The Associations between Socioeconomic Position, Obesity and the Development and Progression of Arthritis

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List of abbreviations

ACPA	Anti-citrullinated protein antibody
ACR	American College of Rheumatology
ADL	Activities of daily living
BMI	Body mass index
CCP	Cyclic citrullinated peptide
CDAI	Clinical Disease Activity Index
CI	Confidence interval
CRP	C-reactive protein
CPRD	Clinical Practice Research Datalink
CT	Computed tomography
CVD	Cardiovascular disease
DMARDs	Disease modifying anti-rheumatic drugs
DAS	Disease Activity Score
EHR	Electronic health records
ELSA	English Longitudinal Study of Aging
ESR	Erythrocyte sedimentation rate
ESRC	Economic and Social Research Council
EULAR	European Alliance of Associations for Rheumatology
GB	Great Britain
GBD	Global burden of disease
GWAS	Genome wide association study
HAQ	Health Assessment Questionnaire
HES	Hospital Episode Statistics
HR	Hazard ratio
HSE	Health Survey for England
JRS	Joint replacement surgery
MAR	Missing at random
MCAR	Missing completely at random
MeSH	Medical subject heading
MNAR	Missing not at random
MRI	Magnetic resonance imaging
MTX	Methotrexate

NHANES	National Health and Nutrition Examination Survey
NHS	National Health Service
NICE	National Institute for Health and Clinical Care
NR	Not reported
OA	Osteoarthritis
OECD	Organisation for Economic Co-operation and Development
OR	Odds ratio
PICO	Population, intervention, comparison, outcome
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QUIPS	Quality in Prognosis Studies
RA	Rheumatoid arthritis
RAMS	Rheumatoid Arthritis Medication Study
RAPID3	Routine Assessment of Patient Index Data 3
RCT	Randomised controlled trial
RDCI	Rheumatic Disease Comorbidity Index
RF	Rheumatoid factor
RMDs	Rheumatic and musculoskeletal diseases
RR	Risk ratio
SD	Standard deviation
SDAI	Simplified Disease Activity Index
SEM	Structural equation modelling
SEP	Socioeconomic position
SF-36	36-item Short-Form Health Survey
T2DM	Type 2 diabetes mellitus
UI	Uncertainty interval
UK	United Kingdom
UN	United Nations
USA	United States of America
vs	Versus
WC	Waist circumference
WHO	World Health Organisation
WHR	Waist hip ratio
WHtR	Waist to height ratio

Abstract

Aim: Consistent evidence suggests that people with lower socioeconomic position (SEP) are more likely to be obese. Although research points towards social inequalities in arthritis, prospective cohort studies are lacking. Obesity is also related to both osteoarthritis (OA) and rheumatoid arthritis (RA). This PhD project aimed to improve our understanding of the complex relationships between SEP, obesity and the development and progression of OA and RA.

Methods: First, a systematic literature review (SLR) and a meta-analysis were performed to summarise the current understanding of the relationship between SEP and obesity. Meta-regression analyses were performed to investigate differences between measures of obesity (body mass index (BMI) and waist circumference (WC)) and gender. Then, using longitudinal data from the English Longitudinal Study of Ageing (ELSA) and the Rheumatoid Arthritis Medication Study (RAMS), the relationships between different indicators of SEP (education, occupation, income, wealth and area-level deprivation), obesity (BMI of ≥30 kg/m^2) and the development and progression of arthritis were investigated. Cox regression analyses estimated associations of SEP and obesity with incident arthritis and knee joint replacement surgery (JRS) in OA. Linear mixed models were used to study associations of SEP and obesity with repeated measures of disability and disease activity scores in OA and RA. Structural equation modelling and causal mediation analyses were performed to estimate the mediating effect of BMI on the relationships between lower SEP and the development and progression of OA and RA.

Results: The SLR indicated an association between having a lower education and obesity; this relationship was stronger among women than men (adj odds ratio (OR) women vs men 1.66 (95% CI 1.32, 2.08)). Only in men, the relationship was found to be stronger for obesity measured by WC compared to obesity measured by BMI (adjOR central vs total obesity in men 1.27 (95% CI 0.97, 1.67)). In ELSA, lower SEP was associated with higher rates of OA and RA (adj hazard ratios (HRs) lowest vs highest education category OA: 1.52 (95% CI 1.30, 1.79); RA: 2.23 (95% CI 1.74, 2.86)), which was mediated through BMI (completely for OA and partially for RA). Lower SEP was also associated with increased functional limitations over time in people with knee OA (e.g. difficulty walking 100 yards: no qualification vs degree adjOR 4.33 (95% CI 2.20, 8.55)). A small proportion of the association between lower SEP and functional limitations could be explained by BMI (6.2–12.5%). Those with lower SEP were less likely to have knee JRS (e.g. adjHR most vs least deprived 0.37 (95% CI 0.19, 0.73)). Using RAMS, deprivation was associated with higher disability (adj regression coefficients highest vs lowest deprivation fifths 0.32 (95% CI 0.19, 0.45)) and disease activity (0.34 (95% CI 0.11, 0.58)). BMI mediated part of the association between higher deprivation and self-reported disability (14.24%) and disease activity scores (17.26%).

Conclusion: Lower SEP is associated with the development and progression of arthritis, partially mediated through BMI. These findings illustrate the need to investigate the effectiveness of weight management strategies in people with arthritis from lower SEP.

Declaration

No portion of the work referred to in the thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.

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I dedicate this thesis to my family. Lieve **Opa** and **Oma**, thank you for being so enthusiastic about my research and for always being the first persons wanting to read my publications. You are both an inspiration to me. Thanks to my brother, **Sebastiaan**, and sisters, **Willemijn** and **Annemijn,** and their partners for supporting me through my PhD journey and for being the best siblings I could wish for. **Papa** & **mama**, thank you for helping me become the person that I am today. Without your encouragement and support, I would not have been standing here. I am forever grateful for your lessons to work hard and to follow my dreams.

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The Author

I graduated from the *Vrije Universiteit* Amsterdam with a BSc in Health & Life Science and an MSc in Public Health. After my degrees, I worked as a Healthcare IT Consultant for Cerner Cooperation, implementing electronic health records in hospitals, and subsequently as a Medical Writer at Nucleus Global, communicating the latest obesity and diabetes research to healthcare professionals and pharmaceutical companies. Because I was eager to learn and improve my understanding of science, I started my PhD programme at the Centre for Epidemiology Versus Arthritis at the University of Manchester. I will continue my career as a Research Associate at the University of Liverpool, researching population-based obesity interventions.

Publications

Witkam, R., Gwinnutt, J. M., D.A, Cooper, R., Humphreys, J.,& Verstappen, S. M. (2022). Is the relationship between deprivation and outcomes in rheumatoid arthritis mediated by body mass index?. (Under Review) In: Rheumatology.

Witkam, R., Gwinnutt, J. M., D.A, Cooper, R., Humphreys, J.,& Verstappen, S. M. (2022). The associations between obesity, socioeconomic position and progression of osteoarthritis: results from the English Longitudinal Study of Ageing. (Under Review) In: Osteoarthritis & Cartilage.

Witkam, R., Gwinnutt, J. M., Selby, D.A, Cooper, R., Humphreys, J.,& Verstappen, S. M. (2022). Does body mass index mediate the relationship between socioeconomic position and incident osteoarthritis?. Seminars in arthritis and rheumatism, 56, 152063.

Witkam, R., Gwinnutt, J. M., Humphreys, J., Gandrup, J., Cooper, R., & Verstappen, S. M. (2021). Do associations between education and obesity vary depending on the measure of obesity used? A systematic literature review and meta-analysis. SSM-population health, 15, 100884.

