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A Model for Measuring the Health Burden of Classic Congenital Adrenal Hyperplasia in Adults

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Abstract

Aim: Patients with classic Congenital Adrenal Hyperplasia (CAH) have poor health outcomes. In the absence of a comprehensive observational study, this manuscript provides a model to estimate the lifetime disease burden of adults with classic CAH.

Methods: The model, built in Excel, comprises sub-domains addressing the health consequences of CAH, and synthesises evidence from clinical and epidemiological studies on health outcomes.

Results: The model estimates that adults with classic CAH will implement "sick day rules" (doubling or tripling glucocorticoid and/or use of parenteral therapy) 171 times over their lifetime, and attend hospital for adrenal crisis on 11 occasions. In a population of 1,000, over 200 will die of a condition complicated by adrenal crisis resulting, on average, in a loss of 7 years of life. CAH patients may also suffer from excess CVD events. Treatment with glucocorticoids almost doubles the risk of bone fractures in CAH patients compared to the general population, leading on average to an additional 0.8 fractures per CAH patient over their lifetime.

Conclusions: The disease burden model highlights gaps in evidence, particularly regarding intensity of care and adrenal crisis, and the relationship between control of CAH and risks of CVD, osteoporosis, diabetes and infertility. The model can be used for research on the impact of new clinical pathways and therapeutic interventions in terms of clinical events and cost.

Introduction

Congenital Adrenal Hyperplasia (CAH) is the commonest congenital endocrine disorder, arising from defective steroidogenesis [1]. The most frequent mutation is in the gene encoding 21-hydroxylase (21-OH) resulting in failure of cortisol synthesis and consequently increased pituitary adrenocorticotropic hormone (ACTH) release, which in turn promotes over-production of 17-hydroxyprogesterone (17-OHP), progesterone, and adrenal androgens – termed classic CAH. Patients with CAH due to 21-OH deficiency have two major problems: cortisol deficiency and androgen excess. In addition, many patients also have mineralocorticoid deficiency as 21-OH mediates a key step in aldosterone synthesis. The clinical classification of 21-OH deficiency is based on the severity of mutations. The most severe classic form occurs in about 1 in 15,000 births [2]. The classic form usually presents early in life or at neonatal screening and comprises salt wasting and simple virilising subgroups based on whether the severity of aldosterone deficiency causes a salt-wasting hypotensive crisis in the new-born. Classic CAH is characterised by sexual ambiguity at birth in females, and by precocious puberty, short stature and fertility problems in both males and females.

Treatment of CAH is by glucocorticoid and mineralocorticoid replacement. However, this presents a challenge as no current glucocorticoid regimen replicates the normal circadian rhythm of cortisol. There is no consensus on what glucocorticoid regimen to use in adults with CAH and patients receive a variety of treatments including hydrocortisone, prednisolone, prednisone, and dexamethasone give in a circadian or reverse circadian fashion [3, 4]. As a result glucocorticoid under- and over-treatment is a risk, and is linked to complications including adrenal crisis, obesity, hyperlipidaemia, hypertension, cardiovascular disease (CVD) and reduced bone mineral density (BMD) [5]. Health-related quality of life (HRQoL) has been variously reported reduced in some studies and normal in others [3, 6, 7].

The need for regular physician visits to manage and adjust treatment, the risk of adrenal crisis (AC), and the long-term impacts of both CAH symptoms and glucocorticoid therapy lead to a considerable burden on the health service. This is the first study to model and estimate the disease burden and excess mortality associated with classic CAH in adults.

Methods and Model

Model Overview

The model computes Life Years (LYs) and Quality Adjusted Life Years (QALYs) for adults with classic CAH compared to the general population. The QALY is a measure of health that attempts to capture mortality and morbidity. The impact of morbidity on the patient is measured in terms of health-related quality of life (HRQoL), using a single scale anchored on one (which represents perfect health) and zero (which represents death). QALYs are then calculated by multiplying the HRQoL value with the length of life spent in that health state, for example, 10 years at 0.5, produces 5 QALYs. This approach can be extended to estimate the QALYs across complex chronic disease profiles. Whilst the QALY is too crude to be used clinically, QALYs can be used as a measure of disease burden, or combined with costs to estimate cost-effectiveness [8]. International guidelines for cost-effectiveness recommend the use of QALYs for the assessment of patient outcomes [9], and this has been followed by similar recommendations at the national level in several countries, including the UK. The core model addresses the direct effect of CAH on patients including HRQoL and mortality associated with adrenal crisis (AC). The sub-models examine co-morbidities associated with CAH (Figure 1).

