of mammary artery to coronary artery
37719	7925y00	Connection of mammary artery to coronary artery OS
39449	G312.00	Coronary thrombosis not resulting in myocardial infarction
39546	Gyu3000	[X]Other forms of angina pectoris
39693	G31y200	Subendocardial ischaemia
41547	7928y00	Transluminal balloon angioplasty of coronary artery OS
41757	7927z00	Other open operation on coronary artery NOS
42304	7929500	Insertion of drug-eluting coronary artery stent
42462	7928200	Percut translum balloon angioplasty bypass graft coronary a
42708	7921300	Autograft replacement of four of more coronary arteries NEC
43939	793G.00	Perc translumin balloon angioplasty stenting coronary artery
44561	7921000	Autograft replacement of one coronary artery NEC
44585	792Bz00	Repair of coronary artery NOS
44723	7925200	Single anast mammary art to left ant descend coronary art
45370	7922300	Allograft replacement of four or more coronary arteries

45476	14AL.00	H/O: Treatment for ischaemic heart disease
45809	G350.00	Subsequent myocardial infarction of anterior wall
45886	7922200	Allograft replacement of three coronary arteries
45960	8B27.00	Antianginal therapy
47637	Gyu3300	[X]Other forms of chronic ischaemic heart disease
47788	7927	Other open operations on coronary artery
48767	7922z00	Allograft replacement of coronary artery NOS
48822	7925011	LIMA sequential anastomosis
51507	7925300	Single anastomosis of mammary artery to coronary artery NEC
51515	7920z00	Saphenous vein graft replacement coronary artery NOS
52517	Gyu3.00	[X]Ischaemic heart diseases
52938	7924000	Revision of bypass for one coronary artery
54535	G33z100	Stenocardia
55092	792C000	Replacement of coronary arteries using multiple methods
55598	792C.00	Other replacement of coronary artery
56905	792Ay00	Diagnostic transluminal operation on coronary artery OS
56990	7925z00	Connection of mammary artery to coronary artery NOS
57062	14AJ.00	H/O: Angina in last year
57241	7922100	Allograft replacement of two coronary arteries
57634	7924z00	Revision of bypass for coronary artery NOS
59193	G341200	Aneurysm of coronary vessels
59423	7922y00	Other specified allograft replacement of coronary artery
60067	793G000	Perc translum ball angio insert 1-2 drug elut stents cor art
60753	7926300	Single implantation thoracic artery into coronary artery NEC
61208	793Gz00	Perc translum balloon angioplasty stenting coronary art NOS
61248	792Az00	Diagnostic transluminal operation on coronary artery NOS
61310	7921y00	Other autograft replacement of coronary artery OS
62608	7926000	Double anastom thoracic arteries to coronary arteries NEC
66236	7923200	Prosthetic replacement of three coronary arteries
66388	G33z000	Status anginosus
66583	7929200	Percut translum inject therap subst to coronary artery NEC
66664	7923100	Prosthetic replacement of two coronary arteries
67554	7924100	Revision of bypass for two coronary arteries
67591	7926200	Single anastomosis of thoracic artery to coronary artery NEC
67761	7923300	Prosthetic replacement of four or more coronary arteries
68123	7925312	RIMA single anastomosis
68139	7925400	Single implantation of mammary artery into coronary artery
68401	Gyu3200	[X]Other forms of acute ischaemic heart disease
69247	792By00	Other specified repair of coronary artery
70111	7922000	Allograft replacement of one coronary artery
70755	792Cz00	Replacement of coronary artery NOS
72780	7926z00	Connection of other thoracic artery to coronary artery NOS
85947	793G200	Perc translum balloon angioplasty insert 1-2 stents cor art
86071	7928300	Percut translum cutting balloon angioplasty coronary artery

87849	793G100	Perc tran ball angio ins 3 or more drug elut stents cor art
91737	793H.00	Transluminal operations on cardiac conduit
92233	7925012	RIMA sequential anastomosis
92419	7923000	Prosthetic replacement of one coronary artery
92927	793G300	Percutaneous cor balloon angiop 3 more stents cor art NEC
93516	793Hy00	Other specified transluminal operations on cardiac conduit
93618	7929600	Percutaneous transluminal atherectomy of coronary artery
93706	793H000	Percutaneous transluminal balloon dilation cardiac conduit
93828	792Cy00	Other specified replacement of coronary artery
94783	792B100	Repair of rupture of coronary artery
95382	7927y00	Other specified other open operation on coronary artery
96537	793Gy00	OS perc translumina balloon angioplast stenting coronary art
96804	7926	Connection of other thoracic artery to coronary artery
97953	7924y00	Other specified revision of bypass for coronary artery
99434	793Hz00	Transluminal operations on cardiac conduit NOS
101121	8L40.00	Coronary artery bypass graft operation planned
101373	8L41.00	Coronary angioplasty planned
101569	7924300	Revision of bypass for four or more coronary arteries
103655	187..00	Frequency of angina
105184	792E.00	Percutaneous coronary intervention
105479	G39..00	Coronary microvascular disease
1735	G71..00	Aortic aneurysm
1867	G714.00	Abdominal aortic aneurysm without mention of rupture
6872	G71z.00	Aortic aneurysm NOS
9759	G718.00	Leaking abdominal aortic aneurysm
11430	G715000	Thoracoabdominal aortic aneurysm, ruptured
13572	G713.11	Ruptured abdominal aortic aneurysm
15304	G715.00	Ruptured aortic aneurysm NOS
16034	G716.00	Aortic aneurysm without mention of rupture NOS
16521	G710.00	Dissecting aortic aneurysm
16800	G711.11	Ruptured thoracic aortic aneurysm
16993	14AE.00	H/O: aortic aneurysm
17220	7A13.11	Emergency repair of aortic aneurysm
17345	G714.11	AAA - Abdominal aortic aneurysm without mention of rupture
17767	G713.00	Abdominal aortic aneurysm which has ruptured
23532	G712.00	Thoracic aortic aneurysm without mention of rupture
27563	G711.00	Thoracic aortic aneurysm which has ruptured
28109	G714100	Inflammatory abdominal aortic aneurysm
31613	7A13.00	Emergency replacement of aneurysmal segment of aorta
40787	G716000	Thoracoabdominal aortic aneurysm, without mention of rupture
45474	7A13z00	Emergency replacement of aneurysmal segment of aorta NOS
45477	7A13y00	Emergency replacement of aneurysmal segment of aorta OS
45521	G714000	Juxtarenal aortic aneurysm
51061	7A1B200	Endovascular stenting of thoracic aortic aneurysm

51166	7A11311	Y graft abdominal Aortic aneurysm
52358	7A11.00	Replacement of aneurysmal bifurcation of aorta
54192	7A13400	Emerg replace aneurysm abdom aorta by anast aorta/aorta NEC
56495	7A11100	Replace aneurysm bifurc aorta by anast aorta to femoral art
56510	7A11300	Replace aneurysm bifurc aorta by anast aorta to iliac artery
62301	7A11y00	Replacement of aneurysmal bifurcation of aorta OS
63408	7A13411	Tube graft abdominal Aortic aneurysm (emergency)
63920	G713000	Ruptured suprarenal aortic aneurysm
66232	7A13300	Emerg replace aneurysm infrarenal aorta by anast aorta/aorta
66761	7A11z00	Replacement of aneurysmal bifurcation of aorta NOS
69922	7A11200	Emerg repl aneurysm bifurc aorta by anast aorta to iliac a
70446	7A1B000	Endovascular stenting infrarenal abdominal aortic aneurysm
83577	7A1C000	Endovas ins stent graft for infrarenal abdom aortic aneurysm
90861	7A1Bz00	Transluminal operations on aneurysmal segment of aorta NOS
91462	7A1C200	Endov insertion of stent graft for thoracic aortic aneurysm
92925	7A11211	Y graft of abdominal Aortic aneurysm (emergency)
93060	7A13100	Emerg replace aneurysm thor aorta by anastom aorta to aorta
93627	7A1Cz00	Translum ins stent graft for aneurysmal segment of aorta NOS
93959	7A1B.00	Transluminal operations on aneurysmal segment of aorta
94331	7A1C.00	Translum insert stent graft for aneurysmal segment of aorta
94682	7A1C100	Endovas insert of stent graft for suprarenal aortic aneurysm
95976	7A1B500	Endovascular stenting of aorto-uniiliac aneurysm
96654	7A11000	Emerg repl aneurysm bifurc aorta by anast aorta to fem art
97030	7A1B100	Endovascular stenting of suprarenal aortic aneurysm
97109	7A1B700	Endovascular stenting for aorto-uniiliac aneurysm
97217	7A1B800	Endovascul insert stent infrarenal abdominal aortic aneurysm
98175	7A1BD00	Endovascular insertion of stent for aorto-uniiliac aneurysm
98542	7A1BA00	Endovascular insertion of stent for thoracic aortic aneurysm
98565	7A1Cy00	OS translum ins stent graft for aneurysmal segment of aorta
99722	7A13000	Emerg replace aneurysm asc aorta by anastom aorta to aorta
99859	7A1BC00	Endovas insert stent for aortic aneurysm of bifurcation NEC
100195	7A1B600	Endovascular stenting for aortic aneurysm of bifurcation NEC
101195	G714300	Aneurysm of suprarenal aorta
101379	G714200	Infrarenal abdominal aortic aneurysm
101698	68B5100	Aortic aneurysm screening abnormal
102719	Gyu7200	[X]Aortic aneurysm of unspecified site, nonruptured
102725	Gyu7100	[X]Aortic aneurysm of unspecified site, ruptured
103427	7A1C500	Endovas insertion of stent graft for aorto-uniiliac aneurysm
105621	Gyu7800	[X]Aneurysm of aorta in diseases classified elsewhere
106780	7A1B900	Endovascular insertion stent for suprarenal aortic aneurysm
1517	G73z000	Intermittent claudication
2760	G73zz00	Peripheral vascular disease NOS
3530	G73z.00	Peripheral vascular disease NOS
6853	G73z011	Claudication

7975	16I..00	Claudication distance
98174	G733.00	Ischaemic foot
101866	G73z012	Vascular claudication
105317	G734.00	Peripheral arterial disease
15661	G310.11	Dressler's syndrome
61072	G311000	Myocardial infarction aborted
55137	G311011	MI - myocardial infarction aborted
39655	G311.12	Impending infarction
20095	G330.00	Angina decubitus
18125	G330000	Nocturnal angina
29902	G330z00	Angina decubitus NOS
12986	G331.00	Prinzmetal's angina
11048	G331.11	Variant angina pectoris
36854	G332.00	Coronary artery spasm
7696	G33z200	Syncope anginosa
32450	G33z400	Ischaemic chest pain
25583	G574011	Cardiac arrest-ventricular fibrillation
2099	G575.00	Cardiac arrest
33899	G575000	Cardiac arrest with successful resuscitation
21195	G575100	Sudden cardiac death, so described
25407	G575.11	Cardio-respiratory arrest
33402	G575.12	Asystole
49882	G575z00	Cardiac arrest, unspecified
5051	G61..00	Intracerebral haemorrhage
31595	G610.00	Cortical haemorrhage
40338	G611.00	Internal capsule haemorrhage
6960	G61..11	CVA - cerebrovascular accid due to intracerebral haemorrhage
18604	G61..12	Stroke due to intracerebral haemorrhage
46316	G612.00	Basal nucleus haemorrhage
13564	G613.00	Cerebellar haemorrhage
7912	G614.00	Pontine haemorrhage
62342	G615.00	Bulbar haemorrhage
30045	G616.00	External capsule haemorrhage
30202	G617.00	Intracerebral haemorrhage, intraventricular
57315	G618.00	Intracerebral haemorrhage, multiple localized
31060	G61X.00	Intracerebral haemorrhage in hemisphere, unspecified
28314	G61X000	Left sided intracerebral haemorrhage, unspecified
19201	G61X100	Right sided intracerebral haemorrhage, unspecified
3535	G61z.00	Intracerebral haemorrhage NOS
24446	G63y100	Cerebral infarction due to embolism of precerebral arteries
15019	G641.00	Cerebral embolism
27975	G641000	Cerebral infarction due to embolism of cerebral arteries
34758	G641.11	Cerebral embolus
40053	G671.00	Generalised ischaemic cerebrovascular disease NOS

70536	G671000	Acute cerebrovascular insufficiency NOS
12555	G671z00	Generalised ischaemic cerebrovascular disease NOS
5640	G70..00	Atherosclerosis
1318	G700.00	Aortic atherosclerosis
5943	G73..00	Other peripheral vascular disease
1826	G73..12	Ischaemia of legs
38907	G73y.00	Other specified peripheral vascular disease
4325	G73yz00	Other specified peripheral vascular disease NOS
15302	G742z00	Peripheral arterial embolism and thrombosis NOS
27494	G74y300	Embolism and thrombosis of the iliac artery unspecified
8610	G76z000	Iliac artery occlusion
53810	Gyu6200	[X]Other intracerebral haemorrhage
96630	Gyu6F00	[X]Intracerebral haemorrhage in hemisphere, unspecified
73961	Gyu7400	[X]Other specified peripheral vascular diseases

Suppl. Table 2.6: ICD 10 and ICD 9 codes for cause of death classified according to the organ systems and particular diseases

	ICD-10 codes	**ICD-9 codes**
Organ systems		
Neoplasms	C00-D48	140-239
Diseases of the respiratory system	J00-J99	460-519
Diseases of the digestive	K00-K92	520-579
Endocrine, nutritional and metabolic diseases	E00-E89	240-279
Mental and behavioural disorders	F00-F99	290-319
Diseases of the nervous system	G00-G99	320-389
Disease of the genitourinary system	N00-N99	580-629
Certain infectious and parasitic diseases	A00-B99	001-139
Diseases if the musculoskeletal system and connective tissue	M00-M99	710-739
Other systems	D50-D89, H00-H59, H60-H95, L00-L99, O00-O99, P00-P96, Q00-Q99, R00-R99, S00-T98, V01-Y98, Z00-Z99, U00-U85	280-289, 680-709, 630-679, 740-759, 760-779, 780-799, 800-999
Particular diseases		
Ischaemic Heart Disease	I20.0-I25.9	410-414
Malignant neoplasms	C00.0-C96.9, C97	140-209
Urinary tract infection	N39.0	590.0-590.9, 599.0
Adrenal insufficiency	E27.1-E27.4, E27.8, E27.9	255.4, 255.5, 255.8, 255.9
Hypopituitarism and pituitary disorders	E23.0-E23.3, E23.6, E23.7, D35.2	253.2, 253.3, 253.4, 253.5, 253.6, 253.7, 253.8, 253.9
Lower respiratory tract infections and pneumonia	J09, J10.0-J18.9, J69, J69.0-J69.8, J20, J20.0-J21.9, J22	480-488, 507, 507.0, 507.1, 507.8
Alcoholic liver disease	K70, K70.0-K70.9	No ICD-9 code
Connective tissue disease and rheumatoid arthritis	M30.0-M35.9, M36, M05.0-M06.9	710, 714, 714.0, 714.3
Combined infectious diseases	A00-B99, J09, J10.0-J18.9, J69, J69.0-J69.8, J20, J20.0-J21.9, J22, N39.0	001-139, 480-488, 507, 507.0, 507.1, 507.8, 590.0-590.9, 599.0

Suppl. Table 2.7: ICD-9 and ICD-10 codes for the outcome of cardiovascular mortality and hospitalisation due to cardiovascular disease

ICD-10 codes	Diseases
Diseases in the circulatory systems	
I00-I20	**Acute rheumatic fever**
I00	Rheumatic fever without mention of heart involvement
I01	Rheumatic fever with heart involvement
I02	Rheumatic chorea
I05-I09	**Chronic rheumatic heart diseases**
I05	Rheumatic mitral valve diseases
I06	Rheumatic aortic valve diseases
I07	Rheumatic tricuspid valve diseases
I08	Multiple valve diseases
I09	Other rheumatic heart diseases
I10-I15	**Hypertensive diseases**
I10	Essential (primary) hypertension
I11	Hypertensive heart disease
I12	Hypertensive renal disease
I13	Hypertensive heart and renal disease
I15	Secondary hypertension
I20-I25 †	**Ischaemic heart diseases**
I20	Angina pectoris
I21	Acute myocardial infarction
I22	Subsequent myocardial infarction
I23	Certain current complications following acute myocardial infarction
I24	Other acute ischaemic heart diseases
I25	Chronic ischaemic heart disease
I26-I28	**Pulmonary heart disease and diseases of pulmonary circulation**
I26	Pulmonary embolism
I27	Other pulmonary heart diseases
I28	Other diseases of pulmonary vessels
I30-I50	**Other forms of heart diseases**
I30	Acute pericarditis
I31	Other diseases of pericardium
I32	Pericarditis in diseases classified elsewhere
I33	Acute and subacute endocarditis
I34	Nonrheumatic mitral valve disorders
I35	Nonrheumatic aortic valve disorders
I36	Nonrheumatic tricuspid valve disorders
I37	Pulmonary valve disorders
I38	Endocarditis, valve unspecified
I39	Endocarditis and heart valve disorders in diseases classified elsewhere
I40	Acute myocarditis
I41	Myocarditis in diseases classified elsewhere
I42	Cardiomyopathy
I43	Cardiomyopathy in diseases classified elsewhere
I44	Atrioventricular and left bundle-branch block
I45	Other conduction disorders
I46	Cardiac arrest
I47	Paroxysmal tachycardia
I48	Atrial fibrillation and flutter
I49	Other cardiac arrhythmias
I50	Heart failure
I51	Complications and ill-defined descriptions of heart disease
I52	Other heart disorders in diseases classified elsewhere
I60-I69 ‡	**Cerebrovascular diseases**
I60	Subarachnoid haemorrhage
I61	Intracerebral haemorrhage
I62	Other nontraumatic intracranial haemorrhage
I63	Cerebral infarction