Awards and achievements

2022	EULAR travel bursary
2022	Doctoral Academy Conference Fund
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2021	4th MethodsX Conference, 1st prize for 3-minute thesis presentation
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Conference presentations and talks

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2022	EULAR 2022, Copenhagen (**poster** and **poster tour**)
2021	American College for Rheumatology 2021, online (**poster**)
2021	Society for Social Medicine & Population Health Annual Virtual Meeting 2021, online (**oral**)
2021	UK-RiME, Bristol (**PhD elevator pitch**)
2021	MethodsX, online (**3-minute thesis presentation**)
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2021	Teaching Assistant at the Master of Public Health, in: Climate Change and Health
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Role of the candidate in this PhD

I worked on all aspects of this PhD, including:

- Design and development of research questions
- Establishing collaborations
- Planning analyses
- Data cleaning and preparation
- Statistical analyses
- Interpretation of the results
- Presenting findings at conferences
- Writing manuscripts
- Writing this thesis

Journal format

This PhD thesis is was written in the journal format. The main aim of this thesis could be subdivided into four separate objectives. Each of these objectives answer a specific research question; therefore, the different results chapters (Chapters 3, 4, 5 and 6) are in a format suitable for publication in a journal. Each results chapter includes their own table and figure numbers and reference list. Chapters 3 and 4 have already been published and Chapters 5 and 6 are currently under review.

Chapter 1

1. Introduction

"*There can be no more important task for those concerned with the health of the population than to reduce health inequalities*".

This was said by the well-respected Professor Sir Michael Marmot. In his influential reports *Fair Society Healthy Lives*[1] and *Health Equity in England: The Marmot Review 10 years on*[2], he highlights the realities of widening health inequalities in England. As this PhD demonstrates, health disparities in musculoskeletal diseases are currently under-researched. The aim of this PhD thesis is to advance the understanding of the relationships between socioeconomic factors, obesity and the development and progression of arthritis. For this PhD project, I will specifically focus on osteoarthritis (OA) and rheumatoid arthritis (RA), two of the most common rheumatic and musculoskeletal diseases (RMDs) worldwide. The introduction will explain the epidemiology and risk factors for obesity, OA and RA.

1.1 Obesity

1.1.1 Definition and classification

For most of human history, fatness and excess body weight was seen as a sign of being healthy and affluent[3]. The negative impact of obesity on health started to be appreciated in the 19th century and, subsequently, insurance companies started to document the morbidity and mortality of obesity in the 20th century as they noted increased mortality claims for policy holders with excess weight[3]. The exponential increase of obesity in the last few decades (section 1.1.2) has led the World Health Organisation (WHO) to acknowledge obesity as a 'global epidemic'[4].

The WHO defines obesity as 'abnormal or excessive fat accumulation that presents a risk to health'[5]. The most precise methods to measure body fat are underwater weighing, dual-energy X-ray absorptiometry scanning, computed tomography (CT) and magnetic resonance imaging (MRI). However, these methods are expensive, time-consuming and resource-intensive, and therefore not practical to use in large scale epidemiological studies or every day clinical encounters[6].

More commonly applied estimates include body mass index (BMI), waist circumference (WC) and waist-to-height ratio (WHtR); although these methods do not measure fatness directly (e.g. they do not differentiate between fat and muscle), they are considered acceptable proxies to estimate fatness and have been demonstrated to be directly related to health risks, such as hypertension, type 2 diabetes mellitus (T2DM) and cardiovascular diseases (CVDs)[6]. Furthermore, they are practical and inexpensive to measure in both population studies and for clinical assessments[6]. The following sections will discuss BMI, WC and WHtR in more detail.

1.1.1.1 Body mass index

In 1823, Adolphe Quetelet first proposed a measure of weight in kilograms divided by the square of height in metres (kg/m^2) based on the proportion of the 'average man'[3]. Later, in 1972, Ancel Keys used kg/m^2 together with other existing weight-relative-to-height indices (kg/m and kg/m^3) and compared it with body fat (using skinfold and body density measurements) in a group of men aged 18–60 years from the US, South Africa, Italy, Finland and Japan[7]. Keys concluded that kg/m^2 had the highest correlation with body fat and thus was "preferable over other indices"; he named it BMI[7]. Although initially the relationship between BMI and body fat was only studied in men, later studies have confirmed a similar relationship in children (of the same sex and age)[8, 9] and women[10, 11].

Following validation studies of BMI with body fat, BMI cut-off points by the WHO and the National Institute of Health (NIH) were developed to classify people in different weight categories based on risk for cardio-metabolic diseases (T2DM and CVDs) and mortality[12, 13]: underweight (BMI <18.5 kg/m^2), normal weight (BMI 18.5–24.9 kg/m^2), overweight (BMI 25.0–29.9 kg/m^2) and obesity (BMI ≥30.0 kg/m^2). These categories were initially based on visual inspection of the U-shaped relationship between BMI and mortality[12, 13]. Whilst this is an imprecise method of determining cut-off points, further studies confirmed that these cut-

off points were the same for men and women based on results of studies linking BMI to the risk of developing T2DM and CVDs[13-23]. These cut-off points may be less valid for populations aged ≥65 years, where BMIs of <23.0 and >33.0 are associated with increased mortality (compared to those with BMIs between 23 and 33)[24]. However, official cut-off points for the elderly have not been established. Therefore, the National Institute for Health and Care Excellence (NICE) recommends that in the elderly, BMI categories should be interpreted based on "comorbidities, functional capacity and the possible protective effect of adiposity"[25].

Moreover, the cut-off points are based on studies including mainly White and Hispanic populations and are therefore valid for determining the risk of cardio-metabolic diseases and mortality in these ethnicities[12, 13]. However, it has been recognised that they underestimate these risks in Asian and Black populations[26-29]. Therefore, both WHO and NICE recommend a cut-off point of ≥27.5 kg/m^2 to define obesity for Asian, South-Asian and Black populations[26, 30]. This is important to take into account when studying populations including a diverse ethnic population. Moreover, in general, categorising a continuous variable such as BMI leads to a loss of information. Therefore, in this PhD, I will include BMI both as a continuous and a categorical measure.

BMI is most commonly used in population-based studies[6]; however, it is important to note that BMI may not be useful for all groups. Some groups, including athletes and body builders, have an elevated BMI because of increased muscle mass; therefore, they might be classified as obese but not have increased health risks[31]. Consequently, measurements reflecting abdominal fat mass such as WC, explained in the following section, are now increasingly used. This PhD uses the term 'total obesity' to describe obesity defined by BMI and 'central obesity' to describe obesity defined by WC.

1.1.1.2 Central obesity

1.1.1.2.1 Waist circumference and waist-to-hip ratio

Fat distribution in the abdominal area is called central obesity and is typically measured using WC or WHR. WC is measured with a measuring tape around a person's middle, just above the hipbones, and WHR is calculated by dividing the WC by the hip circumference measurement (usually in centimetres). Both WC and WHR are acceptable measures of central obesity and associated morbidities; however, WC is a preferred measure because it is easier to measure than WHR[32].

Compared to total obesity, central obesity has a stronger association with inflammatory markers (including C-reactive protein (CRP), tumor necrosis factor alpha, amyloid A, white blood cells and interleukin-6)[33]; low grade and persistent inflammation has been implicated in a wide range of diseases, including CVDs[34], T2DM[35], cancers[36], depression[37], OA[38] and RA[39]. Some studies also suggest that central obesity is a better predictor for cardio-metabolic diseases compared with total obesity[40-42]. For example, a meta-analysis including data of 300,000 people globally, concluded that WC was more predictive of obesity-related cardio-metabolic diseases than BMI based on area under the Receiving Operating Characteristic (ROC)

curve (AUC) metrics (Table 1)[42]. The ROC curve is based on the sensitivity (i.e. true positives) and specificity (i.e. true negatives) of a predictor; an AUC of 1 would suggest perfect prediction and an AUC of 0.5 would suggest the prediction is no better than chance[42].

Table 1: Differences in AUC between WC and BMI for cardio-metabolic disease risk (T2DM, dyslipidaemia, hypertension and CVD) for men and women[42]

	Men		Women	
	Mean AUC (95% CI)	p-value compared to BMI	Mean AUC (95% CI)	p-value compared to BMI
BMI	0.667 (0.650, 0.684)		0.681 (0.658, 0.704)	
WC	0.694 (0.678, 0.709)	0.026	0.714 (0.698, 0.731)	0.022

AUC, area under the curve; BMI, body mass index; CI, confidence interval; WC, waist circumference.