The models are life tables tracking health-related events, LYs and QALYs each year for men and women separately from age 18 years for life. National general population mortality rates are applied, adjusted for increases in fatalities from AC and CVD in the separate sub-models [10]. Baseline age-related utility for the general population (measured with the EQ-5D scale) was calculated using published evidence [11]. Model parameters were taken from the literature, where available.

Model Sub-domains

Direct CAH burden including Adrenal Crisis: Studies have reported reduced QoL in CAH adults, in particular reduced general health and vitality [3, 6, 12]. EQ-5D utility values were derived from the SF-36 scores for CAH and the general population reported in the CaHASE study [3, 13].

During illness CAH patients need to increase their dose of glucocorticoid to meet the increased demand for adrenal steroids, i.e. invoke "sick day rules". If this is delayed, or not done, patients are more likely to have an AC requiring attendance at hospital and parenteral steroids, and a proportion of patients will die during an AC. There is limited data available regarding care for AC, so some parameters have had to be estimated by a clinical expert (Author RJR). Sensitivity analysis was conducted on these parameters. All parameter values are shown in Table 1.

The rate of AC was reported as 0.066 per patient-year in patients with primary adrenal insufficiency [14]. Ninety-five percent confidence limits were estimated from the reported number of AC and patient-years (0.058, 0.074). A similar rate of AC (similarly defined) was reported in CAH patients [15], but the rate fell to 0.038 per patient year when the initial salt-wasting crises which precipitated the diagnosis in infants were excluded. This latter figure is used in sensitivity analysis.

Cardiovascular Disease (CVD): CAH patients may have increased Body Mass Index (BMI), blood pressure and cholesterol compared to the general population, all known risk factors for CVD [3, 16]. A Swedish study reports CVD mortality in Addison's Disease to be approximately twice that for the general population, although no excess CVD mortality was found in a similar Norwegian population [17, 18]. The model uses data from the general population for CVD events and death, and applies to these a relative risk (RR) of CVD events for CAH patients, thus yielding estimates of CVD event rates for CAH patients. The RR of CVD in CAH patients was estimated using an approximation of the QRISK2 CVD risk equation using mean differences in BMI and systolic blood pressure between CAH and the general population from the CAHASE study [3, 16]. This yielded a 10% increase in risk of CVD events for women. Note for men in the CaHASE study there was no significant difference in BMI or blood pressure between CAH patients and the general population so the baseline assumption is no increased CVD risk for men. For maximum value sensitivity analysis the results of Bergthorsdottir (2006)[17] were used: RR of CVD of 2.31 for women and 1.97 for men. For the minimum scenario no increased risk of CVD arising from CAH was assumed. The model includes incident angina, stroke and MI events, deaths from stroke and MI, as well as all CVD deaths. CVD age-related event rates for the general population were taken from national data [19, 20] (a supplementary table is available summarising this data). A conservative approach was taken to estimate the HRQoL reductions due to CVD events: the loss of HRQoL due to stroke or MI was applied in the year of the event only leading to an underestimate of total QALY loss associated with these events [21].

Obesity: Women with CAH have an average BMI of 6.2 kg/m^2 greater than the general population of similar age [3]. Obesity has a negative effect on HRQoL independent of the associated chronic illnesses [22]. High BMI particularly affects pain and mobility. Using data from Macran (2004)[22] a linear relationship was derived showing a loss of 0.0033 in utility for every unit increase in BMI (kg/m^2) for BMI greater than 21kg/m^2 in a population of median age 46 years. For men there was no independent relationship between BMI and utility, and no difference in in BMI between men with CAH and the general population [3, 22].