I64	Stroke, not specified as haemorrhage or infarction
I65	Occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction
I66	Occlusion and stenosis of cerebral arteries, not resulting in cerebral infarction
I67	Other cerebrovascular diseases
I68	Cerebrovascular disorders in diseases classified elsewhere
I69	Sequelae of cerebrovascular disease
I70-I79	**Diseases of arteries, arterioles and capillaries**
I70	Atherosclerosis
I71	Aortic aneurysm and dissection
I72	Other aneurysm and dissection
I73	Other peripheral vascular diseases
I74	Arterial embolism and thrombosis
I77	Arterial embolism and thrombosis
I78	Diseases of capillaries
I79	Disorders of arteries, arterioles and capillaries in diseases classified elsewhere
I80-I89	**Diseases of veins, lymphatic vessels and lymph nodes, not elsewhere classified**
I81	Phlebitis and thrombophlebitis
I82	Portal vein thrombosis
I83	Varicose veins of lower extremities
I85	Oesophageal varices
I86	Varicose veins of other sites
I87	Other disorders of veins
I88	Nonspecific lymphadenitis
I89	Other noninfective disorders of lymphatic vessels and lymph nodes
I95-I99	**Other and unspecified disorders of the circulatory system**
I95	Hypotension
I97	Postprocedural disorders of circulatory system, not elsewhere classified
I98	Other disorders of circulatory system in diseases classified elsewhere
I99	Other and unspecified disorders of circulatory system
Diseases in the nervous systems	
G45 ‡	**Transient cerebral ischaemic attacks and related syndromes**
ICD-9 codes	**Diseases**
Diseases in the circulatory systems	
390-392	**Acute rheumatic fever**
390	Rheumatic fever without mention of heart involvement
391	Rheumatic fever with heart involvement
392	Rheumatic chorea
393-398	**Chronic rheumatic heart diseases**
393	Chronic rheumatic pericarditis
394	Diseases of mitral valve
395	Diseases of aortic valve
396	Diseases of mitral and aortic valves
397	Diseases of other endocardial structures
398	Other rheumatic heart disease
401-405	**Hypertensive diseases**
401	Essential hypertension
402	Hypertensive heart disease
403	Hypertensive renal disease
404	Hypertensive heart and renal disease
405	Secondary hypertension
410-414 †	**Ischaemic heart disease**
410	Acute myocardial infarction
411	Other acute and subacute form of ischemic heart disease
412	Old myocardial infarction
413	Angina pectoris
414	Other forms of chronic ischemic heart disease
415-417	**Diseases of pulmonary circulation**
415	Acute pulmonary heart disease
416	Chronic pulmonary heart disease
417	Other diseases of pulmonary circulation
420-429	**Other forms of heart disease**
420	Acute pericarditis

421	Acute and subacute endocarditis
422	Acute myocarditis
423	Other diseases of pericardium
424	Other diseases of endocardium
425	Cardiomyopathy
426	Conduction disorders
427	Cardiac dysrhythmias
428	Heart failure
429	Ill-defined descriptions and complications of heart disease
430-438 ‡	**Cerebrovascular disease**
430	Subarachnoid hemorrhage
431	Intracerebral hemorrhage
432	Other and unspecified intracranial hemorrhage
433	Occlusion and stenosis of precerebral arteries
434	Occlusion of cerebral arteries
435	Transient cerebral ischemia
436	Acute but ill-defined cerebrovascular disease
437	Other and ill-defined cerebrovascular disease
438	Late effects of cerebrovascular disease
440-448	**Diseases of arteries, arterioles, and capillaries**
440	Atherosclerosis
441	Aortic aneurysm and dissection
442	Other aneurysm
443	Other peripheral vascular disease
444	Arterial embolism and thrombosis
445	Atheroembolism
446	Polyarteritis nodosa and allied conditions
447	Other disorders of arteries and arterioles
448	Diseases of capillaries
451-459	**Diseases of veins and lymphatics, and other diseases of circulatory system**
451	Phlebitis and thrombophlebitis
452	Portal vein thrombosis
453	Other venous embolism and thrombosis
454	Varicose veins of lower extremities
455	Hemorrhoids
456	Varicose veins of other sites
457	Noninfective disorders of lymphatic channels
458	Hypotension
459	Other disorders of circulatory system
Diseases in the nervous systems	
342 ‡	Hemiplegia, Hemiparesis

Note: † outcomes for deaths or hospitalisations from ischaemic heart disease; ‡ outcomes for deaths or hospitalisation from cerebrovascular disease

Suppl. Table 2.8: Medical codes, Read codes, and Read term for diabetes mellitus

Medical code	Read code	Read term (Clinical terminology)
28622	2E+06	Diabetes resolved
711	C10..00	Diabetes mellitus
38986	C100.00	Diabetes mellitus with no mention of complication
24490	C100000	Diabetes mellitus, juvenile type, no mention of complication
1038	C100011	Insulin dependent diabetes mellitus
14803	C100100	Diabetes mellitus, adult onset, no mention of complication
14889	C100111	Maturity onset diabetes
506	C100112	Non-insulin dependent diabetes mellitus
50972	C100z00	Diabetes mellitus NOS with no mention of complication
1682	C101.00	Diabetes mellitus with ketoacidosis
53200	C101000	Diabetes mellitus, juvenile type, with ketoacidosis
54856	C101100	Diabetes mellitus, adult onset, with ketoacidosis
38617	C101y00	Other specified diabetes mellitus with ketoacidosis
42505	C101z00	Diabetes mellitus NOS with ketoacidosis
21482	C102.00	Diabetes mellitus with hyperosmolar coma
40023	C102000	Diabetes mellitus, juvenile type, with hyperosmolar coma
43139	C102100	Diabetes mellitus, adult onset, with hyperosmolar coma
72345	C102z00	Diabetes mellitus NOS with hyperosmolar coma
15690	C103.00	Diabetes mellitus with ketoacidotic coma
42567	C103000	Diabetes mellitus, juvenile type, with ketoacidotic coma
68843	C103100	Diabetes mellitus, adult onset, with ketoacidotic coma
59288	C103y00	Other specified diabetes mellitus with coma
65062	C103z00	Diabetes mellitus NOS with ketoacidotic coma
16502	C104.00	Diabetes mellitus with renal manifestation
93922	C104000	Diabetes mellitus, juvenile type, with renal manifestation
35105	C104100	Diabetes mellitus, adult onset, with renal manifestation
2475	C104.11	Diabetic nephropathy
13279	C104y00	Other specified diabetes mellitus with renal complications
35107	C104z00	Diabetes mellitus with nephropathy NOS
33254	C105.00	Diabetes mellitus with ophthalmic manifestation
69748	C105000	Diabetes mellitus, juvenile type, + ophthalmic manifestation
41389	C105100	Diabetes mellitus, adult onset, + ophthalmic manifestation
47377	C105y00	Other specified diabetes mellitus with ophthalmic complicatn
34283	C105z00	Diabetes mellitus NOS with ophthalmic manifestation
16230	C106.00	Diabetes mellitus with neurological manifestation
67853	C106000	Diabetes mellitus, juvenile, + neurological manifestation
39317	C106100	Diabetes mellitus, adult onset, + neurological manifestation
59903	C106.11	Diabetic amyotrophy
7795	C106.12	Diabetes mellitus with neuropathy
16491	C106.13	Diabetes mellitus with polyneuropathy
61523	C106y00	Other specified diabetes mellitus with neurological comps
22573	C106z00	Diabetes mellitus NOS with neurological manifestation
35399	C107.00	Diabetes mellitus with peripheral circulatory disorder

70448	C107000	Diabetes mellitus, juvenile +peripheral circulatory disorder
63357	C107100	Diabetes mellitus, adult, + peripheral circulatory disorder
32403	C107.11	Diabetes mellitus with gangrene
32556	C107.12	Diabetes with gangrene
33807	C107200	Diabetes mellitus, adult with gangrene
69124	C107300	IDDM with peripheral circulatory disorder
56803	C107400	NIDDM with peripheral circulatory disorder
65025	C107z00	Diabetes mellitus NOS with peripheral circulatory disorder
1647	C108.00	Insulin dependent diabetes mellitus
46963	C108000	Insulin-dependent diabetes mellitus with renal complications
61344	C108011	Type I diabetes mellitus with renal complications
21983	C108012	Type 1 diabetes mellitus with renal complications
49276	C108100	Insulin-dependent diabetes mellitus with ophthalmic comps
18505	C108.11	IDDM-Insulin dependent diabetes mellitus
102740	C108112	Type 1 diabetes mellitus with ophthalmic complications
17858	C108.12	Type 1 diabetes mellitus
24423	C108.13	Type I diabetes mellitus
52283	C108200	Insulin-dependent diabetes mellitus with neurological comps
49146	C108211	Type I diabetes mellitus with neurological complications
61829	C108212	Type 1 diabetes mellitus with neurological complications
52104	C108300	Insulin dependent diabetes mellitus with multiple complicatn
26855	C108400	Unstable insulin dependent diabetes mellitus
60107	C108411	Unstable type I diabetes mellitus
97474	C108412	Unstable type 1 diabetes mellitus
44443	C108500	Insulin dependent diabetes mellitus with ulcer
51957	C108511	Type I diabetes mellitus with ulcer
68390	C108512	Type 1 diabetes mellitus with ulcer
60499	C108600	Insulin dependent diabetes mellitus with gangrene
6509	C108700	Insulin dependent diabetes mellitus with retinopathy
38161	C108711	Type I diabetes mellitus with retinopathy
41049	C108712	Type 1 diabetes mellitus with retinopathy
6791	C108800	Insulin dependent diabetes mellitus - poor control
46850	C108811	Type I diabetes mellitus - poor control
45914	C108812	Type 1 diabetes mellitus - poor control
31310	C108900	Insulin dependent diabetes maturity onset
63017	C108911	Type I diabetes mellitus maturity onset
97446	C108912	Type 1 diabetes mellitus maturity onset
56448	C108A00	Insulin-dependent diabetes without complication
95992	C108A11	Type I diabetes mellitus without complication
24694	C108B00	Insulin dependent diabetes mellitus with mononeuropathy
99231	C108B11	Type I diabetes mellitus with mononeuropathy
41716	C108C00	Insulin dependent diabetes mellitus with polyneuropathy
57621	C108D00	Insulin dependent diabetes mellitus with nephropathy
66872	C108D11	Type I diabetes mellitus with nephropathy
44440	C108E00	Insulin dependent diabetes mellitus with hypoglycaemic coma
42729	C108E11	Type I diabetes mellitus with hypoglycaemic coma

70766	C108E12	Type 1 diabetes mellitus with hypoglycaemic coma
44260	C108F00	Insulin dependent diabetes mellitus with diabetic cataract
17545	C108F11	Type I diabetes mellitus with diabetic cataract
64446	C108G00	Insulin dependent diab mell with peripheral angiopathy
65616	C108H00	Insulin dependent diabetes mellitus with arthropathy
62352	C108H11	Type I diabetes mellitus with arthropathy
39809	C108J00	Insulin dependent diab mell with neuropathic arthropathy
60208	C108J11	Type I diabetes mellitus with neuropathic arthropathy
18230	C108J12	Type 1 diabetes mellitus with neuropathic arthropathy
46290	C108y00	Other specified diabetes mellitus with multiple comps
64449	C108z00	Unspecified diabetes mellitus with multiple complications
4513	C109.00	Non-insulin dependent diabetes mellitus
52303	C109000	Non-insulin-dependent diabetes mellitus with renal comps
50225	C109011	Type II diabetes mellitus with renal complications
18209	C109012	Type 2 diabetes mellitus with renal complications
50429	C109100	Non-insulin-dependent diabetes mellitus with ophthalm comps
5884	C109.11	NIDDM - Non-insulin dependent diabetes mellitus
59725	C109111	Type II diabetes mellitus with ophthalmic complications
70316	C109112	Type 2 diabetes mellitus with ophthalmic complications
17859	C109.12	Type 2 diabetes mellitus
18219	C109.13	Type II diabetes mellitus
55842	C109200	Non-insulin-dependent diabetes mellitus with neuro comps
67905	C109211	Type II diabetes mellitus with neurological complications
45919	C109212	Type 2 diabetes mellitus with neurological complications
62146	C109300	Non-insulin-dependent diabetes mellitus with multiple comps
34912	C109400	Non-insulin dependent diabetes mellitus with ulcer
55075	C109411	Type II diabetes mellitus with ulcer
65704	C109412	Type 2 diabetes mellitus with ulcer
40401	C109500	Non-insulin dependent diabetes mellitus with gangrene
62107	C109511	Type II diabetes mellitus with gangrene
46150	C109512	Type 2 diabetes mellitus with gangrene
17262	C109600	Non-insulin-dependent diabetes mellitus with retinopathy
58604	C109611	Type II diabetes mellitus with retinopathy
42762	C109612	Type 2 diabetes mellitus with retinopathy
8403	C109700	Non-insulin dependent diabetes mellitus - poor control
24458	C109711	Type II diabetes mellitus - poor control
45913	C109712	Type 2 diabetes mellitus - poor control
39406	C109800	Reaven's syndrome
29979	C109900	Non-insulin-dependent diabetes mellitus without complication
72320	C109A00	Non-insulin dependent diabetes mellitus with mononeuropathy
50813	C109A11	Type II diabetes mellitus with mononeuropathy
45467	C109B00	Non-insulin dependent diabetes mellitus with polyneuropathy
47409	C109B11	Type II diabetes mellitus with polyneuropathy
59365	C109C00	Non-insulin dependent diabetes mellitus with nephropathy
64571	C109C11	Type II diabetes mellitus with nephropathy
24836	C109C12	Type 2 diabetes mellitus with nephropathy

43785	C109D00	Non-insulin dependent diabetes mellitus with hypoglyca coma
56268	C109D11	Type II diabetes mellitus with hypoglycaemic coma
61071	C109D12	Type 2 diabetes mellitus with hypoglycaemic coma
69278	C109E00	Non-insulin depend diabetes mellitus with diabetic cataract
48192	C109E11	Type II diabetes mellitus with diabetic cataract
44779	C109E12	Type 2 diabetes mellitus with diabetic cataract
54212	C109F00	Non-insulin-dependent d m with peripheral angiopath
54899	C109F11	Type II diabetes mellitus with peripheral angiopathy
60699	C109F12	Type 2 diabetes mellitus with peripheral angiopathy
24693	C109G00	Non-insulin dependent diabetes mellitus with arthropathy
18143	C109G11	Type II diabetes mellitus with arthropathy
49869	C109G12	Type 2 diabetes mellitus with arthropathy
40962	C109H00	Non-insulin dependent d m with neuropathic arthropathy
47816	C109H11	Type II diabetes mellitus with neuropathic arthropathy
66965	C109H12	Type 2 diabetes mellitus with neuropathic arthropathy
18278	C109J00	Insulin treated Type 2 diabetes mellitus
37648	C109J11	Insulin treated non-insulin dependent diabetes mellitus
18264	C109J12	Insulin treated Type II diabetes mellitus
36633	C109K00	Hyperosmolar non-ketotic state in type 2 diabetes mellitus
52236	C10A.00	Malnutrition-related diabetes mellitus
66675	C10A000	Malnutrition-related diabetes mellitus with coma
33969	C10A100	Malnutrition-related diabetes mellitus with ketoacidosis
100347	C10A500	Malnutritn-relat diabetes melitus wth periph circul complctn
11551	C10B.00	Diabetes mellitus induced by steroids
26108	C10B000	Steroid induced diabetes mellitus without complication
43453	C10C.00	Diabetes mellitus autosomal dominant
46624	C10C.11	Maturity onset diabetes in youth
98392	C10C.12	Maturity onset diabetes in youth type 1
36695	C10D.00	Diabetes mellitus autosomal dominant type 2
59991	C10D.11	Maturity onset diabetes in youth type 2
1549	C10E.00	Type 1 diabetes mellitus
47582	C10E000	Type 1 diabetes mellitus with renal complications
102946	C10E012	Insulin-dependent diabetes mellitus with renal complications
47649	C10E100	Type 1 diabetes mellitus with ophthalmic complications
12455	C10E.11	Type I diabetes mellitus
99311	C10E111	Type I diabetes mellitus with ophthalmic complications
98071	C10E112	Insulin-dependent diabetes mellitus with ophthalmic comps
51261	C10E.12	Insulin dependent diabetes mellitus
42831	C10E200	Type 1 diabetes mellitus with neurological complications
101735	C10E212	Insulin-dependent diabetes mellitus with neurological comps
47650	C10E300	Type 1 diabetes mellitus with multiple complications
91942	C10E311	Type I diabetes mellitus with multiple complications
45276	C10E312	Insulin dependent diabetes mellitus with multiple complicat
43921	C10E400	Unstable type 1 diabetes mellitus
49949	C10E411	Unstable type I diabetes mellitus
54600	C10E412	Unstable insulin dependent diabetes mellitus

18683	C10E500	Type 1 diabetes mellitus with ulcer
93878	C10E511	Type I diabetes mellitus with ulcer
98704	C10E512	Insulin dependent diabetes mellitus with ulcer
69993	C10E600	Type 1 diabetes mellitus with gangrene
102112	C10E611	Type I diabetes mellitus with gangrene
18387	C10E700	Type 1 diabetes mellitus with retinopathy
95343	C10E711	Type I diabetes mellitus with retinopathy
93875	C10E712	Insulin dependent diabetes mellitus with retinopathy
35288	C10E800	Type 1 diabetes mellitus - poor control
72702	C10E812	Insulin dependent diabetes mellitus - poor control
40682	C10E900	Type 1 diabetes mellitus maturity onset
96235	C10E911	Type I diabetes mellitus maturity onset
97849	C10E912	Insulin dependent diabetes maturity onset
69676	C10EA00	Type 1 diabetes mellitus without complication
62613	C10EA11	Type I diabetes mellitus without complication
99719	C10EA12	Insulin-dependent diabetes without complication
68105	C10EB00	Type 1 diabetes mellitus with mononeuropathy
46301	C10EC00	Type 1 diabetes mellitus with polyneuropathy
91943	C10EC11	Type I diabetes mellitus with polyneuropathy
101311	C10EC12	Insulin dependent diabetes mellitus with polyneuropathy
10418	C10ED00	Type 1 diabetes mellitus with nephropathy
102163	C10ED12	Insulin dependent diabetes mellitus with nephropathy
39070	C10EE00	Type 1 diabetes mellitus with hypoglycaemic coma
99716	C10EE12	Insulin dependent diabetes mellitus with hypoglycaemic coma
49554	C10EF00	Type 1 diabetes mellitus with diabetic cataract
100770	C10EF12	Insulin dependent diabetes mellitus with diabetic cataract
93468	C10EG00	Type 1 diabetes mellitus with peripheral angiopathy
18642	C10EH00	Type 1 diabetes mellitus with arthropathy
54008	C10EJ00	Type 1 diabetes mellitus with neuropathic arthropathy
30323	C10EK00	Type 1 diabetes mellitus with persistent proteinuria
30294	C10EL00	Type 1 diabetes mellitus with persistent microalbuminuria
102620	C10EL11	Type I diabetes mellitus with persistent microalbuminuria
10692	C10EM00	Type 1 diabetes mellitus with ketoacidosis
62209	C10EM11	Type I diabetes mellitus with ketoacidosis
40837	C10EN00	Type 1 diabetes mellitus with ketoacidotic coma
66145	C10EN11	Type I diabetes mellitus with ketoacidotic coma
22871	C10EP00	Type 1 diabetes mellitus with exudative maculopathy
97894	C10EP11	Type I diabetes mellitus with exudative maculopathy
55239	C10EQ00	Type 1 diabetes mellitus with gastroparesis
95636	C10ER00	Latent autoimmune diabetes mellitus in adult
758	C10F.00	Type 2 diabetes mellitus
18777	C10F000	Type 2 diabetes mellitus with renal complications
57278	C10F011	Type II diabetes mellitus with renal complications
47321	C10F100	Type 2 diabetes mellitus with ophthalmic complications
22884	C10F.11	Type II diabetes mellitus
100964	C10F111	Type II diabetes mellitus with ophthalmic complications