The WHO's cut-off points for WC and WHR, associated with cardiovascular risk factors, are shown in Table 2[32]. These cut-off points were first suggested by Lean et al (1995)[43] and later validated in a study from the Netherlands including 2183 men and 2698 women aged 20–59 years, which investigated the risk for CVD risk factors (i.e. cholesterol and hypertension) (Table 3)[44]. Initially based on this study, the WHO published these cut-off points in its report *Obesity: Preventing and Managing the Global Epidemic* published in 2000[32].

Table 2: WHO's cut-off points and risk for metabolic complications[32]

Indicator	Cut-off points		Risk of metabolic complications
	Men	Women	
WC	>94 cm (37 in)	>80 cm (31.5 in)	Increased
WC	>102 cm (40 in)	>88 cm (34.5 in)	Substantially increased
WHR	≥0.90	≥0.85	Substantially increased

cm, centimetres; in, inches; WC, waist circumference; WHO, world health organisation; WHR, waist-to-hip ratio.

Table 3: Odds ratios of cardiovascular risk factors by WC categories

Cardiovascular risk factors	Men OR (95% CI)			Women OR (95% CI)		
	<94 cm	94–102 cm	>102 cm	<80 cm	80–88 cm	>88 cm
High total cholesterol (≥6.5 mmol/l)	ref	1.38 (1.02, 1.87)	2.29 (1.67, 3.14)	ref	1.51 (1.14, 2.00)	1.42 (1.06, 1.89)
Low high density lipoprotein cholesterol (≤0.9 mmol/l)	ref	2.37 (1.85, 3.04)	3.64 (2.75, 4 80)	ref	1.54 (1.00 to 2.38)	3.80 (2.59, 5.59)
Hypertension (systolic blood pressure ≥160 mm Hg / diastolic blood pressure ≥95 mm Hg)	ref	1.98 (1.33 to 2.95)	4.03 (2.72, 5.96)	ref	1.84 (1.17 to 2.88)	4.23 (2.83, 6.33)

CI, confidence interval; cm, centimetres; ref, reference category; OR, odds ratio. Adjusted for age, alcohol, cigarette smoking, physical activity and education

These cut-off points are based on a Caucasian population and it has been recognised that the relationship between central obesity and comorbidities varies by ethnicity[45, 46]. According to the International Diabetes Federation, Asian (South Asians, Chinese and Japanese) and Ethnic South and Central American men have an increased risk of metabolic complications at WC of >90 cm (compared to >94 cm for Europeans). For females, the cut-off stays at >80 cm[47].

In contrast to the cut-off points for BMI, there are differences between men and women for the cut-off points for WC. Although women have more total body fat than men (reasons have been attributed to parity and hormones[48]), men have substantially more abdominal fat accumulation than women[49]. Specifically abdominal fat rather than total fat is predictive of T2DM and CVDs[50]. Moreover, the aforementioned Dutch study showed that women have an increased risk in CVDs at lower WC compared to men[44]. As a result, the cut-off points for WC are sex-specific.

Similarly to BMI, researchers have argued that the WC cut-off points should be higher for older populations[51-53]. Optimal cut-off points for Caucasian elderly have been proposed based on health outcomes, such as CVDs and T2DM; for instance, 109 cm in men and 98 cm in women[53] and 123 cm in men and 105 cm in women[52]. However, optimal cut-off values for people aged 65 years and older have not yet been formally developed. As such, studies including older populations still use cut-off points mentioned in Table 1. This may lead to the underestimation of the consequences of a high WC in an older population. Further research and expert consensus are needed to establish the correct cut-off values for older adults in different ethnic groups. Similarly to BMI, due to the limitations of using cut-off points, this PhD will use both a continuous and a categorical measure of WC.

1.1.1.2.2 Waist to height ratio

Updated NICE guidelines suggested the use of waist-to-height ratios (WHtR) (dividing WC by height) in addition to BMI for adults[25]. Based on increased risks for T2DM, hypertension and CVD, it defines a healthy WHtR as 0.4–0.49, increased WHtR as 0.5–0.59 and high WHtR as ≥0.6. As these categories are valid for both genders and all ethnicities, it provides an easy public health message: "keep your waist to less than half or your height". As WC does not take into account height, WHtR may be more appropriate to assess populations with different heights and ethnicities; for example, people with the same WC but different heights may have different cardio-metabolic risk (i.e. shorter people have higher risks)[54]. The next section will discuss the epidemiology of obesity.

1.1.2 Epidemiology

According to WHO estimates, globally 650 million had total obesity in 2019[5]. In a report from the Non-Communicable Diseases Risk Factor Collaboration (NCD-RisC) in 2017[55], trends of global obesity prevalence rates were estimated based on 2416 population-based data sources from 200 countries: obesity prevalence rose from 3.2% (95% CI 2.4%, 4.1%) in 1975 to 10.8% (95% CI 9.7%, 12.0%) in 2014 in men, and from 6.4% (95% CI 5.1%, 7.8%) to 14.9% (95% CI 13.6%, 16.1%) in women. These numbers highlight that, globally, obesity has more than tripled in men and doubled in women in the last four decades.

In England, the latest results from the Health Survey for England 2019 (HSE19)[56], a yearly survey studying the health of the English population, demonstrated that, defined by BMI, the majority of the adult population aged ≥16 years (68% (95% CI 66%, 70%) for men and 60% (95% CI 59%, 62%) for women) was either overweight or obese. The proportions of people with total obesity were 27% (95% CI 25%, 29%) for

men and 29% (95% CI 27%, 31%) for women. The proportion of obese adults has almost doubled from 14.9% in 1993 to 28% in 2019[56], and are substantially higher than the global prevalence estimates mentioned above. The HSE19 also estimated central obesity[56]: 36% of men and 48% of women had central obesity. This highlights that central obesity is more common than total obesity in England. For these specific figures, it is not mentioned whether ethnic-specific BMI and WC categories were used; therefore, these figures may even be an underestimation of the real total and central obesity prevalence in England.

The results of HSE19 indicate that total obesity prevalence increases until adulthood (for men until the age of 75 and for women until age 45), after which it decreases at the age of 75 years and older (Figure 1). Whilst central obesity drops at that age too, the reduction of WC appears lower than BMI. This can be explained by normal processes in ageing, including a decrease in muscle mass and a relative increase in body fat[57]. Another reason for the drop after 75 years of age could be that obese people die earlier than non-obese people[58], reducing its prevalence in the older age groups.

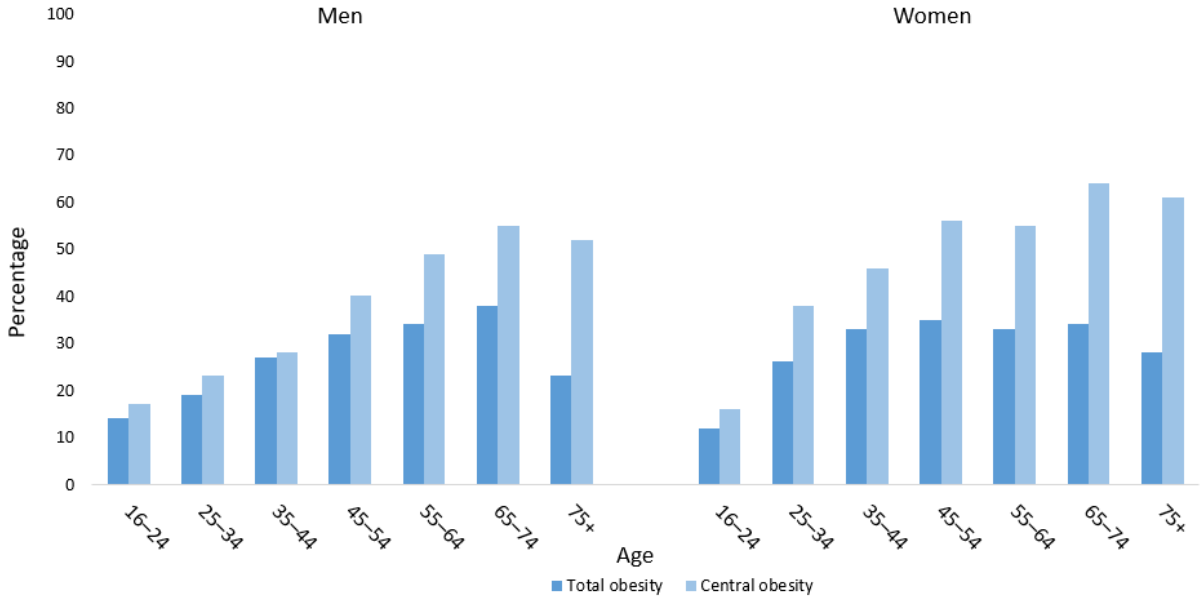


Figure 1: Prevalence of total and central obesity among English adults (aged 16+) by gender and age in the year 2019 (Adapted from: NHS digital, 2019[56])

Differences in ethnicity were not reported in the most recent HSE in 2019; however, the 2017 report did report obesity data stratified by ethnicity, pooling data from 2015, 2016 and 2017 (Figure 2)[59]. The HSE17 defined ethnic-specific obesity cut-off points for Black and Asian populations at BMI ≥27.5 kg/m^2, but not for the Mixed ethnicity group (e.g. White and Black, White and Asian). Obesity of the Mixed ethnicity group may therefore be underestimated. There are ethnic variations for obesity rates, with Black women having the highest obesity rates (66%) and White/Mixed men and women the lowest (24–27%).