Bone Fractures: Glucocorticoid treatment is known to reduce BMD and put patients at increased risk of fractures, with fracture risk associated with dose [23]. The lifetime number of fractures was estimated for people with CAH and the general population (a supplementary table is available summarising this data). Baseline fracture incidence by age for non-vertebral and hip fractures was taken from the literature [23, 24]. Similar data was not identified for vertebral or forearm fractures: it was assumed that the relationship between fracture incidence and age is the same for forearm fractures as for all non-vertebral fractures, and that the relationship between age and fracture incidence for vertebral fractures is similar to hip fractures, adjusted for absolute incidence in both cases [23]. It was assumed the mean equivalent hydrocortisone dose for CAH adults was 29.6mg per day [3]. Curves were fitted to data from van Staa [25] to establish the RR of fractures by glucocorticoid dose (daily hydrocortisone dose equivalent mg/day = DD):

$$\text{All fracture RR} = -0.00009 * DD^2 + 0.267 * DD + 1$$

$$\text{Femur/hip fracture RR} = -0.0002 * DD^2 + 0.0343 * DD + 1$$

$$\text{Vertebral fracture RR} = 0.0702 * DD + 1$$

EQ-5D utility values were from Stevenson (2007) [26]. As no utility for wrist fracture was reported, that for "other" fractures was used as this was the most conservative (highest). Excess mortality from hip fractures was not considered, as mortality directly attributable to fractures is relatively low, especially in younger age groups (estimated 2% age 50-60 years, rising to 16% age 90 years or more) [26].

Fertility: CAH affects fertility in both men and women. In the CaHASE study 25% of women attempted to conceive, of which 54% were successful indicating that, of all women with classic CAH, 13.5% conceived, and 11.5% sought fertility and failed [3]. In the same study, 37% of men attempted to conceive, of which 67% were successful, so 25% of all men with classic CAH fathered children and 12% sought fertility and failed [3]. However, data on fertility choices of both CAH patients and the general population is limited, and therefore it is included as a sensitivity analysis only. The NICE clinical guideline on fertility quotes figures indicating that 92% of women in the general population will conceive after two years and 93% after three years [27, 28]. However a study of infertility in UK general practice reports a rate of 5.9 per 1000 person-years, suggesting a far lower proportion of women (approximately 0.6%) seeking help for infertility [29]. The greater estimate of 7% unwanted infertility is used in the model [27], adjusted for the proportion of couples seeking help for infertility who already have at least one child (41% [30]): to be consistent with the scenario for CAH patients only totally infertile couples in the general population are considered. Outcomes from a specialist fertility clinic indicate a 51% success rate within 5 years, with approximately half of all patients receiving active treatment [30]. All the data discussed refers to women: it has been assumed that men in the general population are similarly affected by infertility.

There is little information on the effect of unwanted infertility on HRQoL. The utility decrement (0.07) was taken from the NICE fertility guideline and applied in the same way; that is a constant decrement applied for life [27]. Note this may overestimate QALY losses from infertility if the utility decrement decreases with time. In the absence of other data it is assumed that the utility decrement is the same for men. The utility decrement is applied from the average age at which the general population has their first child (Table 2).

Results

Core model - CAH

The model estimates that on average adults with CAH will implement "sick day rules" (doubling or tripling glucocorticoid and/or use of parenteral therapy) 171 times over their lifetime, and attend hospital for AC on 11 occasions. In a population of 1,000 over 200 will die of a condition complicated by AC resulting, on average, in a loss of 7.3 years of life, or 9.0 QALYs (Figure 2 and Table 3).

It can be seen that the direct effects of CAH and associated AC, are the main cause of excess morbidity and mortality in CAH adults. The comorbidities do not affect all CAH patients, and CVD and bone fractures affect people mostly later in life. When comorbidities are considered the survival difference between CAH adults and the general population is 7.4 years, or taking into account the effect on HRQoL, 10.2 QALYs. If the (uncertain) effects of infertility are included the difference in QALYs increases to 10.6.

The effects of CVD are modest, but for the baseline model an increased risk of only 10% was estimated, and for women only. Nevertheless, in a population of 1000 CAH women they will experience an estimated additional 11 MI, 41 strokes and 17 CVD deaths compared to the general population.

Obesity (independent of CVD effects) and bone fractures are assumed to affect HRQoL and not survival, and therefore have no effect on LYs. Nevertheless, the estimated effect of obesity on women's QALYs is not negligible: with an average BMI of 6.2 kg/m^2 greater than the general population of similar age [3], the estimated reduction in utility is 0.02 for women aged 46. Over the adult lifetime this leads to a loss of 1.3 QALYs for CAH women compared to the general population.