34268	C10F200	Type 2 diabetes mellitus with neurological complications
98616	C10F211	Type II diabetes mellitus with neurological complications
65267	C10F300	Type 2 diabetes mellitus with multiple complications
43227	C10F311	Type II diabetes mellitus with multiple complications
49074	C10F400	Type 2 diabetes mellitus with ulcer
91646	C10F411	Type II diabetes mellitus with ulcer
12736	C10F500	Type 2 diabetes mellitus with gangrene
104323	C10F511	Type II diabetes mellitus with gangrene
18496	C10F600	Type 2 diabetes mellitus with retinopathy
49655	C10F611	Type II diabetes mellitus with retinopathy
25627	C10F700	Type 2 diabetes mellitus - poor control
47315	C10F711	Type II diabetes mellitus - poor control
54773	C10F800	Reaven's syndrome
39481	C10F811	Metabolic syndrome X
47954	C10F900	Type 2 diabetes mellitus without complication
53392	C10F911	Type II diabetes mellitus without complication
62674	C10FA00	Type 2 diabetes mellitus with mononeuropathy
95351	C10FA11	Type II diabetes mellitus with mononeuropathy
18425	C10FB00	Type 2 diabetes mellitus with polyneuropathy
50527	C10FB11	Type II diabetes mellitus with polyneuropathy
12640	C10FC00	Type 2 diabetes mellitus with nephropathy
102201	C10FC11	Type II diabetes mellitus with nephropathy
46917	C10FD00	Type 2 diabetes mellitus with hypoglycaemic coma
98723	C10FD11	Type II diabetes mellitus with hypoglycaemic coma
44982	C10FE00	Type 2 diabetes mellitus with diabetic cataract
93727	C10FE11	Type II diabetes mellitus with diabetic cataract
37806	C10FF00	Type 2 diabetes mellitus with peripheral angiopathy
59253	C10FG00	Type 2 diabetes mellitus with arthropathy
103902	C10FG11	Type II diabetes mellitus with arthropathy
35385	C10FH00	Type 2 diabetes mellitus with neuropathic arthropathy
1407	C10FJ00	Insulin treated Type 2 diabetes mellitus
64668	C10FJ11	Insulin treated Type II diabetes mellitus
34450	C10FK00	Hyperosmolar non-ketotic state in type 2 diabetes mellitus
26054	C10FL00	Type 2 diabetes mellitus with persistent proteinuria
60796	C10FL11	Type II diabetes mellitus with persistent proteinuria
18390	C10FM00	Type 2 diabetes mellitus with persistent microalbuminuria
85991	C10FM11	Type II diabetes mellitus with persistent microalbuminuria
32627	C10FN00	Type 2 diabetes mellitus with ketoacidosis
51756	C10FP00	Type 2 diabetes mellitus with ketoacidotic coma
25591	C10FQ00	Type 2 diabetes mellitus with exudative maculopathy
63690	C10FR00	Type 2 diabetes mellitus with gastroparesis
95539	C10FS00	Maternally inherited diabetes mellitus
51697	C10G.00	Secondary pancreatic diabetes mellitus
96506	C10G000	Secondary pancreatic diabetes mellitus without complication
61122	C10H.00	Diabetes mellitus induced by non-steroid drugs
67212	C10H000	DM induced by non-steroid drugs without complication

68517	C10J.00	Insulin autoimmune syndrome
37957	C10K.00	Type A insulin resistance
56885	C10K000	Type A insulin resistance without complication
43857	C10M.00	Lipoatrophic diabetes mellitus
22487	C10N.00	Secondary diabetes mellitus
94383	C10N000	Secondary diabetes mellitus without complication
93380	C10N100	Cystic fibrosis related diabetes mellitus
33343	C10y.00	Diabetes mellitus with other specified manifestation
63371	C10y100	Diabetes mellitus, adult, + other specified manifestation
10098	C10yy00	Other specified diabetes mellitus with other spec comps
70821	C10yz00	Diabetes mellitus NOS with other specified manifestation
45491	C10z.00	Diabetes mellitus with unspecified complication
68792	C10z000	Diabetes mellitus, juvenile type, + unspecified complication
63762	C10z100	Diabetes mellitus, adult onset, + unspecified complication
64283	C10zy00	Other specified diabetes mellitus with unspecified comps
64357	C10zz00	Diabetes mellitus NOS with unspecified complication

Supplementary Table 2.9: Medical codes, Read codes, and Read term for hypertension

Medical code	Read code	Read term (Clinical terminology)
204	G2...00	Hypertensive disease
799	G20..00	Essential hypertension
15377	G200.00	Malignant essential hypertension
1894	G201.00	Benign essential hypertension
351	G20..11	High blood pressure
4372	G202.00	Systolic hypertension
83473	G203.00	Diastolic hypertension
10818	G20z.00	Essential hypertension NOS
3712	G20z.11	Hypertension NOS
7329	G24..00	Secondary hypertension
31755	G240.00	Secondary malignant hypertension
59383	G240000	Secondary malignant renovascular hypertension
73293	G240z00	Secondary malignant hypertension NOS
57288	G241.00	Secondary benign hypertension
25371	G241000	Secondary benign renovascular hypertension
51635	G241z00	Secondary benign hypertension NOS
34744	G244.00	Hypertension secondary to endocrine disorders
16059	G24z.00	Secondary hypertension NOS
31387	G24z000	Secondary renovascular hypertension NOS
31341	G24z100	Hypertension secondary to drug
42229	G24zz00	Secondary hypertension NOS
18765	G2y..00	Other specified hypertensive disease
7057	G2z..00	Hypertensive disease NOS

Supplementary Table 2.10: Medical codes, Read codes, and Read term for smoking, ex-smoking and non-smoking codes

Medical code	Read code	Read term (Clinical terminology)
Smoking codes		
12942	137..11	Smoker - amount smoked
12941	1372.1	Occasional smoker
12967	137a.00	Pipe tobacco consumption
31114	137b.00	Ready to stop smoking
30423	137c.00	Thinking about stopping smoking
12964	137C.00	Keeps trying to stop smoking
30762	137d.00	Not interested in stopping smoking
46654	137D.00	Admitted tobacco cons untrue ?
41979	137e.00	Smoking restarted
46321	137f.00	Reason for restarting smoking
12240	137G.00	Trying to give up smoking
62686	137h.00	Minutes from waking to first tobacco consumption
12947	137H.00	Pipe smoker
12943	137J.00	Cigar smoker
776	137K.00	Stopped smoking
12945	137M.00	Rolls own cigarettes
93	137P.00	Cigarette smoker
1823	137P.11	Smoker
12952	137Q.00	Smoking started
12951	137Q.11	Smoking restarted
10558	137R.00	Current smoker
12878	137T.00	Date ceased smoking
12966	137V.00	Smoking reduced
12965	137X.00	Cigarette consumption
12963	137Y.00	Cigar consumption
12960	137Z.00	Tobacco consumption NOS
75170	T509	Smoking codes
84301	T5090OR	Smoking codes
82596	T5090XC	Smoking codes
78118	T5091	Smoking codes
80500	T5091ES	Smoking codes
88431	T5091HS	Smoking codes
58513	T5092	Smoking codes
78283	T5092S	Smoking codes
76139	T5092SA	Smoking codes
86554	T5093N	Smoking codes
84896	T509 SR	Smoking codes
84470	T510	Smoking codes
81862	T510 HS	Smoking codes
80378	T510 SE	Smoking codes
78714	T510 SH	Smoking codes

81573	T511	Smoking codes
82556	T5112	Smoking codes
82557	T5113	Smoking codes
82539	T5114	Smoking codes
82692	T5115	Smoking codes
84047	T5115M	Smoking codes
85733	T5116	Smoking codes
58490	T5117	Smoking codes
84927	T512	Smoking codes
84613	T513	Smoking codes
Ex-smoking codes		
12946	137F.00	Ex-smoker - amount unknown
776	137K.00	Stopped smoking
26470	137N.00	Ex pipe smoker
19488	137O.00	Ex cigar smoker
90	137S.00	Ex smoker
Non-smoking codes		
11788	1371.1	Non-smoker
60	137L.00	Current non-smoker

Supplementary Table 2.11: Product codes and Product names for lipid-lowering agents

Product code	Product name
Statins	
11627	fluvastatin 24 hour modified release tablets 80mg
1219	pravastatin tablets 40mg
1221	LIPOSTAT tablets 10mg [SQUIBB]
1223	LIPOSTAT tablets 40mg [SQUIBB]
13041	SIMVADOR tablets 10mg [DISCOVERY]
15252	CRESTOR tablets 20mg [ASTRAZENEC]
17683	LIPITOR tablets 80mg [PFIZER]
17688	CRESTOR tablets 5mg [ASTRAZENEC]
18442	LIPOBAY tablets 400micrograms [BAYER]
2137	fluvastatin capsules 40mg
22579	ZOCOR tablets 80mg [M S D]
25	simvastatin tablets 20mg
2718	ZOCOR tablets 10mg [M S D]
28	atorvastatin tablets 10mg
2955	LIPITOR tablets 40mg [PFIZER]
31658	cerivastatin tablets 800micrograms
31930	ZOCOR HEART-PRO tablets 10mg [MCNEIL]
32909	SIMVASTATIN tablets 80mg [HILLCROSS]
32921	PRAVASTATIN tablets 10mg [DR REDDY`S]
33082	SIMVASTATIN tablets 20mg [HILLCROSS]
3411	LIPITOR tablets 10mg [PFIZER]
34312	SIMVASTATIN tablets 20mg [GEN (UK)]
34316	SIMVASTATIN tablets 20mg [TEVA]
34353	SIMVASTATIN tablets 40mg [GEN (UK)]
34366	SIMVASTATIN tablets 20mg [IVAX]
34376	SIMVASTATIN tablets 40mg [TEVA]
34381	SIMVASTATIN tablets 40mg [IVAX]
34476	SIMVASTATIN tablets 20mg [RATIOPHARM]
34481	SIMVASTATIN tablets 10mg [IVAX]
34502	SIMVASTATIN tablets 40mg [HILLCROSS]
34535	SIMVASTATIN tablets 10mg [GEN (UK)]
34545	SIMVASTATIN tablets 40mg [RATIOPHARM]
34560	SIMVASTATIN tablets 10mg [RATIOPHARM]
34746	SIMVASTATIN tablets 20mg [NICHE]
34814	SIMVASTATIN tablets 20mg [WOCKHARDT]
34820	PRAVASTATIN tablets 40mg [HILLCROSS]
34879	SIMVASTATIN tablets 40mg [NICHE]
34891	SIMVASTATIN tablets 20mg [KENT]
34907	SIMVASTATIN tablets 40mg [WOCKHARDT]
34955	SIMVASTATIN tablets 10mg [HILLCROSS]
34969	SIMVASTATIN tablets 40mg [ACTAVIS]

36377	PRAVASTATIN tablets 20mg [TEVA]
3690	LIPOSTAT tablets 20mg [SQUIBB]
37434	SIMVASTATIN tablets 40mg [SANDOZ]
379	fluvastatin capsules 20mg
39060	SIMVASTATIN tablets 20mg [DEXCEL]
39652	simvastatin oral suspension sugar-free 40mg/5ml
39675	SIMVASTATIN oral suspension 20mg/5ml [MARTINDALE]
39870	SIMVADOR tablets 80mg [DISCOVERY]
40340	SIMVASTATIN tablets 10mg [TEVA]
40382	PRAVASTATIN tablets 20mg [HILLCROSS]
40601	SIMVASTATIN tablets 20mg [RANBAXY]
41657	SIMVASTATIN tablets 80mg [TEVA]
42	simvastatin tablets 10mg
420	cerivastatin tablets 100micrograms
43218	PRAVASTATIN tablets 10mg [TEVA]
44528	SIMVASTATIN oral suspension sugar-free 20mg/5ml [ROSEMONT]
44650	SIMVASTATIN tablets 40mg [DEXCEL]
44878	RANZOLONT tablets 10mg [RANBAXY]
45219	SIMVASTATIN tablets 40mg [KENT]
45235	SIMVASTATIN tablets 20mg [SANDOZ]
45245	SIMVASTATIN tablets 20mg [ACTAVIS]
45346	SIMVASTATIN tablets 40mg [ARROW]
46878	SIMVASTATIN tablets 40mg [ALMUS]
46956	SIMVASTATIN tablets 80mg [ARROW]
47065	atorvastatin chewable tablet 20mg
47090	atorvastatin chewable tablet 10mg
47630	LIPITOR chewable tablet 20mg [PFIZER]
47721	LIPITOR chewable tablet 10mg [PFIZER]
47774	SIMVASTATIN tablets 10mg [ARROW]
47948	SIMVASTATIN tablets 10mg [TILLOMED]
47988	PRAVASTATIN tablets 40mg [GEN (UK)]
48018	SIMVASTATIN tablets 20mg [ARROW]
48051	SIMVASTATIN tablets 10mg [KENT]
48058	SIMVASTATIN tablets 10mg [RANBAXY]
48078	SIMVASTATIN tablets 10mg [ACTAVIS]
48097	PRAVASTATIN tablets 40mg [TEVA]
48221	Simvastatin 20mg/5ml oral suspension sugar free
48346	Atorvastatin 60mg tablets
48431	Simvastatin 40mg/5ml oral suspension sugar free
48518	Atorvastatin 10mg/5ml oral solution
48867	Simvastatin 40mg tablets (Alliance Healthcare (Distribution) Ltd)
48973	Atorvastatin 30mg tablets
490	pravastatin tablets 10mg
49061	Simvastatin 40mg tablets (Bristol Laboratories Ltd)
49062	Simvastatin 20mg tablets (Alliance Healthcare (Distribution) Ltd)
49558	Atorvastatin 20mg tablets (A A H Pharmaceuticals Ltd)

49587	Simvastatin 80mg tablets (Almus Pharmaceuticals Ltd)
4961	LIPOBAY tablets 300micrograms [BAYER]
49751	Atorvastatin 40mg tablets (Alliance Healthcare (Distribution) Ltd)
5009	cerivastatin tablets 200micrograms
50236	Atorvastatin 10mg tablets (Zentiva)
50272	Atorvastatin 40mg tablets (Pfizer Ltd)
50483	Simvastatin 40mg tablets (Relonchem Ltd)
50564	Simvastatin 20mg tablets (Relonchem Ltd)
50670	Simvastatin 40mg tablets (Aurobindo Pharma Ltd)
50703	Simvastatin 40mg tablets (Accord Healthcare Ltd)
50754	Simvastatin 20mg tablets (Medreich Plc)
50788	Atorvastatin 20mg tablets (Pfizer Ltd)
50790	Atorvastatin 20mg tablets (Dexcel-Pharma Ltd)
50882	Simvastatin 40mg tablets (Somex Pharma)
50925	Pravastatin 10mg tablets (Sigma Pharmaceuticals Plc)
50963	Atorvastatin 40mg tablets (Teva UK Ltd)
51	simvastatin tablets 40mg
51085	Simvastatin 10mg tablets (Medreich Plc)
51134	Atorvastatin 10mg tablets (A A H Pharmaceuticals Ltd)
51166	Simvastatin 40mg tablets (Medreich Plc)
51200	Atorvastatin 40mg tablets (Arrow Generics Ltd)
51233	Simvastatin 10mg tablets (Alliance Healthcare (Distribution) Ltd)
51359	Atorvastatin 20mg tablets (Arrow Generics Ltd)
5148	simvastatin tablets 80mg
51483	Simvastatin 20mg tablets (Aurobindo Pharma Ltd)
51622	Atorvastatin 20mg tablets (Consilient Health Ltd)
51676	Pravastatin 40mg tablets (Medreich Plc)
51715	Simvastatin 10mg tablets (Sigma Pharmaceuticals Plc)
51876	Atorvastatin 40mg tablets (Consilient Health Ltd)
51890	Pravastatin 20mg tablets (Medreich Plc)
52097	Atorvastatin 40mg tablets (Wockhardt UK Ltd)
52098	Simvastatin 40mg tablets (Ranbaxy (UK) Ltd)
52168	Atorvastatin 20mg tablets (Aspire Pharma Ltd)
52211	Atorvastatin 20mg tablets (Actavis UK Ltd)
52257	Simvastatin 20mg tablets (Accord Healthcare Ltd)
52397	Atorvastatin 40mg tablets (Dr Reddy's Laboratories (UK) Ltd)
52398	Atorvastatin 40mg tablets (A A H Pharmaceuticals Ltd)
52459	Atorvastatin 80mg tablets (Actavis UK Ltd)
52460	Atorvastatin 40mg tablets (Aspire Pharma Ltd)
5251	cerivastatin tablets 300micrograms
52625	Simvastatin 10mg tablets (Wockhardt UK Ltd)
52676	Simvastatin 10mg/5ml oral suspension
52755	Pravastatin 20mg tablets (Alliance Healthcare (Distribution) Ltd)
5278	cerivastatin tablets 400micrograms
52812	Simvastatin 20mg tablets (Sigma Pharmaceuticals Plc)
52821	Atorvastatin 80mg tablets (Dr Reddy's Laboratories (UK) Ltd)