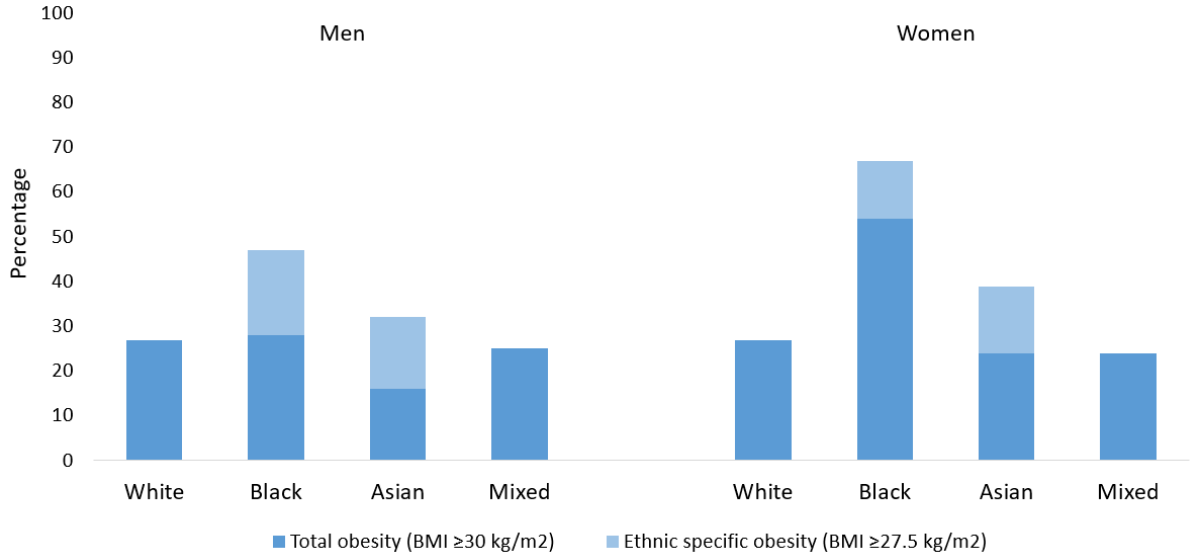


Figure 2: Prevalence of (ethnic-specific) obesity among English adults (aged 16+) by gender and ethnicity in the years 2015, 2016, 2017 (Adapted from: NHS digital, 2017)[59]

The HSE19 also reported that those who live in the most deprived areas (defined by the Index of Multiple Deprivation (IMD) quintiles[60]) are more likely to have total and central obesity compared to those living in the least deprived areas in the UK (deprivation is explained in more detail in section 1.1.3.3.5). The difference of total obesity is greater between the least and most deprived areas for women compared with men: 22% versus 39% for women and 22% versus 30% for men (Figure 3)[56].

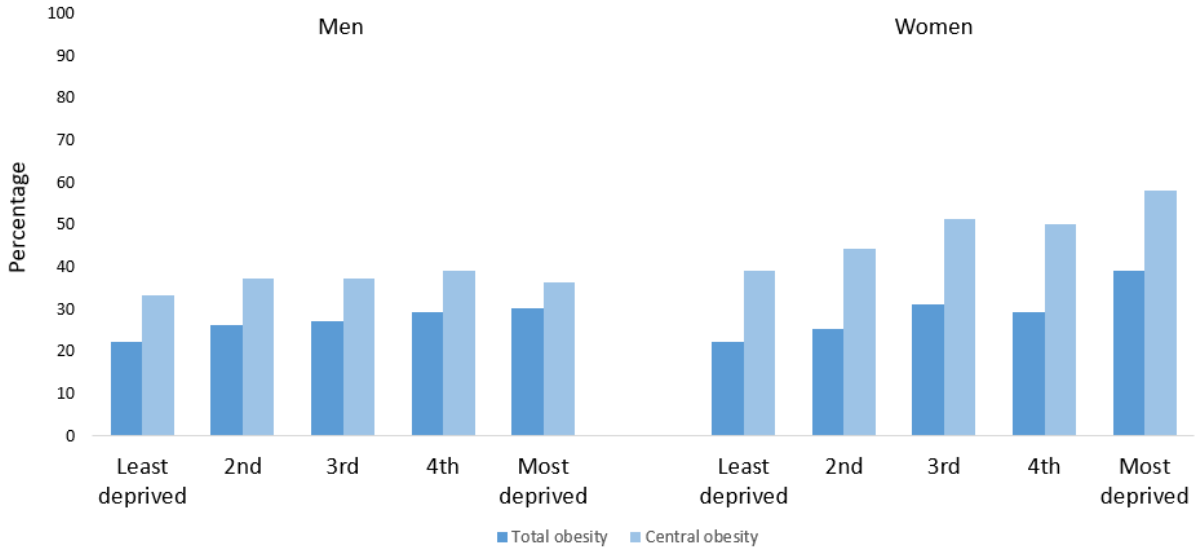


Figure 3: Prevalence of total and central obesity among English adults (aged 16+) by gender and deprivation status in the year 2019 (Adapted from: NHS digital, 2019[56]). Deprivation is defined by the Index of Multiple Deprivation quintiles.

1.1.3 Risk factors of obesity

Managing, reducing and preventing obesity has not been successful to date due to the complex and multifactorial aetiology of the disease[32]. The primary cause of obesity can be simply explained as an imbalance of calories consumed, calories stored and calories burned. The energy imbalance is, however, heavily influenced by a complex interaction of genetic factors, lifestyle factors and the wider social environment.

1.1.3.1 Non-modifiable risk factors: genetics, age, gender, ethnicity

The role of genetics in obesity is an ongoing field of study[61] and with the first genome-wide association studies (GWAS) for obesity starting in 2007, over 1100 different genetic variations have now been reported that could be associated with obesity[61]. However, for most of these genes the underlying mechanisms of how they affect weight are unknown[61]. Nonetheless, it is generally agreed that the rise in obesity prevalence over the last few decades cannot be attributed to genes alone as it is unlikely that our genes have changed that substantially in a relatively short timeframe[62].

As mentioned in the previous section, obesity prevalence varies by age, gender and ethnicity. Although obesity may occur at any age, the prevalence increases until adulthood and decreases again after the age of 75 years[56]. Moreover, evidence suggests that the prevalence of obesity in most countries is greater and more variable in women compared with men[63-65]. The variability in women may be due to social factors, which are explained in more detail in section 1.1.3.4. Variation in ethnicity is considered to be due to genes and lifestyle factors that may increase susceptibility for weight gain when exposed to certain environmental factors[66], cultural differences in body image[67] and social factors[68].