The incidence of fractures is approximately doubled in persons with CAH compared to the general population (Figure 3). For women this means an average of one additional fracture over their lifetime; for men 0.7 fractures. Despite this the estimated effect of additional bone fractures on QALYs is relatively small (Table 3), affecting people mainly in old age.

Sensitivity analysis

The sensitivity analysis focused on the core CAH/AC model as almost all the difference in LYs and QALYs between CAH adults and the general population arise from the direct effects of CAH. A sensitivity analysis on the RR of CVD for CAH adults is also presented given the uncertainty and potential effect of this parameter on outcomes (Table 3).

The parameter that contributes to the greatest uncertainty in the results is the average number of times a year CAH adults need to implement "sick day rules". No data was available for this parameter, which was estimated to be between one and six times per year, with a baseline value of three. The estimated number of deaths from conditions exacerbated by AC is related to this parameter as the probability of death from AC is applied to the number of patients admitted as inpatients for AC, which in turn depends on the number needing to implement "sick day rules". The other parameters in the CAH/AC module contribute to a similar level of uncertainty: all, with the exception of CAH utility, contributing to the estimated number of deaths from AC.

A 10% increase in RR of CVD events for women only is estimated for the baseline scenario: the maximum, based on observational evidence, uses a RR of approximately two [17]. The resulting additional CVD mortality reduces survival in CAH adults by approximately two years.

Discussion

Adults with CAH experience reduced HRQoL and reduced survival. In recent years there has been a growing literature on the epidemiology of the condition but to our knowledge no previous attempt has been made to estimate the overall lifetime burden of CAH, including associated co-morbidities. Our results show that despite the many co-morbidities experienced by adults with CAH, it is CAH itself, and in particular the mortality arising from conditions exacerbated by AC, which results in average survival being 7 years less than for the general population. Consideration of the effect of reduced lifelong HRQoL gives an estimated reduction of 9 QALYs. There is uncertainty in all the model parameters associated with this estimate, and both the number of times a year patients implement sick day rules and the proportion of patients experiencing AC who are admitted as inpatients were estimated by the authors. The effect of the uncertainty in all the CAH/AC parameters on the results (LY and QALYs) are of a similar order of magnitude, giving a range in estimated reduction in survival of between 2 and 13 years, and 5 to 14 QALYs.

CVD has a very limited effect on survival and QALYs in the baseline model: the effect of CAH on CVD is uncertain as life-saving glucocorticoid therapy was only introduced in the 1950s so there are few patients in their sixties. An increased risk of just 10% was applied for women only: CAH men in the CAHASE study did not have increased BMI or systolic blood pressure compared to the general population. The baseline analysis assumes that the relationship between risk factors and CVD events in the CAH population is the same as that for the general population. In fact there is some evidence that the CVD burden in CAH may be much greater [17]. Sensitivity analysis using an RR of approximately two for CVD risk for both men and women [17], suggests CVD mortality may reduce survival in CAH adults by up to two years. Mortality is calculated separately in the CAH core model and CVD sub-model so the mortality reductions are not additive. The effect of CVD morbidity is underestimated as the disutility of CVD events is only applied in the year of occurrence.

We did not include diabetes in our model as the relationship between markers of insulin sensitivity and glucocorticoid treated CAH patients is complex. Patients with CAH and adrenal insufficiency (AI) who are under replaced with glucocorticoid are at risk of hypoglycaemia and this is a presenting feature of AI in neonates and children as cortisol reduces insulin sensitivity. The physiological rise in the early morning hours reduces insulin sensitivity and protects from nocturnal hypoglycaemia and replacement of cortisol in patients with CAH has a similar effect with a rise in HOMA-IR [31]. Thus, the use of change in HOMA-IR as a risk factor for diabetes is not appropriate in CAH.

The effects of long term glucocorticoid treatment on fractures is well established, with risk increasing with higher doses [25]. This relationship was used to model the likely increase in fractures in adults with CAH. A recent paper has examined fractures in patients with CAH and found no-statistically significant relationship with GC exposure, although the sample size was small [32]. However, the authors did find an increase in fractures associated with classic CAH compared to non-classic CAH, which suggests an increased fracture risk over that of the general population. This may suggest an increased risk independent of GC exposure; however, there is insufficient evidence at this time for this to be reliably modelled.