52953	Simvastatin 20mg tablets (Bristol Laboratories Ltd)
52962	Simvastatin 80mg tablets (Medreich Plc)
53087	Simvastatin 20mg tablets (Somex Pharma)
53340	Zocor 40mg tablets (Lexon (UK) Ltd)
53415	Simvastatin 10mg tablets (Aurobindo Pharma Ltd)
53460	Crestor 10mg tablets (DE Pharmaceuticals)
53594	Lipitor 80mg tablets (Mawdsley-Brooks & Company Ltd)
53676	Simvastatin 20mg tablets (Tillomed Laboratories Ltd)
53770	Fluvastatin 40mg capsules (A A H Pharmaceuticals Ltd)
53772	Atorvastatin 80mg tablets (Alliance Healthcare (Distribution) Ltd)
53822	Simvastatin 10mg tablets (Bristol Laboratories Ltd)
53887	Atorvastatin 40mg tablets (Actavis UK Ltd)
53890	Atorvastatin 80mg tablets (Pfizer Ltd)
53908	Simvastatin 10mg tablets (Dexcel-Pharma Ltd)
53966	Simvastatin 40mg tablets (Phoenix Healthcare Distribution Ltd)
54240	Simvastatin 40mg tablets (Sigma Pharmaceuticals Plc)
54266	Simvastatin 20mg/5ml oral suspension
54435	Pravastatin 40mg tablets (Almus Pharmaceuticals Ltd)
54493	Simvastatin 10mg tablets (Relonchem Ltd)
54535	Atorvastatin 10mg tablets (Pfizer Ltd)
54606	Simvastatin 20mg/5ml oral suspension sugar free (A A H Pharmaceuticals Ltd)
54607	Pravastatin 20mg tablets (Almus Pharmaceuticals Ltd)
54655	Simvastatin 10mg tablets (Accord Healthcare Ltd)
54819	Simvastatin 40mg/5ml oral suspension sugar free (Rosemont Pharmaceuticals Ltd)
54947	Simvastatin 20mg tablets (Almus Pharmaceuticals Ltd)
54976	Simvastatin 10mg tablets (Somex Pharma)
54985	Simvastatin 40mg/5ml oral suspension
54992	Atorvastatin 10mg/5ml oral suspension
55032	Atorvastatin 10mg tablets (Dexcel-Pharma Ltd)
55034	Atorvastatin 40mg/5ml oral suspension
55444	Atorvastatin 40mg tablets (Zentiva)
55452	Simvastatin 20mg tablets (Phoenix Healthcare Distribution Ltd)
55727	Atorvastatin 10mg tablets (Actavis UK Ltd)
55912	Pravastatin 40mg tablets (Alliance Healthcare (Distribution) Ltd)
56016	Lipitor 20mg chewable tablets (Pfizer Ltd)
56065	Simvastatin 20mg/5ml oral suspension sugar free (Waymade Healthcare Plc)
56097	Atorvastatin 10mg chewable tablets sugar free
56146	Pravastatin 10mg tablets (Waymade Healthcare Plc)
56165	Atorvastatin 20mg chewable tablets sugar free
56182	Atorvastatin 80mg tablets (Zentiva)
56248	Atorvastatin 20mg tablets (Sigma Pharmaceuticals Plc)
56481	Zocor 10mg tablets (Sigma Pharmaceuticals Plc)
56494	Zocor 20mg tablets (Sigma Pharmaceuticals Plc)
56564	Atorvastatin 20mg tablets (Almus Pharmaceuticals Ltd)
56607	Pravastatin 20mg tablets (Waymade Healthcare Plc)
56735	Pravastatin 20mg tablets (Mylan Ltd)

56841	Atorvastatin 40mg tablets (Dexcel-Pharma Ltd)
56893	Pravastatin 40mg tablets (Accord Healthcare Ltd)
56916	Pravastatin 40mg tablets (PLIVA Pharma Ltd)
57108	Pravastatin 40mg tablets (Waymade Healthcare Plc)
57117	Atorvastatin 80mg tablets (Waymade Healthcare Plc)
57137	Pravastatin 10mg tablets (Almus Pharmaceuticals Ltd)
57296	Pravastatin 20mg tablets (Phoenix Healthcare Distribution Ltd)
57329	Simvastatin 25mg/5ml oral suspension
57348	Atorvastatin 10mg tablets (Consilient Health Ltd)
57397	Pravastatin 10mg tablets (Accord Healthcare Ltd)
57568	Zocor 10mg tablets (Lexon (UK) Ltd)
5775	atorvastatin tablets 80mg
57763	Rosuvastatin 10mg tablets (Waymade Healthcare Plc)
57834	Atorvastatin 40mg tablets (DE Pharmaceuticals)
57836	Atorvastatin 80mg tablets (Teva UK Ltd)
57999	Crestor 40mg tablets (Lexon (UK) Ltd)
58041	Atorvastatin 20mg tablets (Teva UK Ltd)
58110	Atorvastatin 20mg tablets (Zentiva)
58315	Simvastatin 20mg tablets (Waymade Healthcare Plc)
58394	Atorvastatin 20mg tablets (Alliance Healthcare (Distribution) Ltd)
58418	Atorvastatin 80mg tablets (A A H Pharmaceuticals Ltd)
58617	Rosuvastatin 20mg/5ml oral suspension
58742	Atorvastatin 80mg tablets (Arrow Generics Ltd)
58755	Simvastatin 10mg tablets (Phoenix Healthcare Distribution Ltd)
58834	Atorvastatin 10mg tablets (DE Pharmaceuticals)
58868	Atorvastatin 10mg tablets (Sigma Pharmaceuticals Plc)
59272	Atorvastatin 20mg tablets (Waymade Healthcare Plc)
59278	Fluvastatin 20mg capsules (Zentiva)
59331	Lipitor 10mg tablets (DE Pharmaceuticals)
59357	Atorvastatin 10mg tablets (Ranbaxy (UK) Ltd)
59446	Atorvastatin 40mg tablets (Almus Pharmaceuticals Ltd)
59447	Crestor 20mg tablets (Waymade Healthcare Plc)
59452	Rosuvastatin 5mg tablets (Waymade Healthcare Plc)
59508	Pravastatin 20mg tablets (Accord Healthcare Ltd)
59776	Atorvastatin 80mg tablets (Aspire Pharma Ltd)
5985	LESCOL XL tablets 80mg [NOVARTIS]
59859	Atorvastatin 10mg tablets (Teva UK Ltd)
60160	Rosuvastatin 5mg tablets (Mawdsley-Brooks & Company Ltd)
60251	Pravastatin 10mg tablets (Sandoz Ltd)
60464	Atorvastatin 20mg/5ml oral suspension
60511	Atorvastatin 40mg tablets (Ranbaxy (UK) Ltd)
60607	Atorvastatin 80mg tablets (DE Pharmaceuticals)
60989	Atorvastatin 80mg tablets (Phoenix Healthcare Distribution Ltd)
61134	Pravastatin 20mg tablets (Sigma Pharmaceuticals Plc)
61149	Atorvastatin 10mg tablets (Waymade Healthcare Plc)
61155	Simvastatin 40mg/5ml oral suspension sugar free (A A H Pharmaceuticals Ltd)

61321	Simvastatin 10mg tablets (Sandoz Ltd)
61360	Simvastatin 10mg tablets (Almus Pharmaceuticals Ltd)
61665	Simvastatin 10mg tablets (Waymade Healthcare Plc)
6168	ZOCOR tablets 40mg [M S D]
6213	rosuvastatin tablets 20mg
62137	Simvastatin 40mg tablets (Waymade Healthcare Plc)
62148	Fluvastatin 20mg capsules (Actavis UK Ltd)
62219	Atorvastatin 20mg tablets (DE Pharmaceuticals)
62429	Atorvastatin 20mg tablets (DE Pharmaceuticals)
62476	Atorvastatin 80mg tablets (Almus Pharmaceuticals Ltd)
62979	Pravastatin 40mg tablets (Kent Pharmaceuticals Ltd)
63074	Pravastatin 20mg tablets (PLIVA Pharma Ltd)
63140	Atorvastatin 10mg tablets (Alliance Healthcare (Distribution) Ltd)
63249	Atorvastatin 80mg tablets (Consilient Health Ltd)
63469	Atorvastatin 30mg tablets (Consilient Health Ltd)
63787	Pravastatin 10mg tablets (Tillomed Laboratories Ltd)
64067	Atorvastatin 20mg/5ml oral solution
64104	Simvastatin 20mg tablets (Crescent Pharma Ltd)
64180	Simvastatin 10mg tablets (Crescent Pharma Ltd)
64307	Simvastatin 40mg tablets (Crescent Pharma Ltd)
64702	Atorvastatin 30mg tablets (A A H Pharmaceuticals Ltd)
64810	Atorvastatin 40mg tablets (Phoenix Healthcare Distribution Ltd)
64825	Atorvastatin 10mg tablets (Phoenix Healthcare Distribution Ltd)
64868	Atorvastatin 40mg tablets (Sigma Pharmaceuticals Plc)
64968	Simvastatin 10mg tablets (DE Pharmaceuticals)
65181	Simvastatin 40mg tablets (DE Pharmaceuticals)
65193	Atorvastatin 20mg tablets (Ranbaxy (UK) Ltd)
65679	Simvastatin 20mg tablets (DE Pharmaceuticals)
65901	Simvastatin 40mg tablets (Zentiva)
65925	Simvastatin 20mg/5ml oral suspension sugar free (Alliance Healthcare (Distribution) Ltd)
66963	Atorvastatin 80mg tablets (Sigma Pharmaceuticals Plc)
713	rosuvastatin tablets 10mg
7196	ZOCOR tablets 20mg [M S D]
730	pravastatin tablets 20mg
7347	CRESTOR tablets 10mg [ASTRAZENEC]
7374	LIPITOR tablets 20mg [PFIZER]
745	atorvastatin tablets 40mg
75	atorvastatin tablets 20mg
7554	rosuvastatin tablets 5mg
802	SIMVADOR tablets 40mg [DISCOVERY]
818	simvastatin oral suspension sugar-free 20mg/5ml
8380	LESCOL capsules 20mg [NOV/SANDOZ]
9153	LESCOL capsules 40mg [NOV/SANDOZ]
9315	LIPOBAY tablets 100micrograms [BAYER]
9316	LIPOBAY tablets 200micrograms [BAYER]
9897	rosuvastatin tablets 40mg

9920	SIMVADOR tablets 20mg [DISCOVERY]
9930	CRESTOR tablets 40mg [ASTRAZENEC]
Other lipid lowering agents	
1214	BEZALIP mono-tablets 400mg [ROCHE]
1215	fenofibrate capsules 100mg
1217	LIPANTIL MICRO 200 capsules 200mg [FOURNIER]
1324	BEZALIP tablets 200mg [ROCHE]
14379	LIPANTIL MICRO capsules 67mg [ABBOTT]
17614	ZIMBACOL XL modified release tablet 400mg [ARCHIMEDES]
184	bezafibrate tablets 200mg
2215	LOPID capsules 300mg [PFIZER]
23153	LIPAROL XL modified release tablet 400mg [ASHBOURNE]
2435	LIPANTIL capsules 100mg [FOURNIER]
29213	BEZAGEN XL modified release tablet 400mg [GEN (UK)]
29328	BEZAFIBRATE tablets 200mg [HILLCROSS]
3089	ciprofibrate tablets 100mg
31221	BEZAFIBRATE tablets 200mg [GEN (UK)]
3159	fenofibrate capsules 200mg
31783	FENOGAL capsules 200mg [GENUS]
3318	gemfibrozil capsules 300mg
33603	FIBRAZATE XL tablets 400mg [SANDOZ]
33944	BEZAFIBRATE tablets 200mg [TEVA]
34181	BEZAFIBRATE modified release tablet 400mg [HILLCROSS]
34277	GEMFIBROZIL tablets 600mg [TEVA]
39420	BEZALIP MONO modified release tablet 400mg [ACTAVIS]
39576	BEZALIP tablets 200mg [ACTAVIS]
4062	LOPID tablets 600mg [PFIZER]
41396	FENOFIBRATE MICRO capsules 200mg [HILLCROSS]
42801	BEZAFIBRATE XL modified release tablet 400mg [GEN (UK)]
47935	FENOFIBRATE capsules 200mg [TEVA]
4920	fenofibrate micronised capsules 200mg
4928	LIPANTIL MICRO capsules 200mg [ABBOTT]
49609	Bezafibrate 400mg Modified-release tablet (Sandoz Ltd)
50071	Fenofibrate 160mg Tablet (Teva UK Ltd)
5216	BEZALIP MONO modified release tablet 400mg [ROCHE]
52814	Bezafibrate 400mg modified-release tablets (Alliance Healthcare (Distribution) Ltd)
53250	Modalim 100mg tablets (Lexon (UK) Ltd)
5390	fenofibrate micronised capsules 267mg
57219	Fenofibrate micronised 200mg capsules (Sandoz Ltd)
57489	Ciprofibrate 100mg tablets (Zentiva)
58635	Bezalip Mono 400mg modified-release tablets (DE Pharmaceuticals)
59002	Bezafibrate 400mg modified-release tablets (DE Pharmaceuticals)
602	bezafibrate modified release tablet 400mg
60385	Bezalip Mono 400mg modified-release tablets (Lexon (UK) Ltd)
60788	Fenofibrate micronised 267mg capsules (Zentiva)
63737	Fenofibrate micronised 267mg capsules (Sigma Pharmaceuticals Plc)

64503	Bezalip Mono 400mg modified-release tablets (Waymade Healthcare Plc)
64933	Fenofibrate micronised 267mg capsules (Ranbaxy (UK) Ltd)
64984	Fenofibrate micronised 160mg tablets (Phoenix Healthcare Distribution Ltd)
65572	Fenofibrate micronised 160mg tablets (Genus Pharmaceuticals Ltd)
66087	Modalim 100mg tablets (Mawdsley-Brooks & Company Ltd)
66425	Bezafibrate 400mg modified-release tablets (A A H Pharmaceuticals Ltd)
66564	Bezafibrate 400mg modified-release tablets (Phoenix Healthcare Distribution Ltd)
7540	LIPANTIL MICRO capsules 267mg [ABBOTT]
8082	gemfibrozil tablets 600mg
8706	MODALIM tablets 100mg [SANOFI/AVE]
9491	fenofibrate micronised capsules 67mg
9639	fenofibrate micronised tablets 160mg
9716	SUPRALIP tablets 160mg [ABBOTT]
10094	NIASPAN TITRATION PACK modified release tablet 375mg + 500mg + 750mg [ABBOTT]
11785	colestyramine powder sugar-free 4g
11976	NIASPAN modified release tablet 500mg [ABBOTT]
1212	colestipol granules
12211	nicotinic acid tablets 50mg
14963	nicotinic acid modified release tablet 500mg
1716	QUESTRAN sachets 4g [BRISTOL]
1764	QUESTRAN LIGHT sachets 4g [BRISTOL]
17813	nicotinic acid tablets 100mg
17824	nicotinic acid tablets 25mg
18081	COLESTID ORANGE granules [PHARMACIA]
18098	nicotinic acid modified release tablet 375mg + 500mg + 750mg
18126	nicotinic acid modified release tablet 1000mg
19938	colestipol with aspartame granules
23956	MAXEPA emulsion [SEVEN SEAS]
24084	COLESTYRAMINE sachets 4g [PLIVA]
24583	nicotinic acid modified release tablet 750mg
2662	MAXEPA capsules 1g [SEVEN SEAS]
3204	MAXEPA liquid [SEVEN SEAS]
32110	COLESTYRAMINE sachets 4g [DOMINION]
34201	COLESTYRAMINE sachets 4g [ACTAVIS]
37266	colesevelam hydrochloride tablets 625mg
37953	CHOLESTAGEL tablets 625mg [GENZYME]
4067	OLBETAM capsules 250mg [PHARMACIA]
40729	TREDAPTIVE modified release tablet 1g + 20mg [M S D]
40885	nicotinic acid with laropiprant modified release tablet 1g + 20mg
5564	COLESTID orange sachets [PHARMACIA]
60101	colestyramine 4g oral powder sachets sugar free (Teva UK Ltd)
61087	Questran Light 4g oral powder sachets (Mawdsley-Brooks & Company Ltd)
6120	EZETROL tablets 10mg [M S D]
6155	colestyramine with aspartame powder sugar-free 4g
6365	COLESTID granules [PHARMACIA]
644	colestyramine powder 4g

653	ezetimibe tablets 10mg
6572	OMACOR capsules [ABBOTT]
7544	NIASPAN modified release tablet 750mg [ABBOTT]
7551	NIASPAN modified release tablet 1000mg [ABBOTT]
8104	acipimox capsules 250mg

Suppl. Table 4.1: Incidence rates and hazard ratios of cardiovascular events in patients with unspecified adrenal insufficiency and matched controls

Outcomes	Unspecified adrenal insufficiency				Controls				Incidence rate difference per 1000 person-years (95% CI)	P	Unadjusted HR (95% CI)	P	Adjusted HR (95% CI)	P
	No. at risk	No. 1st event	Person-years	Incidence per 1000 person-years (95% CI)	No. at risk	No. 1st event	Person-years	Incidence per 1000 person-years (95% CI)						
Composite cardiovascular disease	821	139	3607	38.5 (32.6-45.5)	8064	1150	38340	30.0 (28.3-31.8)	8.5 (1.9-15.2)	0.0033	1.26 (1.05-1.50)	0.011	0.98 (0.81-1.17)	0.80
Ischaemic heart disease	821	63	3822	16.5 (12.9-21.1)	8064	473	407445	11.6 (10.6-12.7)	4.9 (0.7-9.1)	0.0060	1.39 (1.07-1.81)	0.014	1.07 (0.81-1.40)	0.63
Cerebrovascular disease	821	40	3928	10.2 (7.5-13.9)	8064	405	41537	9.8 (8.8-10.7)	0.4 (-2.9 to 3.7)	0.38	1.03 (0.74-1.42)	0.87	0.85 (0.61-1.19)	0.34