1.1.3.2 Lifestyle factors: diet and physical activity

Lifestyle factors, such as diet and exercise, are two factors that impact the energy balance in the body. Measuring dietary intake in epidemiological studies is difficult due to recall bias and social desirability bias (i.e. underreporting of unhealthy foods)[69]. Traditionally, nutritional epidemiological studies focussed on single nutrients when studying the relationship between food and disease; however, single nutrients do not take into account the complicated interactions between nutrients[70]. Therefore, dietary pattern analysis, using factor analysis or principal component analysis, has become a more popular method, which describes an overall diet (i.e. combinations, frequency or quantity of foods)[70]. A recent meta-analysis assessed 14 cross-sectional and four longitudinal studies that used this type of dietary pattern analysis in Europe, Asia and South, Central and North America. It demonstrated that an unhealthy diet pattern (high factor loadings of red/processed meats, refined grains, potatoes, sugary food and high-fat dairy) were more likely to have total obesity compared to people who eat a healthy diet (high factor loadings of fruit, vegetables, poultry, fish, low-fat dairy and whole grains) (OR 1.65 (95% CI 1.45, 1.87))[71]. The review noted that the association was stronger for smaller studies (n<1000) (OR 2.12 (95% CI 1.74, 2.58) compared to larger studies (n>1000) (OR 1.59 (95% CI 1.46, 1.74)), and the association was slightly stronger for longitudinal studies (OR 1.84 (95% CI 1.34, 2.51) than cross-sectional studies (OR 1.59 (95% CI 1.45, 1.73)).

This may indicate that people's diet change once they become obese; however, the number of longitudinal studies in this review was too small to make these type of conclusions. No subgroup analysis by region was performed, but there was some indication that the association was slightly stronger for "yellow and other race (sic)" (OR 1.66 (95% CI 1.31, 2.10)) than "white race" (OR 1.59 (95% CI 1.45, 1.73); however, this difference may not be meaningful as the confidence intervals overlap and the authors did not perform any formal statistical comparisons.

Physical activity refers to 'any bodily movement produced by skeletal muscle that results in a substantial increase over the resting energy expenditure'[72]. It includes activities undertaken during work, household activities and free time (e.g. exercise and sports). In contrast, sedentary behaviour refers to 'a state when body movement is minimal'[73] and includes, among other things, television viewing, computer work and driving a car. Research about the relationship between physical activity and weight is conflicting. Cross-sectional studies typically yield stronger associations between sedentary behaviour and total and central obesity[74, 75] compared to longitudinal studies[76-78]. In a cross-sectional study, physical activity levels and obesity are measured at the same time-point; therefore, reverse causation in cross-sectional studies may explain some of these associations (i.e. obesity leads to physical inactivity rather than physical inactivity leads to obesity). Randomised controlled trials (RCTs) remove some of the biases of observational studies, as randomisation of the population in a treatment versus control group balances (observed and unobserved) participant characteristics between the two groups[79]. Therefore differences in the outcome of the study can be attributed to the intervention[79]. A meta-analysis of RCTs reported that aerobic exercise yielded only modest, not clinically significant (i.e. more than 5% weight loss over 6–12 months[80]), loss in weight in overweight men and women[81]. Another narrative review argued that to reach clinically meaningful weight loss without changing diet, 225–420 minutes/week of moderate intensity aerobic exercise was needed[82]. This would indicate that the current NHS guidelines to exercise at least 150 minutes of moderate intensity or 75 minutes of vigorous activity a week[83] is insufficient for weight loss (although it is associated with improved health status[84]). From this evidence, it is likely that physical inactivity plays a modest role in the development of obesity, but is not the main cause.

Many interventions aiming to tackle obesity have focussed on individual lifestyle factors, such as diet and physical activity (either together or separately); however, research has shown that it is challenging to change individual behaviour[85]. This might be because individual behaviours are influenced by socioeconomic factors, explained in the next section.

1.1.3.3 Socioeconomic position

Section 1.1.2 described that the prevalence of obesity was higher in the most deprived communities compared to the least deprived communities. Before discussing the relationship between socioeconomic position (SEP) and obesity further in section 1.1.3.4, this section will first introduce the concept of SEP.

SEP refers to an individual's economic and social position within a society[86, 87] that influences "life chances"[88]. It is a multifactorial concept and includes a range of indicators that are all interconnected, such as education, income, wealth, occupation and area-level deprivation. The relationship between SEP and health is usually not due to a single indicator; rather, a complex interaction between multiple pathways during the life course are important, where an individual's health is affected by their standard of living, work and social interactions[87]. There is no single indicator best suited for all study aims. Therefore, this section will explain the advantages and disadvantages of different SEP indicators, including education, income, wealth and occupation as individual level indicators and deprivation as an area-level indicator.

1.1.3.3.1 Education

Education not only aims to capture the knowledge of a person, it also reflects childhood and adolescent SEP as it is influenced by parental/carer characteristics and their economic situation[86]. Education also strongly influences future occupation, income and wealth. Consequently, the effect of education on health may be influenced by many processes over the life course, including early life circumstances, accrued knowledge and analytical thinking skills, and through the effect of education on income and occupation (how these concepts impact health are explained in sections 1.1.3.3.2 and 1.1.3.3.4). Together, these processes may influence whether someone understands health education messages and has access to health care services[86]. However, it is important to note that social selection may also explain some of the relationship between education and health: being ill during childhood may limit educational opportunities and affect health later on in adulthood[89].

Advantages of using education in epidemiological studies include that it is easy to measure and usually has a high response rate[86]. Furthermore, in contrast to other SEP indicators, formal education is stable over the life course as it is not likely to change in adulthood. This reduces the chance of reverse causation: education is unlikely to be influenced by health conditions later in life. However, it is important to note that the meaning of education differs for different birth cohorts; movements towards improving educational opportunities have resulted in increased educational attainment for women and ethnic minorities in recent decades[90]. For example, the less educated might be overrepresented in older cohorts. Therefore, education may not be the most appropriate SEP indicator for older cohorts. To minimise this limitation, it is possible to define education level based on the relevance to a specific birth cohort (i.e. high, medium, low education relative to the birth cohort) or to stratify the cohort by age[86].

There is no universally accepted measure of education and, therefore, within-country and between-country comparison between studies may be problematic[90]. It can be measured using years of completed education (usually continuous) or qualifications achieved (for example, a University degree) (categorical). The first measure focusses on time spent in the education system (the more years in education, the higher the SEP)[91]. An advantage of this measure is that it can be added to regression models as a continuous variable, which is easy to interpret (i.e. one extra year of education leads to x increase in outcome)[90], has

more statistical power due to greater precision[92] and may be easier to compare to other studies. A limitation is that years of education does not equal educational qualifications; for example, in the UK, different levels and types of qualifications may require the same amount of study time[90]. It therefore measures the input, but not always the output[93]. Moreover, years of education is only modestly associated with educational qualifications[94].

The second measure, based on achieved qualifications, presumes the importance of specific qualifications in affecting someone's SEP. The advantage is that it provides more detail about whether the qualification is vocational or academic, potentially influencing health status through future occupation and income. However, given the many different qualifications in the UK, it is sometimes challenging to create appropriate categories. Even within the UK, categories of different national surveys vary making comparisons between them challenging[90]. Moreover, there is usually a category 'I don't know', 'other' or 'foreign education' for respondents who do not identify with existing categories. This can impact the ordinal nature of the categories and therefore create difficulties for interpretation[93]. Lastly, qualifications and quality of education are not standardised across different countries and therefore comparing educational categories across countries is challenging[95].

1.1.3.3.2 Income

Income refers to money received as a return for paid work or investments. Income is dynamic; it tends to increase over time and it may change quickly (e.g. due to loss of employment)[96]. It can be measured on the individual level, capturing a person's earning ability, or household level, reflecting living standards of the household[97]. In research, income is typically measured at the household level rather than the individual level. This takes into consideration that some people might not be the main earner of the household, but that the income is spread across the household. Equivalised income also takes into account the amount of people who are dependent on the household income (e.g. family size)[86].

Income affects health in two main ways. Firstly, earnings can be used for commodities and services that affect health, such as housing, childcare, healthy food and gym/leisure memberships[98]. Secondly, it also provides the opportunity to participate in social activities (e.g. cultural events, social gatherings) and being able to "control life circumstances"[98].

An advantage of using income as an indicator for SEP is that it directly measures financial resources. However, research participants may not always be willing to disclose their income as it is considered personal; therefore, non-response can be an issue[86]. Moreover, current income for young and older adults might be less reliable as income usually increases over time when a person progresses in his/her career as well as for older adults as they may be retired. Reverse causality should also be considered in cross-sectional studies; those that are healthy are more likely to work full-time and to secure and retain a high income[86]. Prospective studies reduce the effects of reverse causality.