Structural and hormonal problems inhibit fertility in CAH adults, and unwanted infertility has been shown to reduce HRQoL, at least in women [33]. Estimation of the consequences on QALYs of unwanted infertility resulting from CAH is uncertain as data is limited for the general population, especially men, as well as for CAH adults. Data reported in the CAHASE study was used to estimate unwanted infertility in the CAH population, but many subjects were of an age where their fertility choices may not have been final [3]. Also the data may underestimate latent desire for fertility as CAH patients may be discouraged from considering fertility.

This is the first attempt to model the overall disease burden of CAH and naturally has the limitations of using historical cross-sectional data from different populations. The model is relatively simple, with a separate lifetable for each co-morbidity resulting in potential overestimation of the total effects when the results of each are summed. However, given the dominance of the direct effects of CAH/AC on outcomes this has little effect on the results. Caution needs to be taken in interpretation of other published models when applied to CAH; however we have had to use these in the absence of validated models in CAH. For example, our estimates of bone fractures come from the use of glucocorticoids as anti-inflammatory agents whereas in CAH it is substitution therapy and there may be a balancing effect of excess androgens. Similarly obesity has a complex relationship with fractures and bone density and this would be expected to be more complex in the face of androgen and glucocorticoid imbalance.

As a generic measure of health, QALYs are used to capture the effects of treatments across many conditions. Their ability to combine mortality and morbidity effects makes them useful for complex conditions, such as those of the endocrine system. The use of QALYs and cost-effectiveness analysis within diabetes has shown how multiple clinical effects can be captured and evaluated within this framework. However, the methods by which the HRQoL of patients is captured have drawn criticism as they have been found to be insensitive to clinical change in many situations. In our study, the HRQoL effects were measured using the EQ-5D descriptive system and scoring algorithm[34], yet the EQ-5D doesn't directly measure vitality which is an important feature of CAH. As such, the HRQoL scores and QALYs may underestimate the impact of CAH on health. Despite these potential problems, an alternative summary measure of burden of disease that is also applicable to cost-effectiveness analysis is not available.

Development of the model has highlighted gaps in the evidence, particularly intensity of care for AC, and the relationship between control of CAH and risks of CVD, osteoporosis and infertility. This modelling approach has the potential to assess the long-term patient effects of therapeutic changes via their impact on the estimated model parameters, for example, number of sick day rules, BMI, systolic blood pressure and steroid use.

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Table and Figure Legends:

Table 1: Data used to estimate lifetime CAH burden

Table 2: Fertility model parameters

Table 3: Differences in LYs and QALYs between CAH and the general population, base case and sensitivity analysis

Figure 1: Diagram of the conceptual model

Figure 2: Effect of CAH on survival

Figure 3: Lifetime average number of fractures per person

Tables

Table 1: Data used to estimate lifetime CAH burden

	Mean	Max	Min	Source
Sick day rules per year	3	6	1	Clinical expert (RJR)
Hospital for IV hydrocortisone per year	0.066	0.074	0.038	Hahner 2010, Reisch 2012
Of which inpatient	0.75	1	0.25	Clinical expert (RJR)
P(death) after inpatient admission for AC	0.025	0.032	0.005	Clinical expert (RJR) , Rushworth 2014
Utility multiplier CAH	0.93	0.97	0.89	Derived from CaHASE (Arlt 2010, Rowen 2009)