Note: † Adjustment for previous cardiovascular disease, baseline diabetes mellitus, hypertension and dyslipidaemia, and smoking any time

Suppl. Table 4.2: Incidence rates of cardiovascular events in patients with adrenal insufficiency of any type and controls, according to calendar years of clinical care

Cohort	Adrenal insufficiency of any type				Controls				Incidence rate difference per 1000 person-years (95% CI)	p
	No. at risk	No. 1st event	Person-year	Incidence per 1000 person-years (95% CI)	No. at risk	No.1st event	Person-year	Incidence per 1000 person-years (95% CI)		
Composite cardiovascular disease										
Previous	3455	810	26176	30.9 (28.9-33.2)	34214	6353	268998	23.6 (23.0-24.2)	7.3 (5.1 to 9.5)	<0.0001
Recent	3366	336	10316	32.6 (29.3-36.2)	33350	2600	97714	26.6 (25.6-27.7)	6.0 (2.3 to 9.6)	0.0003
Ischaemic heart disease										
Previous	3455	349	27993	12.5 (11.2-13.8)	34214	3045	284754	10.7 (10.3-11.1)	1.8 (0.4 to 3.1)	0.0038
Recent	3366	126	10775	11.7 (9.8-13.9)	33350	1013	101267	10.0 (9.4-10.6)	1.7 (-0.4 to 3.8)	0.051
Cerebrovascular disease										
Previous	3455	302	28674	10.5 (9.4-11.8)	34214	2120	294383	7.2 (6.9-7.5)	3.3 (2.1 to 4.6)	<0.0001
Recent	3366	110	10796	10.2 (8.5-12.3)	33350	748	102150	7.3 (6.8-7.9)	2.9 (0.9 to 4.8)	0.0009

Note: Earlier care= before mid-2007; Recent care= at or after mid-2007

Suppl. Table 4.3: Incidence rates of cardiovascular events in patients with primary adrenal insufficiency and controls, according to calendar years of clinical care

Cohort	Primary adrenal insufficiency				Controls				Incidence rate difference per 1000 person-years (95% CI)	p
	No. at risk	No. 1st event	Person-year	Incidence per 1000 person-years (95% CI)	No. at risk	No.1st event	Person-year	Incidence per 1000 person-years (95% CI)		
Composite cardiovascular disease										
Previous	1137	232	9042	25.7 (22.6-29.2)	11189	1991	91980	21.6 (20.7-22.6)	4.0 (0.6 to 7.4)	0.0081
Recent	915	82	2696	30.4 (24.5-37.8)	9177	636	26677	23.8 (22.1-25.8)	6.6 (-0.3 to 13.4)	0.021
Ischaemic heart disease										
Previous	1137	107	9524	11.2 (9.3-13.6)	11189	981	96859	10.1 (9.5-10.8)	1.1 (-1.1 to 3.3)	0.15
Recent	915	34	2813	12.1 (8.6-16.9)	9177	252	27626	9.1 (8.1-10.3)	3.0 (-1.3 to 7.2)	0.066
Cerebrovascular disease										
Previous	1137	65	9861	6.6 (5.2-8.4)	11189	663	100223	6.6 (6.1-7.1)	-0.0 (-1.7 to 1.7)	0.49
Recent	915	26	2830	9.2 (6.3-13.5)	9177	191	27796	6.9 (6.0-7.9)	2.3 (-1.3 to 6.0)	0.086

Note: Earlier care= before mid-2007; Recent care= at or after mid-2007

Suppl. Table 4.4: Incidence rates of cardiovascular events in patients with secondary adrenal insufficiency and controls, according to calendar years of clinical care

Cohort	Secondary adrenal insufficiency				Controls				Incidence rate difference per 1000 person-years (95% CI)	p
	No. at risk	No. 1st event	Person-year	Incidence per 1000 person-years (95% CI)	No. at risk	No. 1st event	Person-year	Incidence per 1000 person-years (95% CI)		
Composite cardiovascular disease										
Previous	1962	490	14720	33.3 (30.5-36.4)	19495	3626	150595	24.1 (23.3-24.9)	9.2 (6.2 to 12.3)	<0.0001
Recent	1986	203	6228	31.6 (27.5-36.2)	19639	1550	59120	26.2 (24.9-27.6)	5.4 (0.8 to 9.9)	0.0073
Ischaemic heart disease										
Previous	1962	201	15874	12.7 (11.0-14.5)	19495	1734	159616	10.9 (10.4-11.4)	1.8 (-0.0 to 3.6)	0.021
Recent	1986	70	6733	10.4 (8.2-13.1)	19639	618	61176	10.1 (9.3-10.9)	0.3 (-2.3 to 2.9)	0.40
Cerebrovascular disease										
Previous	1962	211	16132	13.1 (11.4-15.0)	19495	1192	165062	7.2 (6.8-7.6)	5.9 (4.0 to 7.7)	<0.0001
Recent	1986	70	6719	10.4 (8.2-13.2)	19639	417	61915	6.7 (6.1-7.4)	3.7 (1.2 to 6.2)	0.0006

Note: Earlier care= before mid-2007; Recent care= at or after mid-2007

Suppl. Table 4.5: Incidence rates of cardiovascular events in patients with adrenal insufficiency of any type and controls, categorised by men and women

Population category	Adrenal insufficiency of any type				Controls				Incidence rate difference per 1000 person-years (95% CI)	P
	No. at risk	No. 1st event	Person-years	Incidence per 1000 person-years (95% CI)	No. at risk	No. 1st event	Person-years	Incidence per 1000 person-years (95% CI)		
Composite cardiovascular disease										
Men	3173	611	16562	36.9 (34.1-39.9)	31283	5142	165042	31.2 (30.3-32.0)	5.7 (2.7 to 8.8)	0.0001
Women	3648	535	19930	26.8 (24.7-29.2)	36281	3811	201669	18.9 (18.3-19.5)	7.9 (5.6 to 10.3)	<0.0001
Ischaemic heart disease										
Men	3173	273	17719	15.4 (13.8-14.9)	31283	2512	175559	14.3 (13.8-14.9)	1.1 (-0.8 to 3.0)	0.12
Women	3648	202	21049	9.6 (8.4-11.0)	36281	1546	210462	7.3 (7.0-7.7)	2.3 (0.9 to 3.6)	0.0003
Cerebrovascular disease										
Men	3173	200	18236	11.0 (9.5-12.6)	31283	1470	183032	8.0 (7.6-8.5)	2.9 (1.4 to 4.5)	<0.0001
Women	3648	212	21234	10.0 (8.7-11.4)	36281	1398	213500	6.5 (6.2-6.9)	3.4 (2.0 to 4.8)	<0.0001

Suppl. Table 4.6: Incidence rates of cardiovascular events in patients with primary adrenal insufficiency and controls, categorised by men and women

Population category	Primary adrenal insufficiency				Controls				Incidence rate difference per 1000 person-years (95% CI)	P
	No. at risk	No. 1st event	Person-years	Incidence per 1000 person-years (95% CI)	No. at risk	No. 1st event	Person-years	Incidence per 1000 person-years (95% CI)		
Composite cardiovascular disease										
Men	860	147	4892	30.1 (25.6-35.3)	8483	1278	48670	26.3 (24.9-27.7)	3.8 (-1.3 to 8.9)	0.062
Women	1192	167	6846	24.4 (21.0-28.4)	11883	1349	69987	19.3 (18.3-20.3)	5.1 (1.3 to 9.0)	0.0026
Ischaemic heart disease										
Men	860	68	5149	13.2 (10.4-16.8)	8483	659	51271	12.9 (11.9-13.9)	0.4 (-2.9 to 3.6)	0.40
Women	1192	73	7189	10.2 (8.1-12.8)	11883	574	73213	7.8 (7.2-8.5)	2.3 (-0.1 to 4.7)	0.021
Cerebrovascular disease										
Men	860	36	5381	6.7 (4.8-9.3)	8483	354	53594	6.6 (6.0-7.3)	0.1 (-2.2 to 2.4)	0.46
Women	1192	55	7310	7.5 (5.8-9.8)	11883	500	74424	6.7 (6.2-7.3)	0.8 (-1.3 to 2.9)	0.21

Suppl. Table 4.7: Incidence rates of cardiovascular events in patients with secondary adrenal insufficiency and controls, categorised by men and women

Population category	Secondary adrenal insufficiency				Controls				Incidence rate difference per 1000 person-years (95% CI)	P
	No. at risk	No. 1st event	Person-years	Incidence per 1000 person-years (95% CI)	No. at risk	No. 1st event	Person-years	Incidence per 1000 person-years (95% CI)		
Composite cardiovascular disease										
Men	1971	404	10295	39.2 (35.6-42.3)	19474	3292	101321	32.5 (31.4-33.6)	6.8 (2.8 to 10.7)	0.0002
Women	1977	289	10853	26.6 (23.7-29.9)	19660	1884	108393	17.4 (16.6-18.2)	9.2 (6.1 to 12.4)	<0.0001
Ischaemic heart disease										
Men	1971	177	11125	15.9 (13.7-18.4)	19474	1596	108143	14.8 (14.1-15.5)	1.2 (-1.3 to 3.6)	0.17
Women	1977	94	11483	8.2 (6.7-10.0)	19660	756	112649	6.7 (6.2-7.2)	1.5 (-0.2 to 3.2)	0.037
Cerebrovascular disease										
Men	1971	147	11348	13.0 (11.0-15.2)	19474	940	112775	8.3 (7.8-8.9)	4.6 (2.5 to 6.8)	<0.0001
Women	1977	134	11503	11.6 (9.8-13.8)	19660	669	114202	5.9 (5.4-6.3)	5.8 (3.8 to 7.8)	<0.0001

Suppl. Table 4.8: Incidence rates of cardiovascular events in patients with adrenal insufficiency of any type and controls, categorised by younger and older age at start of follow-up

Population category	Adrenal insufficiency of any type				Controls				Incidence rate difference per 1000 person-years (95% CI)	P
	No. at risk	No. 1st event	Person-years	Incidence per 1000 person-years (95% CI)	No. at risk	No. 1st event	Person-years	Incidence per 1000 person-years (95% CI)		
Composite cardiovascular disease										
Age <50	2930	130	18647	7.0 (5.9-8.3)	29407	642	177321	3.6 (3.4-3.9)	3.4 (2.1 to 4.6)	<0.0001
Age ≥50	3891	1016	17846	56.9 (53.5-60.5)	38157	8311	189390	43.9 (42.9-44.8)	13.0 (9.4 to 16.7)	<0.0001
Ischaemic heart disease										
Age <50	2930	47	18987	2.5 (1.9-3.3)	29407	326	178860	1.8 (1.6-2.0)	0.7 (-0.1 to 1.4)	0.028
Age ≥50	3891	428	19781	21.6 (19.7-23.8)	38157	3732	207162	18.0 (17.4-18.6)	3.6 (1.5 to 5.8)	0.0002
Cerebrovascular disease										
Age <50	2930	58	19003	3.1 (2.4-3.9)	29407	184	179931	1.0 (0.9-1.2)	2.0 (1.2-2.8)	<0.0001
Age ≥50	3891	354	20467	17.3 (15.6-19.2)	38157	2684	216602	12.4 (11.9-12.9)	4.9 (3.0 to 6.8)	<0.0001

Suppl. Table 4.9: Incidence rates of cardiovascular events in patients with primary adrenal insufficiency and controls, categorised by younger and older age at start of follow-up

Population category	Primary adrenal insufficiency				Controls				Incidence rate difference per 1000 person-years (95% CI)	P
	No. at risk	No. 1st event	Person-years	Incidence per 1000 person-years (95% CI)	No. at risk	No. 1st event	Person-years	Incidence per 1000 person-years (95% CI)		
Composite cardiovascular disease										
Age <50	960	40	6557	6.1 (4.5-8.3)	9602	229	61749	3.7 (3.3-4.2)	2.4 (0.4 to 4.3)	0.0030
Age ≥50	1092	274	5181	52.9 (47.0-59.5)	10764	2398	56909	42.1 (40.5-43.9)	10.7 (4.3 to 17.2)	0.0003
Ischaemic heart disease										
Age <50	960	20	6624	3.0 (1.9-4.7)	9602	123	62282	2.0 (1.7-2.4)	1.0 (-0.3 to 2.4)	0.045
Age ≥50	1092	121	5713	21.2 (17.7-25.3)	10764	1110	62202	17.8 (16.8-18.9)	3.3 (-0.6 to 7.3)	0.039
Cerebrovascular disease										
Age <50	960	10	6700	1.5 (0.8-2.8)	9602	55	62808	0.9 (0.7-1.1)	0.6 (-0.3 to 1.6)	0.069
Age ≥50	1092	81	5991	13.5 (10.9-16.8)	10764	799	65211	12.3 (11.4-13.1)	1.3 (-1.8 to 4.3)	0.19

Suppl. Table 4.10: Incidence rates of cardiovascular events in patients with secondary adrenal insufficiency and controls, categorised by younger and older age at start of follow-up

Population category	Secondary adrenal insufficiency				Controls				Incidence rate difference per 1000 person-years (95% CI)	P
	No. at risk	No. 1st event	Person-years	Incidence per 1000 person-years (95% CI)	No. at risk	No. 1st event	Person-years	Incidence per 1000 person-years (95% CI)		
Composite cardiovascular disease										
Age <50	1673	79	10553	7.5 (6.0-9.3)	16833	368	99920	3.7 (3.3-4.1)	3.8 (2.1 to 5.5)	<0.0001
Age ≥50	2275	614	10595	58.0 (53.5-62.7)	22301	4808	109794	43.8 (42.6-45.0)	14.2 (9.4 to 18.9)	<0.0001
Ischaemic heart disease										
Age <50	1673	20	10816	1.8 (1.2-2.9)	16833	185	100815	1.8 (1.6-2.1)	0.0 (-0.8 to 0.9)	0.47
Age ≥50	2275	251	11792	21.3 (18.8-24.1)	22301	2167	119976	18.1 (17.3-18.8)	3.2 (0.5 to 6.0)	0.0078
Cerebrovascular disease										
Age <50	1673	48	10716	4.5 (3.4-5.9)	16833	118	101332	1.2 (1.0-1.4)	3.3 (2.0 to 4.6)	<0.0001
Age ≥50	2275	233	12135	19.2 (16.9-21.8)	22301	1491	125644	11.8 (11.3-12.5)	7.3 (4.8 to 9.9)	<0.0001

Suppl. Table 4.11: A comparison of baseline characteristics of patients with adrenal insufficiency of any type and controls, categorised by non-diabetes and diabetes at baseline

Baseline characteristics at the start of follow-up	Non-Diabetes			Diabetes		
	Patients (N= 6109)	Controls (N= 64347)	p	Patients (N= 712)	Controls (N= 3217)	p
Age; year, median (IQR)	53 (37-67)	53 (37-67)	0.15	61 (46-73)	69 (59-77)	<0.001
Men (%)	2806 (46%)	29461 (46%)	0.82	367 (52%)	1822 (57%)	0.013
Cardiovascular disease, (%)	960 (16%)	6385 (10%)	<0.0001	230 (32%)	1201 (37%)	0.012
Hypertension, (%)	1207 (20%)	7539 (12%)	<0.0001	301 (42%)	1652 (51%)	<0.0001
Dyslipidaemia, (%)	1013 (17%)	2654 (4%)	<0.0001	384 (54%)	753 (23%)	<0.0001
Statin use, (%)	965 (16%)	2568 (4%)	<0.0001	374 (53%)	737 (23%)	<0.0001
Ever smoked before end date, (%)	2569 (42%)	27404 (43%)	0.41	359 (50%)	1710 (53%)	0.18

Suppl. Table 4.12: Incidence rates of cardiovascular events in patients with adrenal insufficiency of any type and controls, categorised by non-diabetes and diabetes at baseline

Population category	Adrenal insufficiency of any type				Controls				Incidence rate difference per 1000 person-years (95% CI)	P
	No. at risk	No. 1st event	Person-years	Incidence per 1000 person-years (95% CI)	No. at risk	No. 1st event	Person-years	Incidence per 1000 person-years (95% CI)		
Composite cardiovascular disease										
Non-diabetes	6109	974	33568	29.0 (27.2-30.9)	64347	8086	356098	22.7 (22.2-23.2)	4.4 (6.3 to 8.2)	<0.0001
Diabetes	712	172	2925	58.8 (50.6-68.3)	3217	867	10614	81.7 (76.4-87.3)	-22.9 (-33.2 to -12.5)	<0.0001
Ischaemic heart disease										
Non-diabetes	6109	394	35604	11.1 (10.0-12.2)	64347	3634	374024	9.7 (9.4-10.0)	1.4 (0.2-2.5)	0.0078
Diabetes	712	81	3163	25.6 (20.6-31.8)	3217	424	11997	35.3 (32.1-38.8)	-9.7 (-16.2 to -3.2)	0.0031
Cerebrovascular disease										
Non-diabetes	6109	365	36109	10.1 (9.1-11.2)	64347	2607	383607	6.8 (6.5-7.1)	3.3 (2.2 to 4.4)	<0.0001
Diabetes	712	47	3361	14.0 (10.5-18.6)	3217	261	12926	20.2 (17.9-22.8)	-6.2 (-10.9 to -1.5)	0.0083

Suppl. Table 4.13: Incidence rates of cardiovascular events in patients with primary adrenal insufficiency and controls, categorised by non-diabetes and diabetes at baseline

Population category	Primary adrenal insufficiency				Controls				Incidence rate difference per 1000 person-years (95% CI)	P
	No. at risk	No. 1st event	Person-years	Incidence per 1000 person-years (95% CI)	No. at risk	No. 1st event	Person-years	Incidence per 1000 person-years (95% CI)		
Composite cardiovascular disease										
Non-diabetes	1792	254	10447	24.3 (21.5-27.5)	19525	2404	115734	20.8 (20.0-21.6)	3.5 0.4 to 6.6)	0.0095
Diabetes	260	60	1290	46.5 (36.1-59.9)	841	223	2923	76.3 (66.9-87.0)	-29.8 (-45.2 to -14.3)	0.0002
Ischaemic heart disease										
Non-diabetes	1792	107	10948	9.8 (8.1-11.8)	19525	1119	121198	9.2 (8.7-9.8)	0.5 (-1.4 to 2.5)	0.28
Diabetes	260	34	1389	24.5 (17.5-34.3)	841	114	3287	34.7 (28.9-41.7)	-10.2 (-20.6 to 0.2)	0.034
Cerebrovascular disease										
Non-diabetes	1792	79	11215	7.0 (5.7-8.8)	19525	785	124478	6.3 (5.9-6.8)	0.7 (-0.9 to 2.4)	0.17
Diabetes	260	12	1476	8.1 (4.6-14.3)	841	69	3541	19.5 (15.4-24.7)	-11.4 (-17.9 to -4.9)	0.0012