1.1.3.3.3 Wealth

Wealth is an indicator of financial and material resources accumulated over a lifetime. It combines non-housing assets (i.e. savings, investments, physical assets (i.e. second homes)) and primary housing minus any debts[99]. Wealth is accumulated over the years and therefore it has been suggested that wealth is an appropriate SEP indicator in older age groups[100]. Income in older age groups may decline, but this may not be reflected in their living standards due to accumulated savings and assets[101].

1.1.3.3.4 Occupation

Occupation can be used as an indicator of a person's place in society. It is related to education on the one hand (education may influence the type of occupation) and income on the other hand (type of occupation influences income)[86]. Current or longest held occupation is most commonly asked in studies; however, some studies include parental occupation as a childhood SEP indicator. The 'highest occupational status in the household' can be used as an indicator for dependants[86].

There are different mechanisms for how occupation can be related to health outcomes. Firstly, occupation may be associated with income and thus the ability to buy material goods and services (mentioned in section 1.1.3.3.2) that may impact health[102]. Secondly, occupation can be associated with certain privileges which influence health status (e.g. educational opportunities in the workplace, housing and increased flexibility as well as access to healthcare and insurance which may be especially important in countries without a tax-based healthcare system, such as the USA)[86]. Thirdly, social networks developed through occupation may increase self-esteem and self-worth and subsequently affect health status[103]. Fourthly, occupational exposures (e.g. working in a toxic environment, physical demands) also influence someone's health status[104]. Lastly, the Whitehall Study of British civil servants showed that people at the bottom of the occupational hierarchy typically experience more occupational stress due to lack of "control" and "support" and consequently have poorer health outcomes compared to those at the top of the occupational hierarchy[105].

An advantage of using occupation as an indicator for SEP is that it is widely available in survey data[86]. On the other hand, a major limitation is that some groups are not currently employed, such as students, the unemployed, those receiving disability benefits, the retired, homeworkers, volunteers (who do not have a paid job next to volunteering) or people having informal jobs. Asking 'previous occupation' or the 'highest occupation in the household' can be a solution for some of these excluded groups. However, for the retired, it might not be an accurate representation of their current SEP. Similarly to education, occupation has different meanings for different age groups. In an older population, it might be acceptable to define a women's SEP based on her husband's occupation. However, nowadays, women are more engaged in the workforce and would expect to be recognised for their occupation. Therefore, differences in age groups need to be taken into account[86].

1.1.3.3.5 Deprivation

SEP can also be classified on a neighbourhood level, such as area-level deprivation. Area-level deprivation relates to how people live and can be seen as a consequence of a lack of income and resources[106]. The most commonly used deprivation index in the UK is the Index of Multiple Deprivation (IMD)[60]. The IMD is a measure of relative deprivation of small areas in England based on 39 indicators across seven domains of deprivation (income; employment; education, skills and training; health deprivation and disability; crime; barriers to housing and services; and living environment)[60]. Each domain is measured with the "best possible" indicators available (39 in total) and combined into a composite score based on weights[60]. The composite score can be ranked nationally, from the most deprived to the least deprived areas. These scores are often divided into five equal groups, ranging from the most deprived 20% to the least deprived 20% of small areas nationally. The IMD has been an effective tool to inform the government (both on a local and national level) which areas require funding and resources. Given the complexity of SEP, the use of multiple components in one score can be viewed as an advantage over other simpler indicators, such as education level[107].

However, there are some limitations of deprivation indices. The choice of indicators are usually based on the availability of reliable data sources and can therefore be seen as being based on practicality rather than grounded in a well-developed theory[108]. In addition, the weighting of certain domains have been viewed as "arbitrary"[107]. Moreover, deprivation indices cannot be used to identify deprived individuals; area-level deprivation does not mean that each individual living in a deprived neighbourhood experiences personal deprivation, and people experiencing deprivation may not live in deprived neighbourhoods classified by IMD. Lastly, the boundaries of different areas are rigid in the measure, but may in reality be more complex[107]. Although the IMD gives an overall overview of the relative deprivation experienced in an area, it is important to note that it is a crude measure and it may miss out on a substantial amount of people who experience deprivation[107].

1.1.3.3.6 Summary

To summarise, SEP is a complex concept and is seen as an umbrella term for multiple factors, including education, income, wealth, occupation and deprivation. As discussed, each concept measures something slightly different and has advantages and disadvantages. Moreover, the relationship between SEP and health happens through multiple pathways during the life course, where multiple indicators are important. Therefore, this PhD project will look at the associations between SEP and health through individual indicators as well as combining the indicators into one 'latent variable' (section 2.4.4) to have a complete overview SEP. Sections 2.3.1.3.2 and 2.3.2.3.1 provide information on how each of these indicators are measured in the datasets.

1.1.3.4 The relationship between socioeconomic position and obesity

In high-income countries, there is now widespread consensus that lower SEP is associated with total obesity; however, this association may be gender-specific[109-115]. A meta-analysis by Newton et al (2017) including 14 longitudinal and cross-sectional studies found that a lower life course SEP (using any of the indicators described in section 1.1.3.3) was associated with obesity among women (OR lowest life course SEP category with the highest 1.35 (95% CI 1.04, 1.76), but not among men (OR 0.92 (95% CI 0.60, 1.40)[109]. Although the exact reasons for this are unclear, there are several potential explanations. The first one is that there are gender differences in occupational status. Lower SEP has been linked to a higher level of occupational physical activity among men (i.e. manual occupations) compared to women (i.e. administrative or caring occupations)[116, 117], potentially leading to lower obesity rates among men from lower SEP. Another explanation could be that, compared with men, women experience increased weight-related ideals, where a lower weight is seen as healthier and more attractive. These weight-related ideals might be easier to sustain for women with a higher SEP, who have access to healthy food and gym/leisure memberships[118]. Because of this, SEP may influence weight to a greater extent in women.

Moreover, Newton et al indicated in their systematic review and meta-analysis that both men and women with cumulative exposure to lower SEP across life had a higher mean BMI compared with those with a higher SEP across life (mean BMI difference: 0.21 (95% CI 0.14, 0.28) for men and 1.44 (95% CI 1.35, 1.54) for women). However, men with a lower SEP across life had lower mean WC compared with men with a higher SEP across life (mean WC difference -0.10 (95% CI -0.11, -0.08)), this was not the case for women (mean WC difference 4.67 (95% CI 4.15, 5.20))[109]. Therefore, associations between SEP and obesity may differ depending on whether the outcome is total or central obesity.

Section 1.1.3.3 explained how different SEP indicators may influence health status. Specifically with regards to obesity, it has been proposed that stress[119], health literacy[120], attitudes towards health[121] and costs of healthy food[122] may play a role. Moreover, the higher educated are thought to have better financial and emotional support[123], which are associated with healthier diets[124] and increased physical activity[125] and ultimately reduce the risk of being obese. Living in deprived neighbourhoods has also been related to an increased risk of being obese[126], because of poor access to healthcare centres, less healthy food places and/or having less opportunities to do physical activities[119, 127].

With regards to lifestyle factors, socioeconomic inequalities have also been observed for dietary habits and physical activity. Both of these factors may influence the development of obesity (as explained in section 1.1.3.2). A systematic review conducted in the year 2000 investigated the effect of educational status on fruit and vegetable consumption in seven European countries. The results stated that men with a higher education consumed on average 24.3 grams (95% CI 14.0, 34.7) more fruit per day and 17.0 grams (95% CI 8.6, 25.5) more vegetables per day compared to men with a lower education. Highly educated women consumed 33.6 grams (95% CI 22.5, 44.8) more fruit and 13.4 grams (95% CI 7.1, 19.7) more vegetables per

day compared to women with a low education level. Healthier diets among the highly educated might explain their lower obesity levels[128]. Moreover, two recent systematic reviews suggest that people with a low SEP perform less leisure time physical activity compared to people with a high SEP[129, 130].

Notably, in low-and middle-income countries, the opposite association has been observed, where obesity is related to a higher SEP[131]. Reasons for this have been attributed to food scarcity and manual work among the poor and access to energy-dense food, less manually active work and larger body size being seen as positive status signal among the rich[131]. However, this PhD thesis will focus on high-income countries.