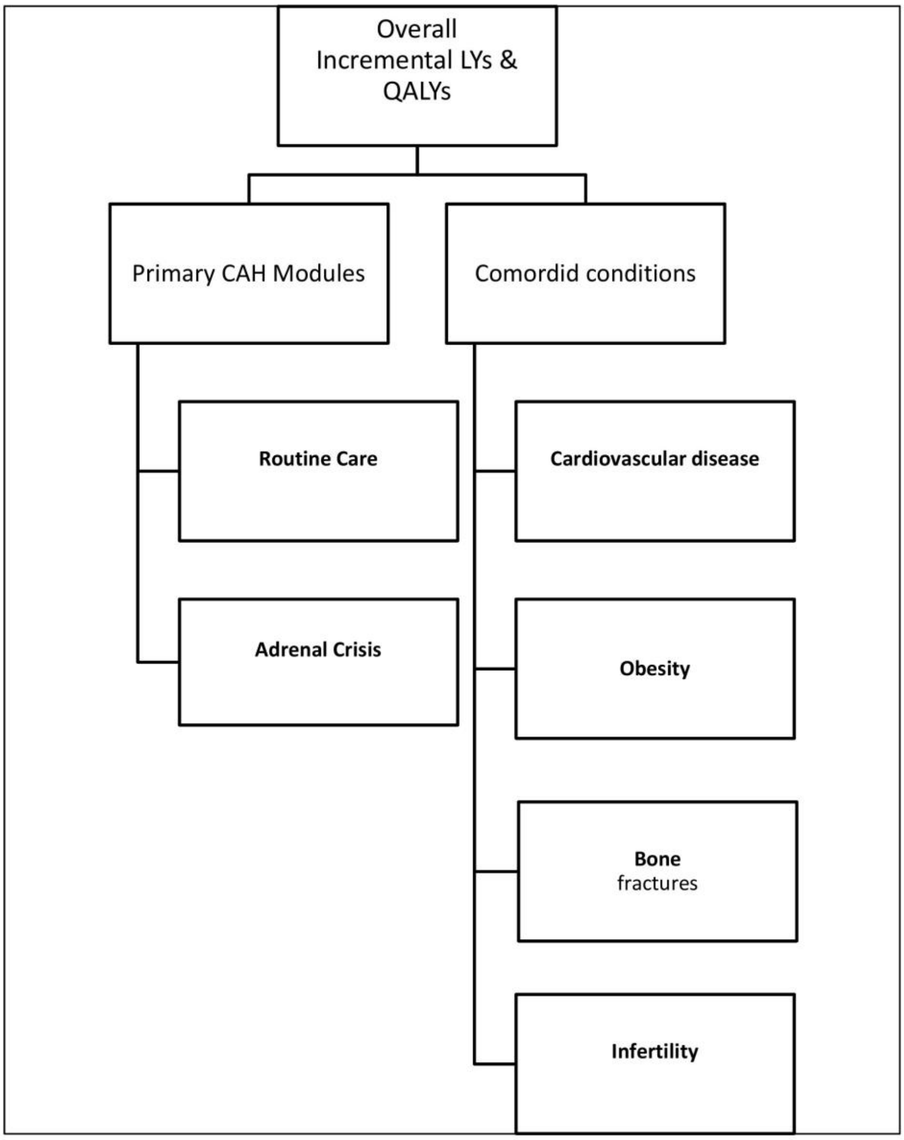
Table 2: Fertility model parameters

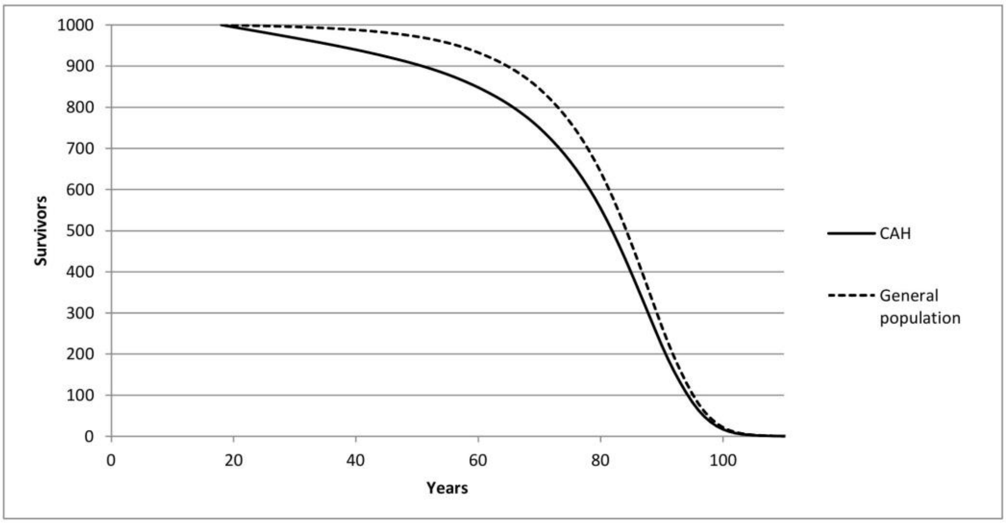
Item		Mean	Source
CAH parameters			
CAH seek fertility	**women**	0.25	CaHASE Arlt 2010
	men	0.37	
CAH succeed (of those seeking)	**women**	0.54	CaHASE Arlt 2010
	men	0.67	
General population parameters			
Unwanted infertility	**all**	0.07	NICE 2013
Proportion no previous child	**all**	0.59	Pandey 2014
Successful outcome	**all**	0.51	Pandey 2014
All			
Mean age 1st child	**women**	27.9	ONS fertility 2013
	men	30.8	ONS fertility 2013
Utility decrement infertility	**women**	0.07	NICE 2013
	men	0.07	Assumption