Suppl. Table 4.14: Incidence rates of cardiovascular events in patients with secondary adrenal insufficiency and controls, categorised by non-diabetes and diabetes at baseline

Population category	Secondary adrenal insufficiency				Controls				Incidence rate difference per 1000 person-years (95% CI)	P
	No. at risk	No. 1st event	Person-years	Incidence per 1000 person-years (95% CI)	No. at risk	No. 1st event	Person-years	Incidence per 1000 person-years (95% CI)		
Composite cardiovascular disease										
Non-diabetes	3590	605	19796	30.6 (28.2-33.1)	37192	4649	203192	22.9 (22.2-23.5)	7.7 (5.2 to 10.2)	<0.0001
Diabetes	358	88	1352	65.1 (52.8-80.2)	1942	527	6523	80.8 (74.2-88.0)	-15.7 (-31.0 to -0.5)	0.028
Ischaemic heart disease										
Non-diabetes	3590	234	21151	11.1 (9.7-12.6)	37192	2097	213389	9.8 (9.4-10.3)	1.2 (-0.2 to 2.7)	0.044
Diabetes	358	37	1457	25.4 (18.4-35.1)	1942	255	7403	34.4 (30.5-38.9)	-9.0 (-18.3 to 0.2)	0.038
Cerebrovascular disease										
Non-diabetes	3590	254	21305	11.9 (10.5-13.5)	37192	1454	218994	6.6 (6.3-7.0)	5.3 (3.8 to 6.8)	<0.0001
Diabetes	358	27	1546	17.5 (12.0-25.5)	1942	155	7983	19.4 (16.6-22.7)	-1.9 (-9.2 to 5.3)	0.31

Suppl. Table 4.15: A comparison of baseline characteristics of patients with adrenal insufficiency of any type and controls, categorised by non-cardiovascular disease and cardiovascular disease at baseline

Baseline characteristics at the start of follow-up	Non-cardiovascular disease			Cardiovascular disease		
	Patients (N= 5631)	Controls (N= 59978)	p	Patients (N= 1190)	Controls (N= 7586)	p
Age, median (IQR)	49 (35-63)	50 (35-64)	0.0008	72 (63-79)	74 (66-80)	<0.0001
Men (%)	2500 (44%)	26696 (45%)	0.87	673 (57%)	4587 (60%)	0.010
Diabetes mellitus, (%)	482 (9%)	2016 (4%)	<0.0001	230 (19%)	1201 (16%)	0.002
Hypertension, (%)	938 (17%)	6076 (10%)	<0.0001	570 (48%)	3115 (41%)	<0.0001
Dyslipidaemia, (%)	755 (13%)	1833 (3%)	<0.0001	642 (54%)	1574 (21%)	<0.0001
Statin use, (%)	712 (13%)	1766 (3%)	<0.0001	627 (53%)	1539 (20%)	<0.0001
Ever smoked before end date, (%)	2296 (41%)	24996 (42%)	0.19	632 (53%)	4118 (54%)	0.44

Suppl. Table 4.16: Incidence rates of cardiovascular events in patients with adrenal insufficiency of any type and controls, categorised by non-cardiovascular disease and cardiovascular disease at baseline (non-CVD vs CVD)

Population category	Adrenal insufficiency of any type				Controls				Incidence rate difference per 1000 person-years (95% CI)	P
	No. at risk	No. 1st event	Person-years	Incidence per 1000 person-years (95% CI)	No. at risk	No. 1st event	Person-years	Incidence per 1000 person-years (95% CI)		
Composite cardiovascular disease										
Non-CVD	5631	640	33389	19.2 (17.7-20.7)	59978	5523	346286	15.9 (15.5-16.4)	3.2 (1.7 to 4.8)	<0.0001
CVD	1190	506	3103	163.1 (149.5-177.9)	7586	3430	20425	167.9 (162.4-173.6)	-4.9 (-20.1 to 10.4)	0.26
Ischaemic heart disease										
Non-CVD	5631	224	34903	6.4 (5.6-7.3)	59978	2224	359944	6.2 (5.9-6.4)	0.2 (-0.6 to 1.1)	0.29
CVD	1190	251	3864	65.0 (57.4-73.5)	7586	1834	26078	70.3 (67.2-73.6)	-5.4 (-14.0 to 3.3)	0.11
Cerebrovascular disease										
Non-CVD	5631	245	35041	7.0 (6.2-7.9)	59978	1815	364642	5.0 (4.8-5.2)	2.0 (1.1 to 2.9)	<0.0001
CVD	1190	167	4429	37.7 (32.4-43.9)	7586	1053	31891	33.0 (31.1-35.1)	4.7 (-1.4 to 10.7)	0.057

Suppl. Table 4.17: Incidence rates of cardiovascular events in patients with primary adrenal insufficiency and controls, categorised by non-cardiovascular disease and cardiovascular disease at baseline (non-CVD vs CVD)

Population category	Primary adrenal insufficiency				Controls				Incidence rate difference per 1000 person-years (95% CI)	P
	No. at risk	No. 1st event	Person-years	Incidence per 1000 person-years (95% CI)	No. at risk	No. 1st event	Person-years	Incidence per 1000 person-years (95% CI)		
Composite cardiovascular disease										
No CVD	1734	184	11028	16.7 (14.4-19.3)	18311	1669	112890	14.8 (14.1-15.5)	1.9 (-0.6 to 4.4)	0.061
CVD	318	130	710	183.2 (154.3-217.6)	2055	958	5767	166.1 (155.9-177.0)	17.1 (-16.1 to 50.3)	0.14
Ischaemic heart disease										
No CVD	1734	72	11422	6.3 (5.0-7.9)	18311	693	117017	5.9 (5.5-6.4)	0.4 (-1.1 to 1.9)	0.30
CVD	318	69	915	75.4 (59.5-95.5)	2055	540	7468	72.3 (66.5-78.7)	3.1 (-15.7 to 21.9)	0.36
Cerebrovascular disease										
No CVD	1734	48	11601	4.1 (3.1-5.5)	18311	540	118596	4.6 (4.2-5.0)	-0.4 (-1.6 to 0.8)	0.26
CVD	318	43	1090	39.4 (29.3-53.2)	2055	314	9423	33.3 (29.8-37.2)	6.1 (-6.2 to 18.5)	0.15

Suppl. Table 4.18: Incidence rates of cardiovascular events in patients with secondary adrenal insufficiency and controls, categorised by non-cardiovascular disease and cardiovascular disease at baseline (non-CVD vs CVD)

Population category	Secondary adrenal insufficiency				Controls				Incidence rate difference per 1000 person-years (95% CI)	P
	No. at risk	No. 1st event	Person-years	Incidence per 1000 person-years (95% CI)	No. at risk	No. 1st event	Person-years	Incidence per 1000 person-years (95% CI)		
Composite cardiovascular disease										
No CVD	3268	387	19194	20.2 (18.3-22.3)	34696	3186	197690	16.1 (15.6-16.7)	4.0 (2.0 to 6.1)	<0.0001
CVD	680	306	1954	156.6 (140.0-175.2)	4438	1990	12024	165.5 (158.4-172.9)	-8.9 (-27.9 to 10.1)	0.18
Ischaemic heart disease										
No CVD	3268	124	20180	6.1 (5.2-7.3)	3496	1283	205559	6.2 (5.9-6.6)	-0.1 (-1.2 to 1.0)	0.43
CVD	680	147	2428	60.5 (51.5-71.2)	4438	1069	15233	70.2 (66.1-74.5)	-9.6 (-20.3 to 1.0)	0.044
Cerebrovascular disease										
No CVD	3268	181	20078	9.0 (7.8-10.4)	34696	1035	208369	5.0 (4.7-5.3)	4.0 (2.7 to 5.4)	<0.0001
CVD	680	100	2773	36.1 (29.6-43.9)	4438	574	18608	30.8 (28.4-33.5)	5.2 (-2.3 to 12.7)	0.076

Suppl. Table 4.19: A comparison of baseline characteristics of patients with adrenal insufficiency of any type and controls, categorised by non-statin use and statin use at baseline

Baseline characteristics at the start of follow-up	Non-statin use			Statin use		
	Patients (N= 5482)	Controls (N= 64259)	p	Patients (N= 1339)	Controls (N= 3305)	p
Age; year, median (IQR)	49 (34-64)	52 (37-67)	<0.0001	67 (59-75)	69 (61-77)	<0.0001
Men (%)	2445 (45%)	29411 (46%)	0.095	728 (54%)	1872 (57%)	0.15
Cardiovascular disease, (%)	563 (10%)	6047 (9%)	0.037	627 (47%)	1539 (47%)	0.87
Diabetes mellitus, (%)	338 (6%)	2480 (4%)	<0.0001	374 (28%)	737 (22%)	<0.0001
Hypertension, (%)	799 (15%)	7676 (12%)	<0.0001	709 (53%)	1515 (46%)	<0.0001
Ever smoked before end date, (%)	2141 (39%)	27095 (42%)	<0.0001	787 (59%)	2019 (61%)	0.14

Note: The proportion of dyslipidaemia is not shown here as it was defined using lipid-lowering agents, where the great majority was statins

Suppl. Table 4.20: Incidence rates of cardiovascular events in patients with adrenal insufficiency of any type and controls, categorised by non-statin use and statin use at baseline

Population category	Adrenal insufficiency of any type				Controls				Incidence rate difference per 1000 person-years (95% CI)	P
	No. at risk	No. 1st event	Person-years	Incidence per 1000 person-years (95% CI)	No. at risk	No. 1st event	Person-years	Incidence per 1000 person-years (95% CI)		
Composite cardiovascular disease										
Non-statin use	5482	784	31894	24.6 (22.9-26.4)	64259	8103	355549	22.8 (22.3-23.3)	1.8 (0.0-3.6)	0.022
Statin use	1339	362	4598	78.7 (71.0-87.3)	3305	850	11162	76.1 (71.2-81.4)	2.6 (-7.0 to 12.2)	0.29
Ischaemic heart disease										
Non-statin use	5482	294	33655	8.7 (7.8-9.8)	64259	3625	373494	9.7 (9.4-10.0)	-1.0 (-2.0 to 0.1)	0.039
Statin use	1339	181	5112	35.4 (30.6-41.0)	3305	433	12527	34.6 (31.5-38.0)	0.8 (-5.3 to 6.9)	0.39
Cerebrovascular disease										
Non-statin use	5482	299	33934	8.8 (7.9-9.9)	64259	2628	382540	6.9 (6.6-7.1)	1.9 (0.9-3.0)	<0.0001
Statin use	1339	113	5536	20.4 (17.0-24.5)	3305	240	13993	17.2 (15.1-19.5)	3.3 (-1.1 to 7.6)	0.065

Suppl. Table 4.21: Incidence rates of cardiovascular events in patients with primary adrenal insufficiency and controls, categorised by non-statin use and statin use at baseline

Population category	Primary adrenal insufficiency				Controls				Incidence rate difference per 1000 person-years (95% CI)	P
	No. at risk	No. 1st event	Person-years	Incidence per 1000 person-years (95% CI)	No. at risk	No. 1st event	Person-years	Incidence per 1000 person-years (95% CI)		
Composite cardiovascular disease										
Non-statin use	1722	224	10597	21.1 (18.5-24.1)	19438	2378	115254	20.6 (19.8-21.5)	0.5 (-2.3 to 3.4)	0.36
Statin use	330	90	1141	78.9 (64.2-97.0)	928	249	3403	73.1 (64.6-82.8)	5.7 (-12.9 to 24.4)	0.26
Ischaemic heart disease										
Non-statin use	1722	91	11058	8.2 (6.7-10.1)	19438	1092	120674	9.0 (8.5-9.6)	-0.8 (-2.6 to 1.0)	0.19
Statin use	330	50	1279	39.1 (29.6-51.6)	928	141	3811	37.0 (31.4-43.6)	2.1 (-10.3 to 14.5)	0.36
Cerebrovascular disease										
Non-statin use	1722	63	11296	5.6 (4.4-7.1)	19438	786	123671	6.4 (5.9-6.8)	-0.8 (-2.2 to 0.7)	0.15
Statin use	330	28	1395	20.1 (13.9-29.1)	928	68	4348	15.6 (12.3-19.8)	4.4 (-3.9 to 12.7)	0.13

Suppl. Table 4.22: Incidence rates of cardiovascular events in patients with secondary adrenal insufficiency and controls, categorised by non-statin use and statin use at baseline

Population category	Secondary adrenal insufficiency				Controls				Incidence rate difference per 1000 person-years (95% CI)	P
	No. at risk	No. 1st event	Person-years	Incidence per 1000 person-years (95% CI)	No. at risk	No. 1st event	Person-years	Incidence per 1000 person-years (95% CI)		
Composite cardiovascular disease										
Non-statin use	3120	464	18188	25.5 (23.3-27.9)	37193	4683	203274	23.0 (22.4-23.7)	2.5 (0.1 to 4.9)	0.019
Statin use	828	229	2960	77.4 (68.0-88.1)	1941	493	6440	76.5 (70.1-83.6)	0.8 (-11.3 to 12.9)	0.44
Ischaemic heart disease										
Non-statin use	3120	166	19312	8.6 (7.4-10.0)	37193	2102	213580	9.8 (9.4-10.3)	-1.2 (-2.6 to 0.1)	0.044
Statin use	828	105	3296	31.9 (26.3-38.6)	1941	250	7212	34.7 (30.6-39.2)	-2.8 (-10.3 to 4.7)	0.23
Cerebrovascular disease										
Non-statin use	3120	208	19310	10.8 (9.4-12.3)	37193	1474	218928	6.7 (6.4-7.1)	4.0 (2.5 to 5.5)	<0.0001
Statin use	828	73	3541	20.6 (16.4-25.9)	1941	135	8048	16.8 (14.2-19.9)	3.8 (-1.7 to 9.3)	0.079

Suppl. Table 4.23: Mortality rates and hazard ratios of cardiovascular mortality in patients with unspecified adrenal insufficiency and matched controls

Outcomes	Unspecified adrenal insufficiency				Controls				Mortality rate difference per 1000 person-years (95% CI)	P	Unadjusted HR (95% CI)	P	Adjusted HR (95% CI) †	P
	No. at risk	No. 1st event	Person-years	Mortality per 1000 person-years (95% CI)	No. at risk	No. 1st event	Person-years	Mortality per 1000 person-years (95% CI)						
Circulatory system disease	396	16	1741	9.2 (5.6-15.0)	3928	140	18050	7.8 (6.6-9.2)	1.4 (-3.3 to 6.1)	0.25	1.18 (0.70-1.98)	0.52	1.07 (0.63-1.84)	0.79
Ischaemic heart disease	396	8	1741	4.6 (2.3-9.2)	3928	60	18050	3.3 (2.6-4.3)	1.3 (-2.0 to 4.6)	0.19	1.37 (0.66-2.87)	0.40	1.05 (0.48-2.27)	0.90
Cerebrovascular disease	396	2	1741	1.1 (0.3-4.6)	3928	40	18050	2.2 (1.6-3.0)	-1.1 (-2.8 to 0.7)	0.18	0.52 (0.12-2.14)	0.36	0.52 (0.12-2.19)	0.37

Note: † Adjustment for previous cardiovascular disease, baseline diabetes mellitus, hypertension and dyslipidaemia, and smoking any time

Suppl. Table 4.24: Mortality rates from cardiovascular disease in patients with adrenal insufficiency of any type and controls, categorised by men and women

Population category	Adrenal insufficiency of any type				Controls				Mortality rate difference per 1000 person-years (95% CI)	P
	No. at risk	No. death	Person-years	Mortality per 1000 person-years (95% CI)	No. at risk	No. death	Person-years	Mortality per 1000 person-years (95% CI)		
Disease of the circulatory system										
Men	1629	97	8560	11.3 (9.3-13.8)	16059	611	84038	7..3 (6.7-7.9)	4.1 (1.7 to 6.4)	0.0001
Women	1918	87	10033	8.7 (7.0-10.7)	18885	546	95795	5.7 (5.2-6.2)	2.3 (1.1 to 4.9)	0.0003
Ischaemic heart disease										
Men	1629	54	8560	6.3 (4.8-8.2)	16059	303	84038	3.6 (3.2-4.0)	2.7 (1.0 to 4.4)	0.0002
Women	1918	38	10033	3.8 (2.8-5.2)	18885	184	95795	1.9 (1.7-2.2)	1.9 (0.6 to 3.1)	0.0002
Cerebrovascular disease										
Men	1629	26	8560	3.0 (2.1-4.5)	16059	164	84038	2.0 (1.7-2.3)	1.1 (-0.1 to 2.3)	0.022
Women	1918	20	10033	2.0 (1.3-3.1)	18885	202	95795	2.1 (1.8-2.4)	-0.1 (-1.0 to 0.8)	0.41

Suppl. Table 4.25: Mortality rates from cardiovascular disease in patients with primary adrenal insufficiency and controls, categorised by men and women

Population category	Primary adrenal insufficiency				Controls				Mortality rate difference per 1000 person-years (95% CI)	P
	No. at risk	No. death	Person-years	Mortality per 1000 person-years (95% CI)	No. at risk	No. death	Person-years	Mortality per 1000 person-years (95% CI)		
Disease of the circulatory system										
Men	410	21	2235	9.4 (6.1-14.4)	4077	151	23098	6.5 (5.6-7.7)	2.9 (-1.3 to 7.0)	0.065
Women	605	37	3239	11.4 (8.3-15.8)	5948	180	31835	5.7 (4.9-6.5)	5.8 (2.0 to 9.5)	0.0002
Ischaemic heart disease										
Men	410	15	2235	6.7 (4.0-11.1)	4077	81	23098	3.5 (2.8-4.4)	3.2 (-0.3 to 6.7)	0.015
Women	605	16	3239	4.9 (3.0-8.1)	5948	63	31835	2.0 (1.5-2.5)	3.0 (0.5 to 5.4)	0.0014
Cerebrovascular disease										
Men	410	3	2235	1.3 (0.4-4.2)	4077	37	23098	1.6 (1.2-2.2)	-0.3 (-1.9 to 1.3)	0.41
Women	605	7	3239	2.2 (1.0-4.5)	5948	67	31835	2.1 (1.7-2.7)	0.1 (-1.6 to 1.7)	0.45