1.1.4 Summary

To conclude, the rising obesity rates worldwide and in the UK are a concern as obesity is associated with increased morbidities and mortality. Practical and inexpensive methods to measure obesity are BMI and WC. Total obesity, measured with BMI, is still the most commonly used measure in research and clinical practice; however, central obesity, measured with WC, has received increased attention because of the additional prognostic information it may provide for some health outcomes, such as CVD and T2DM.

Managing or reducing obesity has not been successful to date due to the complex and multifactorial causes of the disease. Although behavioural factors, such as diet and physical activity, are important, evidence suggest that they are heavily influenced by socioeconomic factors. Research consistently indicates a relationship between lower SEP and total obesity; however, a comparison of the relationships between educational attainment and total obesity and central obesity has yet to be carried out. The first aim of my PhD is to perform a systematic literature review and meta-analysis assessing the association between educational attainment and different definitions of obesity in Organisation for Economic Co-operation and Development (OECD) countries (Chapter 3).

Both obesity and SEP may be associated with the development of other chronic diseases besides cardio-metabolic disease, including rheumatic and musculoskeletal diseases (RMDs). RMDs include a broad range of diseases resulting in pain and disability[132, 133]. This PhD thesis focusses on osteoarthritis (OA) and rheumatoid arthritis (RA), the most common RMDs. The next two sections (1.2 and 1.3) will discuss these two diseases in more detail.

1.2 Osteoarthritis

1.2.1 Definition and classification

OA is the most prevalent form of arthritis and is characterised by degeneration of the articular cartilage between bones[134]. This results from an imbalance of catabolic and anabolic activity in the joint, which leads to a net loss of cartilage. Osteophyte formation (i.e. extra bone growth around joint margins), weakness of muscles surrounding the joint and low grade synovial inflammation are typical features of OA[133]. Disease progression of OA is slow, but it commonly leads to pain and disability, potentially requiring joint replacement surgery[133].OA most commonly affects weight-bearing joints, such as hips and knees, but it can also be present in other joints such as the hand, feet and spine[134].

In clinical practice, diagnosing OA with X-rays was historically considered the gold standard; however, it has been recognised that early OA is not detectable on X-rays[135 136]. Therefore, the European Alliance of Associations for Rheumatology (EULAR) OA taskforce provided frameworks for diagnosing knee OA in 2010[136] and hand OA in 2009[137], these frameworks are based on a systematic literature review and expert opinion. Both frameworks focus on the background risk (the population prevalence of OA), risk factors of the patient, their symptoms, physical examination and, if necessary, imaging[136].

In scientific studies, various instruments are used to assess whether someone has OA. In contrast to clinical practice, X-rays are commonly used in epidemiological studies to classify patients as having OA[138, 139]. OA is then defined as 'radiographic OA'. These studies use the Kellgren-Lawrence scale (grade 0–4), which examines osteophytes and joint-space narrowing; OA is considered present with a grade of 2[140]. MRI scans and CT scans also have the potential to detect early onset of OA, however they are more expensive[141].

Although radiographic OA is objective, it does not take into account symptoms such as pain, disability and stiffness[142]. It is said that there is a "discordance" between radiographic OA and OA symptoms: some people who have radiographic OA may be asymptomatic, whereas others suffer with pain without radiographic changes[143, 144]. A proposed explanation for this is that pain is more than structural changes on a radiograph; the experience of pain is complex and other factors, psychological and environmental, are also involved in the experience of pain[145, 146]. Symptomatic OA combines radiographic OA with symptoms[147], and might be a more accurate representation of the clinical burden of the disease[148 149].

It is not always feasible for large epidemiological studies to obtain radiographic or clinical OA data; hence, some studies use self-reported OA, often based on the response to questions such as 'Have you ever been told by the doctor or nurse that you have any of the following long-term health conditions?', where respondents can answer 'yes' or 'no' to a list of health conditions, including OA[150]. This method may lead to misclassification as some people might not be aware of their diagnosis or confuse OA with other types of arthritis or non-arthritis conditions (e.g. osteoporosis). A systematic review and meta-analysis, including 11 studies comparing OA self-report with medical records or clinical ACR criteria, found that the summary sensitivity and specificity were 0.75 and 0.89, respectively[151]. These figures indicate that 25% of all

participants who self-report OA actually do not have OA, and 11% of participants who do not self-report OA actually have OA. Although these error margins would be unacceptable in clinical practice, they may be acceptable in large clinical studies were it is unfeasible to obtain radiographs or clinical records[151].

1.2.2 Epidemiology

1.2.2.1 Prevalence and incidence rates worldwide

In 2020, a systematic review and meta-analysis estimated the global and regional incidence and prevalence rates for knee OA, defined by radiographic, symptomatic or self-report OA[152]. The global prevalence of knee OA was estimated to be 16.0% (95% CI 14.3%, 17.8%) in adults aged 15 years and older and 22.9% (95% CI 19.8%, 26.1%) in adults aged 40 years and older. The global incidence of knee OA was estimated to be 203 per 10,000 person-years (95% CI 106, 331) in adults aged 20 years and older[152]. The prevalence of knee OA increases with age (Figure 4), and the incidence peaks around 70–79 years of age. Both prevalence and incidence rates are higher among women than men[152]. The prevalence risk has been estimated as 1.69 (95% CI 1.59, 1.80) times higher for women compared with men, whereas the incidence risk is estimated to be 1.39 (95% CI 1.24, 2.56) times higher for women compared with men[152].

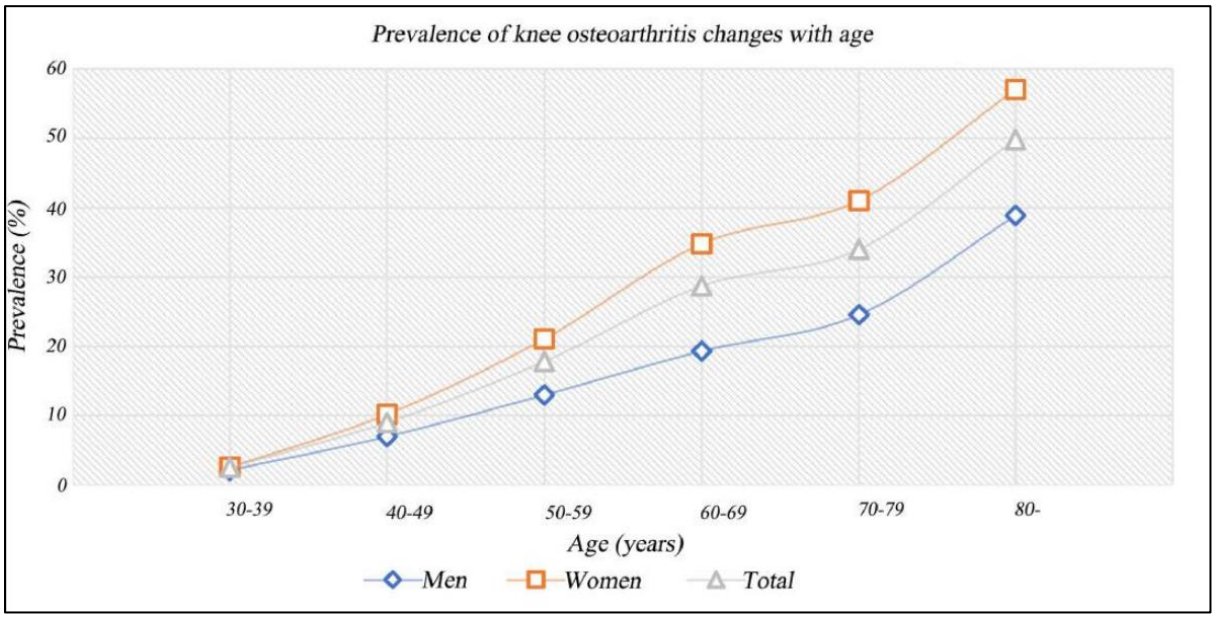


Figure 4: Global prevalence of osteoarthritis over different age groups by gender (source: Cui et al., 2020[152], permission obtained to publish figure)

The above estimates combine studies with different definitions of OA (radiographic, symptomatic and self-report). Global prevalence data was also estimated for different definitions of OA separately (Table 4): radiographic knee OA was more common than symptomatic and self-reported knee OA[152].