Table 3: Differences in LYs and QALYs between CAH and the general population, base case and sensitivity analysis

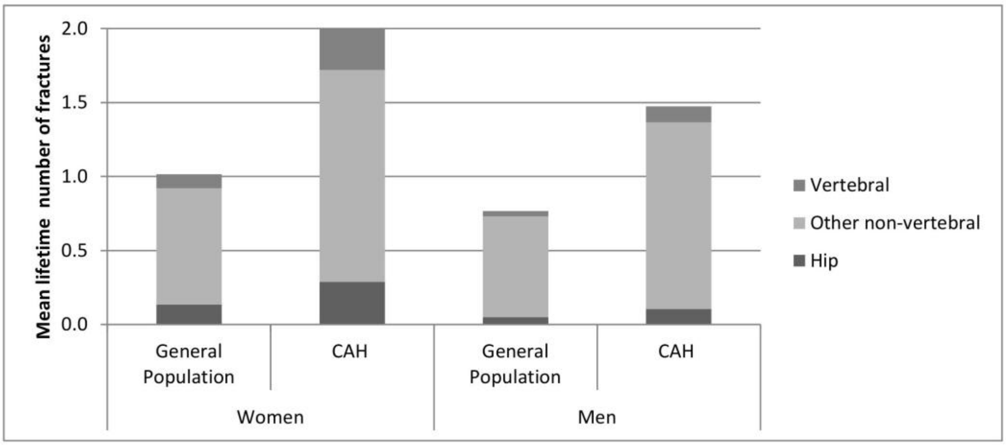
		Life Years			QALYs		
Item		**Women**	**Men**	**All**	**Women**	**Men**	**All**
Base case							
CAH/AC		-7.54	-6.77	-7.25	-9.22	-8.75	-9.04
Sensitivity							
CAH Utility	**max**	-	-	-	-7.35	-6.92	-7.18
	min	-	-	-	-11.10	-10.58	-10.90
AC sick day rules/year	**max**	-13.94	-12.56	-13.42	-13.97	-13.20	-13.68
	min	-2.66	-2.38	-2.55	-5.62	-5.38	-5.53
Hospital for IV hydrocortisone/year	**max**	-8.38	-7.53	-8.06	-9.84	-9.33	-9.65
	min	-4.50	-4.03	-4.32	-6.97	-6.65	-6.85
Of which inpatient	**max**	-9.79	-8.80	-9.42	-10.89	-10.31	-10.67
	min	-2.66	-2.38	-2.55	-5.62	-5.38	-5.53
P(death) following inpatient admission	**max**	-9.44	-8.49	-9.08	-10.63	-10.06	-10.41
	min	-1.61	-1.44	-1.55	-4.85	-4.66	-4.78
Base case							
CVD		-0.19	0.00	-0.12	-0.14	0.00	-0.09
Sensitivity							
RR of CVD	**max**	-2.17	-2.13	-2.16	-1.62	-1.67	-1.64
	min	0.00	0.00	0.00	0.00	0.00	0.00
Base case							
Obesity		-	-	-	-1.29	0.00	-0.80
Bone fractures		-	-	-	-0.39	-0.17	-0.30
Total		**-7.73**	**-6.77**	**-7.37**	**-11.04**	**-8.92**	**-10.24**

Figure 1 Diagram of the conceptual model





1000
900
800
700
600
500
400
300
200
100
0
Survivors
0
20
40
60
80
100
Years
CAH
General population


Mean lifetime number of fractures
2.0
1.5
1.0
0.5
0.0
General Population
CAH
General Population
CAH
Women
Men
Vertebral
Other non-vertebral
Hip