Suppl. Table 4.26: Mortality rates from cardiovascular disease in patients with secondary adrenal insufficiency and controls, categorised by men and women

Population category	Secondary adrenal insufficiency				Controls				Mortality rate difference per 1000 person-years (95% CI)	P
	No. at risk	No. death	Person-years	Mortality per 1000 person-years (95% CI)	No. at risk	No. death	Person-years	Mortality per 1000 person-years (95% CI)		
Disease of the circulatory system										
Men	1054	65	5623	11.6 (9.1-14.7)	10343	394	53540	7.4 (6.7-8.1)	4.2 (1.3 to 7.1)	0.0007
Women	1082	45	5753	7.8 (5.8-10.5)	10648	292	53310	5.5 (4.9-6.1)	2.3 (-0.0 to 4.7)	0.016
Ischaemic heart disease										
Men	1054	33	5623	5.9 (4.2-8.3)	10343	189	53540	3.5 (3.1-4.1)	2.3 (0.3 to 4.4)	0.0054
Women	1082	20	5753	3.5 (2.2-5.4)	10648	94	53310	1.8 (1.4-2.2)	1.7 (0.1 to 3.3)	0.0051
Cerebrovascular disease										
Men	1054	22	5623	3.9 (2.6-5.9)	10343	108	53540	2.0 (1.7-2.4)	1.9 (0.2-3.6)	0.0041
Women	1082	12	5753	2.1 (1.2-3.7)	10648	114	53310	2.1 (1.8-2.6)	-0.1 (-1.3 to 1.2)	0.48

Suppl. Table 4.27: Mortality rates from cardiovascular disease in patients with adrenal insufficiency of any type and controls, categorised by younger and older age at start of follow-up

Population category	Adrenal insufficiency of any type				Controls				Mortality rate difference per 1000 person-years (95% CI)	P
	No. at risk	No. death	Person-years	Mortality per 1000 person-years (95% CI)	No. at risk	No. death	Person-years	Mortality per 1000 person-years (95% CI)		
Disease of the circulatory system										
Age <50	1565	13	8620	1.5 (0.9-2.6)	15641	22	79428	0.3 (0.2-0.4)	1.2 (0.4 to 2.1)	<0.0001
Age ≥50	1982	171	9972	17.1 (14.7-19.9)	19303	1135	100405	11.3 (10.7-12.0)	5.8 (3.2 to 8.5)	<0.0001
Ischaemic heart disease										
Age <50	1565	6	8620	0.7 (0.3-1.5)	15641	12	79428	0.2 (0.1-0.3)	0.5 (-0.0 to 1.1)	0.0034
Age ≥50	1982	86	9972	8.6 (7.0-10.7)	19303	475	100405	4.7 (4.3-5.2)	3.9 (2.0 to 5.8)	<0.0001
Cerebrovascular disease										
Age <50	1565	2	8620	0.2 (0.1-0.9)	15641	6	79428	0.1 (0.0-0.2)	0.2 (-0.2 to 0.5)	0.10
Age ≥50	1982	44	9972	4.4 (3.3-5.9)	19303	360	100405	3.6 (3.2-4.0)	0.8 (-0.5 to 2.2)	0.099

Suppl. Table 4.28: Mortality rates from cardiovascular disease in patients with primary adrenal insufficiency and controls, categorised by younger and older age at start of follow-up

Population category	Primary adrenal insufficiency				Controls				Mortality rate difference per 1000 person-years (95% CI)	P
	No. at risk	No. death	Person-years	Mortality per 1000 person-years (95% CI)	No. at risk	No. death	Person-years	Mortality per 1000 person-years (95% CI)		
Disease of the circulatory system										
Age <50	484	7	2764	2.5 (1.2-5.3)	4855	6	25675	0.2 (0.1-0.5)	2.3 (0.4 to 4.2)	<0.0001
Age ≥50	531	51	2710	18.8 (14.3-24.8)	5170	325	29258	11.1 (10.0-12.4)	7.7 (2.4 to 13.0)	0.0005
Ischaemic heart disease										
Age <50	484	5	2764	1.8 (0.8-4.3)	4855	4	25675	0.2 (0.1-0.4)	1.7 (0.1 to 3.2)	0.0004
Age ≥50	531	26	2710	9.6 (6.5-14.1)	5170	140	29258	4.8 (4.1-5.6)	4.8 (1.0 to 8.6)	0.0013
Cerebrovascular disease										
Age <50	484	0	2764	NA	4855	0	25675	NA	NA	NA
Age ≥50	531	10	2710	3.7 (2.0-6.9)	5170	104	29258	3.6 (2.9-4.3)	0.1 (-2.3 to 2.5)	0.43

Suppl. Table 4.29: Mortality rates from cardiovascular disease in patients with secondary adrenal insufficiency and controls, categorised by younger and older age at start of follow-up

Population category	Secondary adrenal insufficiency				Controls				Mortality rate difference per 1000 person-years (95% CI)	P
	No. at risk	No. death	Person-years	Mortality per 1000 person-years (95% CI)	No. at risk	No. death	Person-years	Mortality per 1000 person-years (95% CI)		
Disease of the circulatory system										
Age <50	931	6	5190	1.2 (0.5-2.6)	9277	16	46960	0.3 (0.2-0.6)	0.8 (-0.1 to 1.8)	0.011
Age ≥50	1205	104	6187	16.8 (13.9-20.4)	11714	670	59890	11.2 (10.4-12.1)	5.6 (2.3 to 9.0)	0.0001
Ischaemic heart disease										
Age <50	931	1	5190	0.2 (0.0-1.4)	9277	8	46960	0.2 (0.1-0.3)	0.0 (-0.4 to 0.4)	0.41
Age ≥50	1205	52	6187	8.4 (6.4-11.0)	11714	275	59890	4.6 (4.1-5.2)	3.8 (1.5 to 6.2)	0.0001
Cerebrovascular disease										
Age <50	931	2	5190	0.4 (0.1-1.5)	9277	6	46960	0.1 (0.0-0.3)	0.3 (-0.3 to 0.8)	0.11
Age ≥50	1205	32	6187	5.2 (3.7-7.3)	11714	216	59890	3.6 (3.2-4.1)	1.6 (-0.3 to 3.4)	0.033

Suppl. Table 4.30: A comparison of baseline characteristics of patients with adrenal insufficiency of any type and controls who had linked data, categorised by non-diabetes and diabetes at baseline

Baseline characteristics at the start of follow-up	Non-Diabetes			Diabetes		
	Patients (N= 3171)	Controls (N= 33071)	p	Patients (N= 376)	Controls (N= 1873)	p
Age; year, median (IQR)	52 (36-67)	51 (36-66)	0.29	61 (45-74)	69 (58-77)	<0.0001
Men (%)	1436 (45%)	14999 (45%)	0.94	193 (51%)	1060 (57%)	0.061
Cardiovascular disease, (%)	461 (15%)	3163 (10%)	<0.0001	117 (31%)	659 (35%)	0.13
Hypertension, (%)	629 (20%)	4214 (13%)	<0.0001	171 (45%)	980 (52%)	0.015
Dyslipidaemia, (%)	554 (17%)	1451 (4%)	<0.0001	216 (57%)	482 (26%)	<0.0001
Statin use, (%)	528 (17%)	1412 (4%)	<0.0001	210 (56%)	474 (25%)	<0.0001
Ever smoked before end date, (%)	1363 (43%)	14643 (44%)	0.16	192 (51%)	1000 (53%)	0.40

Suppl. Table 4.31: Mortality rates from cardiovascular disease in patients with adrenal insufficiency of any type and controls, categorised by non-diabetes and diabetes at baseline

Population category	Adrenal insufficiency of any type				Controls				Mortality rate difference per 1000 person-years (95% CI)	P
	No. at risk	No. death	Person-years	Mortality per 1000 person-years (95% CI)	No. at risk	No. death	Person-years	Mortality per 1000 person-years (95% CI)		
Disease of the circulatory system										
Non-diabetes	3171	155	16848	9.2 (7.9-10.8)	33071	1005	172623	5.8 (5.5-6.2)	3.4 (1.9 to 4.9)	<0.0001
Diabetes	376	29	1745	16.6 (11.6-23.9)	1873	152	7210	**21.1 (18.0-24.7)**	-4.5 (-11.4 to 2.5)	0.11
Ischaemic heart disease										
Non-diabetes	3171	69	16848	4.1 (3.3-5.2)	33071	419	172623	2.4 (2.2-2.7)	1.7 (0.7 to 2.7)	0.0001
Diabetes	376	23	1745	13.2 (8.8-19.8)	1873	68	7210	9.4 (7.4-12.0)	3.8 (-2.1 to 9.6)	0.086
Cerebrovascular disease										
Non-diabetes	3171	43	16848	2.6 (1.9-3.4)	33071	314	172623	1.8 (1.6-2.0)	0.7 (-0.1 to 1.5)	0.022
Diabetes	376	3	1745	1.7 (0.6-5.3)	1873	52	7210	**7.2 (5.5-9.5)**	-5.5 (-8.3 to -2.7)	0.0019

Suppl. Table 4.32: Mortality rates from cardiovascular disease in patients with primary adrenal insufficiency and controls, categorised by non-diabetes and diabetes at baseline

Population category	Primary adrenal insufficiency				Controls				Mortality rate difference per 1000 person-years (95% CI)	P
	No. at risk	No. death	Person-years	Mortality per 1000 person-years (95% CI)	No. at risk	No. death	Person-years	Mortality per 1000 person-years (95% CI)		
Disease of the circulatory system										
Non-diabetes	885	46	4777	9.6 (7.2-12.9)	9575	297	53107	5.6 (5.0-6.3)	4.0 (1.2 to 6.9)	0.00060
Diabetes	130	12	697	17.2 (9.8-30.3)	450	34	1827	**18.6 (13.3-26.0)**	-1.4 (-13.0 to 10.2)	0.41
Ischaemic heart disease										
Non-diabetes	885	21	4777	4.4 (2.9-6.7)	9575	129	53107	2.4 (2.0-2.9)	2.0 (0.0 to 3.9)	0.0090
Diabetes	130	10	697	14.3 (7.7-26.6)	450	15	1827	8.2 (5.0-13.6)	6.1 (-3.7 to 15.9)	0.091
Cerebrovascular disease										
Non-diabetes	885	8	4777	1.7 (0.8-3.3)	9575	89	53107	1.7 (1.4-2.1)	-0.0 (-1.2 to 1.2)	0.51
Diabetes	130	2	697	2.9 (0.7-11.5)	450	15	1827	**8.2 (5.0-13.6)**	-5.3 (-11.1 to 0.4)	0.071

Suppl. Table 4.33: Mortality rates from cardiovascular disease in patients with secondary adrenal insufficiency and controls, categorised by non-diabetes and diabetes at baseline

Population category	Secondary adrenal insufficiency				Controls				Mortality rate difference per 1000 person-years (95% CI)	P
	No. at risk	No. death	Person-years	Mortality per 1000 person-years (95% CI)	No. at risk	No. death	Person-years	Mortality per 1000 person-years (95% CI)		
Disease of the circulatory system										
Non-diabetes	1930	95	10459	9.1 (7.4-11.1)	19819	592	102305	5.8 (5.3-6.3)	3.3 (1.4 to 5.2)	0.0001
Diabetes	206	15	918	16.3 (9.8-27.1)	1172	94	4544	**20.7 (16.9-25.3)**	-4.3 (-13.6 to 4.9)	0.20
Ischaemic heart disease										
Non-diabetes	1930	42	10459	4.0 (3.0-5.4)	19819	238	102305	2.3 (2.0-2.6)	1.7 (0.4 to 2.9)	0.0011
Diabetes	206	11	918	12.0 (6.6-21.6)	1172	45	4544	9.9 (7.4-13.3)	2.1 (-5.6 to 9.7)	0.27
Cerebrovascular disease										
Non-diabetes	1930	33	10459	3.2 (2.2-4.4)	19819	191	102305	1.9 (1.6-2.2)	1.3 (0.2 to 2.4)	0.0043
Diabetes	206	1	918	1.1 (0.2-7.7)	1172	31	4544	**6.8 (4.8-9.7)**	-5.7 (-8.9 to -2.5)	0.011

Suppl. Table 4.34: A comparison of baseline characteristics of patients with adrenal insufficiency of any type and controls who had linked data, categorised by non-cardiovascular disease and cardiovascular disease at baseline

Baseline characteristics at the start of follow-up	Non-cardiovascular disease			Cardiovascular disease		
	Patients (N= 2969)	Controls (N= 31122)	p	Patients (N= 578)	Controls (N= 3822)	p
Age, median (IQR)	49 (35-63)	50 (35-64)	0.13	72 (62-79)	74 (66-81)	<0.0001
Men (%)	1291 (43%)	13765 (44%)	0.43	338 (58%)	2294 (60%)	0.48
Diabetes mellitus, (%)	259 (9%)	1214 (4%)	<0.0001	117 (20%)	659 (17%)	0.078
Hypertension, (%)	511 (17%)	3484 (11%)	<0.0001	289 (50%)	1710 (45%)	0.018
Dyslipidaemia, (%)	436 (15%)	1118 (4%)	<0.0001	334 (58%)	815 (21%)	<0.0001
Statin use, (%)	413 (14%)	1093 (4%)	<0.0001	325 (56%)	793 (21%)	<0.0001
Ever smoked before end date, (%)	1240 (42%)	13504 (43%)	0.088	315 (55%)	2139 (56%)	0.50

Suppl. Table 4.35: Mortality rates from cardiovascular disease in patients with adrenal insufficiency of any type and controls, categorised by non-cardiovascular disease and cardiovascular disease at baseline (non-CVD vs CVD)

Population category	Adrenal insufficiency of any type				Controls				Mortality rate difference per 1000 person-years (95% CI)	P
	No. at risk	No. death	Person-years	Mortality per 1000 person-years (95% CI)	No. at risk	No. death	Person-years	Mortality per 1000 person-years (95% CI)		
Disease of the circulatory system										
No CVD	2969	107	16328	6.6 (5.4-7.9)	31122	651	163792	4.0 (3.7-4.3)	2.6 (1.3 to 3.9)	<0.0001
CVD	578	77	2264	34.0 (27.2-42.5)	3822	506	16041	31.5 (28.9-34.4)	2.5 (-5.6 to 10.5)	0.26
Ischaemic heart disease										
No CVD	2696	52	16328	3.2 (2.4-4.2)	31122	265	163792	1.6 (1.4-1.8)	1.6 (0.7 to 2.5)	<0.0001
CVD	578	40	2264	17.7 (13.0-24.1)	3822	222	16041	13.8 (12.1-15.8)	3.8 (-1.9 to 9.6)	0.081
Cerebrovascular disease										
No CVD	2969	24	16328	1.5 (1.0-2.2)	31122	199	163792	1.2 (1.1-1.4)	0.3 (-0.4 to 0.9)	0.18
CVD	578	22	2264	9.7 (6.4-14.8)	3822	167	16041	10.4 (8.9-12.1)	-0.7 (-5.1 to 3.7)	0.39

Suppl. Table 4.36: Mortality rates from cardiovascular disease in patients with primary adrenal insufficiency and controls, categorised by non-cardiovascular disease and cardiovascular disease at baseline (non-CVD vs CVD)

Population category	Primary adrenal insufficiency				Controls				Mortality rate difference per 1000 person-years (95% CI)	P
	No. at risk	No. death	Person-years	Mortality per 1000 person-years (95% CI)	No. at risk	No. death	Person-years	Mortality per 1000 person-years (95% CI)		
Disease of the circulatory system										
No CVD	875	39	4959	7.9 (5.7-10.8)	9073	195	50435	3.9 (3.4-4.4)	4.0 (1.5 to 6.5)	0.0001
CVD	140	19	515	36.9 (23.5-57.8)	952	136	4498	30.2 (25.6-35.8)	6.7 (-10.7 to 24.0)	0.20
Ischaemic heart disease										
No CVD	875	19	4959	3.8 (2.4-6.0)	9073	84	50435	1.7 (1.3-2.1)	2.2 (0.4 to 3.9)	0.0013
CVD	140	12	515	23.3 (13.2-41.0)	952	60	4498	13.3 (10.4-17.2)	10.0 (-3.6 to 23.6)	0.046
Cerebrovascular disease										
No CVD	875	6	4959	1.2 (0.5-2.7)	9073	57	50435	1.1 (0.9-1.5)	0.1 (-0.9 to 1.1)	0.41
CVD	140	4	515	7.8 (2.9-20.7)	952	47	4998	10.4 (7.9-13.9)	-2.7 (-10.9 to 5.5)	0.30

Suppl. Table 4.37: Mortality rates from cardiovascular disease in patients with secondary adrenal insufficiency and controls, categorised by non-cardiovascular disease and cardiovascular disease at baseline (non-CVD vs CVD)

Population category	Secondary adrenal insufficiency				Controls				Mortality rate difference per 1000 person-years (95% CI)	P
	No. at risk	No. death	Person-years	Mortality per 1000 person-years (95% CI)	No. at risk	No. death	Person-years	Mortality per 1000 person-years (95% CI)		
Disease of the circulatory system										
No CVD	1788	62	9917	6.3 (4.9-8.0)	18647	381	97241	3.9 (3.5-4.3)	2.3 (0.7 to 3.9)	0.0006
CVD	348	48	1460	32.9 (24.8-43.6)	2344	305	9609	31.7 (28.4-35.5)	1.1 (-8.8 to 11.1)	0.40
Ischaemic heart disease										
No CVD	1788	33	9917	3.3 (2.4-4.7)	18647	154	97241	1.6 (1.4-1.9)	1.7 (0.6 to 2.9)	0.0002
CVD	348	20	1460	13.7 (8.8-21.2)	2344	129	9609	13.4 (11.3-16.0)	0.3 (-6.1 to 6.7)	0.45
Cerebrovascular disease										
No CVD	1788	16	9917	1.6 (1.0-2.6)	18647	119	97241	1.2 (1.0-1.5)	0.4 (-0.4 to 1.2)	0.15
CVD	348	18	1460	12.3 (7.8-19.6)	2344	103	9609	10.7 (8.8-13.0)	1.6 (-4.5 to 7.7)	0.28

Suppl. Table 4.38: A comparison of baseline characteristics of patients with adrenal insufficiency of any type and controls who had linked data, categorised by non-statin use and statin use at baseline

Baseline characteristics at the start of follow-up	Non-statin use			Statin use		
	Patients (N= 2809)	Controls (N= 33058)	p	Patients (N= 738)	Controls (N= 1886)	p
Age; year, median (IQR)	48 (34-63)	51 (36-66)	<0.0001	67 (59-75)	69 (61-77)	<0.0001
Men (%)	1224 (44%)	14994 (45%)	0.068	405 (55%)	1065 (56%)	0.46
Cardiovascular disease, (%)	253 (9%)	3029 (9%)	0.78	325 (44%)	793 (42%)	0.35
Diabetes mellitus, (%)	166 (6%)	1399 (4%)	<0.0001	210 (28%)	474 (25%)	0.081
Hypertension, (%)	399 (14%)	4235 (13%)	0.035	401 (54%)	959 (51%)	0.10
Ever smoked before end date, (%)	1125 (40%)	14483 (44%)	<0.0001	430 (58%)	1160 (62%)	0.12

Suppl. Table 4.39: Mortality rates from cardiovascular disease in patients with adrenal insufficiency of any type and controls, categorised by non-statin use and statin use at baseline

Population category	Adrenal insufficiency of any type				Controls				Mortality rate difference per 1000 person-years (95% CI)	P
	No. at risk	No. death	Person-years	Mortality per 1000 person-years (95% CI)	No. death	No. death	Person-years	Mortality per 1000 person-years (95% CI)		
Disease of the circulatory system										
Non-statin use	2809	125	15554	8.0 (6.7-9.6)	33058	1034	172566	6.0 (5.6-6.4)	2.0 (0.6 to 3.5)	0.0014
Statin use	738	59	3039	19.4 (15.0-25.1)	1886	123	7267	16.9 (14.2-20.2)	2.5 (-3.3 to 8.3)	0.19
Ischaemic heart disease										
Non-statin use	2809	56	15554	3.6 (2.8-4.7)	33058	428	172566	2.5 (2.3-2.7)	1.1 (0.1 to 2.1)	0.0059
Statin use	738	36	3039	11.8 (8.5-16.4)	1886	59	7267	8.1 (6.3-10.5)	3.7 (-0.7 to 8.1)	0.039
Cerebrovascular disease										
Non-statin use	2809	29	15554	1.9 (1.3-2.7)	33058	331	172566	1.9 (1.7-2.1)	-0.1 (-0.8 to 0.7)	0.45
Statin use	738	17	3039	5.6 (3.5-9.0)	1886	35	7267	4.8 (3.5-6.7)	0.8 (-2.3 to 3.9)	0.30

Suppl. Table 4.40: Mortality rates from cardiovascular disease in patients with primary adrenal insufficiency and controls, categorised by non-statin use and statin use at baseline

Population category	Primary adrenal insufficiency				Controls				Mortality rate difference per 1000 person-years (95% CI)	P
	No. at risk	No. death	Person-years	Mortality per 1000 person-years (95% CI)	No. at risk	No. death	Person-years	Mortality per 1000 person-years (95% CI)		
Disease of the circulatory system										
Non-statin use	844	40	4784	8.4 (6.1-11.4)	9505	296	52547	5.6 (5.0-6.3)	2.7 (0.1 to 5.4)	0.012
Statin use	171	18	690	26.1 (16.4-41.4)	520	35	2386	14.7 (10.5-20.4)	11.4 (-1.6 to 24.4)	0.027
Ischaemic heart disease										
Non-statin use	844	18	4784	3.8 (2.4-6.0)	9505	127	52547	2.4 (2.0-2.9)	1.3 (-0.4 to 3.1)	0.045
Statin use	171	13	690	18.8 (10.9-32.4)	520	17	2386	7.1 (4.4-11.5)	11.7 (0.9 to 22.5)	0.0058
Cerebrovascular disease										
Non-statin use	844	8	4784	1.7 (0.8-3.3)	9505	94	52547	1.8 (1.5-2.2)	-0.1 (-1.3 to 1.1)	0.44
Statin use	171	2	690	2.9 (0.7-11.6)	520	10	2386	4.2 (2.3-7.8)	-1.3 (-6.1 to 3.5)	0.34

Suppl. Table 4.41: Mortality rates from cardiovascular disease in patients with secondary adrenal insufficiency and controls, categorised by non-statin use and statin use at baseline

Population category	Secondary adrenal insufficiency				Controls				Mortality rate difference per 1000 person-years (95% CI)	P
	No. at risk	No. death	Person-years	Mortality per 1000 person-years (95% CI)	No. at risk	No. death	Person-years	Mortality per 1000 person-years (95% CI)		
Disease of the circulatory system										
Non-statin use	1659	74	9329	7.9 (6.3-10.0)	19866	609	102847	5.9 (5.5-6.4)	2.0 (0.1 to 3.9)	0.010
Statin use	477	36	2048	17.6 (12.7-24.4)	1125	77	4003	19.2 (15.4-24.1)	-1.7 (-8.8 to 5.5)	0.33
Ischaemic heart disease										
Non-statin use	1659	34	9329	3.6 (2.6-5.1)	19866	248	102847	2.4 (2.1-2.7)	1.2 (-0.0 to 2.5)	0.015
Statin use	477	19	2048	9.3 (5.9-14.5)	1125	35	4003	8.7 (6.3-12.2)	0.5 (-4.5 to 5.6)	0.41
Cerebrovascular disease										
Non-statin use	1659	20	9329	2.1 (1.4-3.3)	19866	198	102847	1.9 (1.7-2.2)	0.2 (-0.8 to 1.2)	0.31
Statin use	477	14	2048	6.8 (4.0-11.5)	1125	24	4003	6.0 (4.0-8.9)	0.8 (-3.5 to 5.1)	0.34

Suppl. Table 4.42: Incidence rates and hazard ratios of hospitalisation from cardiovascular disease in patients with unspecified adrenal insufficiency and matched controls

Outcomes	Unspecified adrenal insufficiency				Controls				Incidence rate difference per 1000 person-years (95% CI)	P	Unadjusted HR (95% CI)	P	Adjusted HR (95% CI) †	P
	No. at risk	No. 1st event	Person-years	Incidence per 1000 person-years (95% CI)	No. at risk	No. 1st event	Person-years	Incidence per 1000 person-years (95% CI)						
Circulatory system disease	396	66	1598	41.3 (32.4-52.6)	3928	347	16973	20.4 (18.4-22.7)	20.9 (10.7 to 31.0)	<0.0001	2.02 (1.55-2.63)	<0.0001	1.72 (1.31-2.26)	<0.0001
Ischaemic heart disease	396	15	1715	8.7 (5.3-14.5)	3928	112	17655	6.3 (5.3-7.6)	2.4 (-2.2 to 7.0)	0.12	1.39 (0.81-2.38)	0.23	1.11 (0.64-1.95)	0.70
Cerebrovascular disease	396	13	1722	7.5 (4.4-13.0)	3928	69	17942	3.8 (3.0-4.9)	3.7 (-0.5 to 7.9)	0.018	1.96 (1.08-3.54)	0.026	1.96 (1.08-3.54)	0.026

Note: † Adjustment for previous cardiovascular disease, baseline diabetes mellitus, hypertension and dyslipidaemia, and smoking any time

Suppl. Table 4.43: Incidence rates and hazard ratios of hospitalisation from cardiovascular disease in patients with adrenal insufficiency of any type and controls, categorised by men and women

Population category	Adrenal insufficiency of any type				Controls				Incidence rate difference per 1000 person-years (95% CI)	P
	No. at risk	No. 1st event	Person-years	Incidence per 1000 person-years (95% CI)	No. at risk	No. 1st event	Person-years	Incidence per 1000 person-years (95% CI)		
Disease of the circulatory system										
Men	1629	280	7620	36.7 (32.7-41.3)	16059	1825	77768	23.5 (22.4-24.6)	13.3 (8.8 to 17.7)	<0.0001
Women	1918	242	9296	26.0 (23.0-29.5)	18885	1392	91169	15.3 (14.5-16.1)	10.8 (7.4 to 14.1)	<0.0001
Ischaemic heart disease										
Men	1629	86	8244	10.4 (8.4-12.9)	16059	714	81242	8.8 (8.2-9.5)	1.6 (-0.7 to 3.9)	0.069
Women	1918	53	9906	5.4 (4.1-7.0)	18885	393	94371	4.2 (3.8-4.6)	1.2 (-0.3 to 2.7)	0.047
Cerebrovascular disease										
Men	1629	63	8385	7.5 (5.9-9.6)	16059	359	83339	4.3 (3.9-4.8)	3.2 (1.3 to 5.1)	0.0001
Women	1918	62	9925	6.2 (4.9-8.0)	18885	344	95142	3.6 (3.3-4.0)	2.6 (1.0 to 4.2)	0.0001

Suppl. Table 4.44: Incidence rates and hazard ratios of hospitalisation from cardiovascular disease in patients with primary adrenal insufficiency and controls, categorised by men and women

Population category	Primary adrenal insufficiency				Controls				Incidence rate difference per 1000 person-years (95% CI)	P
	No. at risk	No. 1st event	Person-years	Incidence per 1000 person-years (95% CI)	No. at risk	No. 1st event	Person-years	Incidence per 1000 person-years (95% CI)		
Disease of the circulatory system										
Men	410	65	2023	32.1 (25.2-41.0)	4077	428	21449	20.0 (18.2-21.9)	12.2 (4.1 to 20.2)	0.0004
Women	605	80	2966	27.0 (21.7-33.6)	5948	489	30032	16.3 (14.9-17.8)	10.7 (4.6 to 16.8)	<0.0001
Ischaemic heart disease										
Men	410	18	2165	8.3 (5.2-13.2)	4077	171	22401	7.6 (6.6-8.9)	0.7 (-3.3 to 4.7)	0.35
Women	605	22	3187	6.9 (4.5-10.5)	5948	151	31240	4.8 (4.1-5.7)	2.1 (-0.9 to 5.1)	0.064
Cerebrovascular disease										
Men	410	6	2224	2.7 (1.2-6.0)	4077	84	22931	3.7 (3.0-4.5)	-0.9 (-3.3 to 1.3)	0.24
Women	605	18	3216	5.6 (3.5-8.9)	5948	126	31573	4.0 (3.4-4.8)	1.6 (-1.1 to 4.3)	0.094

Suppl. Table 4.45: Incidence rates and hazard ratios of hospitalisation from cardiovascular disease in patients with secondary adrenal insufficiency and controls, categorised by men and women

Population category	Secondary adrenal insufficiency				Controls				Incidence rate difference per 1000 person-years (95% CI)	P
	No. at risk	No. 1st event	Person-years	Incidence per 1000 person-years (95% CI)	No. at risk	No. 1st event	Person-years	Incidence per 1000 person-years (95% CI)		
Disease of the circulatory system										
Men	1054	185	4954	37.3 (32.3-43.1)	10343	1217	49473	24.6 (23.3-26.0)	12.7 (7.2 to 18.3)	<0.0001
Women	1082	126	5375	23.4 (19.7-27.9)	10648	736	51010	14.4 (13.4-15.5)	9.0 (4.8 to 13.2)	<0.0001
Ischaemic heart disease										
Men	1054	59	5391	10.9 (8.5-14.1)	10343	476	51692	9.2 (8.4-10.1)	1.7 (-1.2 to 4.6)	0.10
Women	1082	25	5692	4.4 (3.0-6.5)	10648	197	52625	3.7 (3.3-4.3)	0.6 (-1.2 to 2.4)	0.22
Cerebrovascular disease										
Men	1054	51	5470	9.3 (7.1-12.3)	10343	244	53049	4.6 (4.1-5.2)	4.7 (2.1 to 7.3)	<0.0001
Women	1082	37	5677	6.5 (4.7-9.0)	10648	180	52986	3.4 (2.9-3.9)	3.1 (1.0 to 5.3)	0.0004

Suppl. Table 4.46: Incidence rates and hazard ratios of hospitalisation from cardiovascular disease in patients with adrenal insufficiency of any type and controls, categorised by younger and older age at start of follow-up

Population category	Adrenal insufficiency of any type				Controls				Incidence rate difference per 1000 person-years (95% CI)	P
	No. at risk	No. 1st event	Person-years	Incidence per 1000 person-years (95% CI)	No. at risk	No. 1st event	Person-years	Incidence per 1000 person-years (95% CI)		
Disease of the circulatory system										
Age <50	1565	93	8225	11.3 (9.2-13.9)	15641	425	77511	5.5 (5.0-6.0)	5.8 (3.5 to 8.2)	<0.0001
Age ≥50	1982	429	8691	49.4 (44.9-54.3)	19303	2792	91426	30.5 (29.4-31.7)	18.8 (14.0 to 23.6)	<0.0001
Ischaemic heart disease										
Age <50	1565	14	8562	1.6 (1.0-2.8)	15641	109	78973	1.4 (1.1-1.7)	0.3 (-0.6 to 1.1)	0.26
Age ≥50	1982	125	9588	13.0 (10.9-15.5)	19303	998	96641	10.3 (9.7-11.0)	2.7 (0.3 to 5.1)	0.0083
Cerebrovascular disease										
Age <50	1565	20	8555	2.3 (1.5-3.6)	15641	42	79295	0.5 (0.4-0.7)	1.8 (0.8 to 2.8)	<0.0001
Age ≥50	1982	105	9756	10.8 (8.9-13.0)	19303	661	99186	6.7 (6.2-7.2)	4.1 (2.0 to 6.2)	<0.0001

Suppl. Table 4.47: Incidence rates and hazard ratios of hospitalisation from cardiovascular disease in patients with primary adrenal insufficiency and controls, categorised by younger and older age at start of follow-up

Population category	Primary adrenal insufficiency				Controls				Incidence rate difference per 1000 person-years (95% CI)	P
	No. at risk	No. 1st event	Person-years	Incidence per 1000 person-years (95% CI)	No. at risk	No. 1st event	Person-years	Incidence per 1000 person-years (95% CI)		
Disease of the circulatory system										
Age <50	484	29	2638	11.0 (7.6-15.8)	4855	144	24947	5.8 (4.9-6.8)	5.2 (1.1 to 9.3)	0.0016
Age ≥50	531	116	2351	49.3 (41.1-59.2)	5170	773	26533	29.1 (27.2-31.3)	20.2 (11.0 to 29.4)	<0.0001
Ischaemic heart disease										
Age <50	484	6	2739	2.2 (1.0-4.9)	4855	36	25532	1.4 (1.0-2.0)	0.8 (-1.0 to 2.6)	0.16
Age ≥50	531	34	2613	13.0 (9.3-18.2)	5170	286	28109	10.2 (9.1-11.4)	2.8 (-1.7 to 7.4)	0.091
Cerebrovascular disease										
Age <50	484	2	2765	0.7 (0.2-2.9)	4855	13	25612	0.5 (0.3-0.9)	0.2 (-0.8 to 1.3)	0.30
Age ≥50	531	22	2675	8.2 (5.4-12.5)	5170	197	22892	6.8 (5.9-7.8)	1.4 (-2.2 to 5.0)	0.20

Suppl. Table 4.48: Incidence rates and hazard ratios of hospitalisation from cardiovascular disease in patients with secondary adrenal insufficiency and controls, categorised by younger and older age at start of follow-up

Population category	Secondary adrenal insufficiency				Controls				Incidence rate difference per 1000 person-years (95% CI)	P
	No. at risk	No. 1st event	Person-years	Incidence per 1000 person-years (95% CI)	No. at risk	No. 1st event	Person-years	Incidence per 1000 person-years (95% CI)		
Disease of the circulatory system										
Age <50	931	56	4937	11.3 (8.7-14.7)	9277	256	45870	5.6 (4.9-6.3)	5.8 (2.7 to 8.8)	<0.0001
Age ≥50	1205	255	5392	47.3 (41.8-53.5)	11714	1697	54613	31.1 (29.6-32.6)	16.2 (10.2 to 22.2)	<0.0001
Ischaemic heart disease										
Age <50	931	6	5160	1.2 (0.5-2.6)	9277	67	46674	1.4 (1.1-1.8)	-0.3 (-1.3 to 0.7)	0.32
Age ≥50	1205	78	5924	13.2 (10.5-16.4)	11714	606	57643	10.5 (9.7-11.4)	2.7 (-0.4 to 5.7)	0.033
Cerebrovascular disease										
Age <50	931	18	5123	3.5 (2.2-5.6)	9277	26	46896	0.6 (0.4-0.8)	3.0 (1.3 to 4.6)	<0.0001
Age ≥50	1205	70	6024	11.6 (9.2-14.7)	11714	398	59140	6.7 (6.1-7.4)	4.9 (2.1 to 7.7)	<0.0001

Suppl. Table 5.1: ICD-10 codes describing primary adrenal insufficiency and the hypothalamic-pituitary disorders

ICD-10 code	Diseases
Primary adrenal insufficiency	
E27.1	Primary adrenocortical insufficiency
E27.2	Addisonian crisis
E27.3	Drug-induced adrenocortical insufficiency
E27.4	Other and unspecified adrenocortical insufficiency
E27.8	Other specified disorders of adrenal gland
E27.9	Disorder of adrenal gland, unspecified
E89.6	Post-procedural adrenocortical (-medullary) hypofunction
Hypothalamic-pituitary disorders	
E23.0	Hypopituitarism
E23.1	Drug-induced hypopituitarism
E23.3	Hypothalamic dysfunction, not elsewhere classified
E23.6	Other disorders of pituitary gland
E23.7	Disorder of pituitary gland, unspecified
D35.2	Benign neoplasm of pituitary gland
E89.3	Post-procedural hypopituitarism

Note: ICD-9 codes were not available in HES linkage data