Table 4: Global prevalence of OA by definition (adapted from Cui et al, 2020)[152]

	Number of studies	Total sample	Prevalence (95% CI)
Radiographic OA	19	41,695	28.7% (23.6%, 34.1%)
Symptomatic OA	56	9,372,778	12.5% (10.8%, 14.3%)
Self-reported OA	3	38,096	10.6% (6.5%, 15.6%)

CI, confidence interval; OA, osteoarthritis.

This finding is consistent with a systematic review by Pereira et al (2011), which also found that prevalence rates were higher for radiographic compared to symptomatic and self-reported OA. As symptomatic OA was defined as radiographic change with symptoms, it is not surprising that prevalence rates are higher in radiographic OA. The systematic review demonstrates a close relationship with symptomatic OA and self-reported OA; both show a prevalence of 10–40% lower than radiographic OA[153].

1.2.2.2 Prevalence and incidence rates in the United Kingdom

In the UK, the most recent study that aimed to estimate prevalence and incident rates of OA (at any site), defined by a clinical diagnosis, was in 2020 by Swain et al[154]. Using Clinical Practice Research Datalink (CRPD) data (a large longitudinal database of general practice electronic medical records in the UK) from 1997 to 2017, the study estimated the UK prevalence among adults aged 20 and older to be 10.7% (95% CI 10.7%, 10.9%). This was higher in women (12.8% (95% CI 12.8%, 12.9%) compared with men (8.6% (95% CI 8.5%, 8.7%)). Prevalence increased with age with the highest prevalence rates observed among adults of 80 years and older (47% for women and 35% for men). The incidence rate was 8.1 (95% CI 7.9, 8.3) per 1000 person years for women and 5.5 (95% CI 5.3, 5.7) per 1000 person years for men of 20 years and older. The incidence rates increased with age, peaking at the age group 75–79 years (27 (95% CI 23.5, 29.8) and 18 (95% CI 15.4, 20.6) per 1000 person years for women and men respectively). Similar incidence estimates were found by Yu et al (2015) also using data from Clinical Practice Research Datalink (CPRD)[145].

The prevalence rates in 2017 were highest for knee OA (2.9% (95% CI 2.7%, 2.9%)), followed by hip OA (1.5% (95% CI 1.4%, 1.5%)), wrist or hand OA (0.5% (95%CI 0.5%, 0.5%)) and the lowest for the ankle or foot OA (0.3% (95% CI 0.3%, 0.3%))[154]. Although primary care medical records may supply efficient and regular data[155], research has shown that OA is often underreported in data from OA diagnostic codes in primary care data[156, 157]. Therefore, the incidence and prevalence of OA in the UK may be even higher than the numbers mentioned in this section.

1.2.3 Risk factors for the development of osteoarthritis

1.2.3.1 Non-modifiable risk factors: genetics, age, gender, ethnicity

Twin studies and familial aggregation studies indicate the heritability of knee and hip OA to be between 40–65%; however, individual gene variations only contribute a modest amount to the development of OA[158]. Genetic variations may contribute to risk factors of OA such as bone mass, synovitis or obesity[158].

Prevalence and incidence of OA increases with age[159, 160], presumably due to a number of factors associated with aging, including thinning of cartilage and weakening of muscles[134]. As mentioned in the previous section, women have higher incidence and prevalence rates of knee, hip and hand OA compared to men[160], particularly after menopausal age[161]. This could point to hormonal involvement; however, the results of a systematic review including 16 studies showed no clear association between sex hormones and OA in women[162]. Another possible explanation relates to differences in the musculoskeletal system; for instance, women have less cartilage than men independent of bone mass, which could ultimately lead to the development of OA[163].

Moreover, OA patterns may differ for different ethnic groups. In the USA, African Americans were more likely to have radiographic knee OA and symptomatic knee OA compared to Caucasians: ORs adjusted for demographic factors 1.65 (95% CI 1.17, 2.37) and 1.52 (95% CI 1.06, 2.19), respectively[164]. The Beijing Osteoarthritis Study found that the prevalence of knee OA was higher in women in Beijing compared to Caucasian women of the same age in the Framingham Study in the USA: prevalence ratio (PR) adjusted for age was 1.45 (95% CI 1.31, 1.60). As Chinese women have a lower BMI than Caucasian women, the results were surprising; however, the researchers noted that this result may be explained by genetic factors and heavy physical occupations/squatting among the Chinese[165]. However, these may not be the only reasons as there were no OA prevalence differences between Chinese and Caucasian men. Further research suggests that these differences may partly be explained by alignment differences of the joints between the Chinese and Caucasians[166], but research on this is still ongoing.

1.2.3.2 Obesity

Obesity is considered to be the main risk factor for knee OA[167]. In 2015, a systematic review and meta-analysis summarised the results of 14 prospective cohort studies with an overall sample size of 896,818, and found that both obesity and overweight compared to normal weight were associated with increased risk for knee OA (pooled RRs 4.55 (95% CI 2.90, 7.13) for obesity and 2.45 (95% CI 1.88, 3.20) for overweight)[168]. Prospective cohort studies published after this meta-analysis also linked obesity with incident knee OA in Spain (HR 3.19 (95% CI 3.09, 3.30))[169] and the USA (RR 2.05 (95% CI 1.56, 2.68)[170]. Moreover, evidence suggests that weight loss reduces the risk of developing knee OA: a decrease of ≥2 units of BMI in 10 years decreased the odds of developing symptomatic knee OA (OR 0.46 (95% CI 0.24, 0.86)) compared to no weight loss among women participating in the Framingham Knee Osteoarthritis Study[171].

Data for hip OA appear to be more inconsistent compared to knee OA, with some studies indicating no association between obesity and hip OA[172, 173]. However, these studies may have been underpowered. When these studies were included in a meta-analysis of a total of 14 prospective and case-control studies, a 5-unit increase in BMI was associated with incident hip OA (pooled RR 1.11 (95% CI 1.07, 1.16)), but the association was stronger for knee OA (RR 1.33 (95% CI 1.19, 1.49))[174].

The mechanism for the relationship between obesity and different forms of OA have historically been attributed to excessive weight causing mechanical stress on the joints[175]. However, obesity has also been associated with non-weight bearing joints, such as hand OA[176]. This indicates that mechanical stress does not fully explain the relationship between obesity and OA. More recently, adipose tissue releasing pro-inflammatory cytokines have been linked to joint inflammation and joint damage[177, 178].

As mentioned in section 1.1.1.2, central obesity has a stronger association with pro-inflammatory factors than total obesity; however, to date, few studies have investigated the association between central obesity and OA. The studies that did found that central obesity independent of total obesity is associated with OA[179-181]; however, most were cross-sectional in design.

Importantly, SEP could be a confounder for the relationship between obesity and OA: a lower SEP is associated with both obesity (section 1.1.3.4) and OA (see next section 1.2.3.3). However, most studies described in this section did not adjust for socioeconomic factors in their analyses. This may lead to a distorted relationship between obesity and OA. To understand the independent relationship between obesity and OA, analyses should take into account SEP.

1.2.3.3 Socioeconomic position

Studies from the USA, Sweden and Spain show that individual SEP factors, such as education and occupation, and neighbourhood SEP, measured by deprivation level, are associated with the development of OA[182-186] (Table 5). Most studies to date are cross-sectional and some of the association may be due to reverse causation (i.e. OA leads to a lower SEP). Moreover, to my knowledge, other SEP indicators, such as income and wealth, have not yet been studied.

Table 5: Overview of studies investigating the relationship between socioeconomic position and osteoarthritis

Study	Country	Design	Sample size	SEP indicator	Type of OA	Covariates	Effect size (95% CI)
Callahan et al (2010)	USA	Cross-sectional	M: 1052 F: 1571	Education (low vs high)	Knee	Age, ethnicity	M: OR 1.55 (1.06, 2.26) F: OR 1.90 (1.42, 2.54)
Reyes et al (2015)	Spain	Retrospective ecological study	3,588,807	Area-level deprivation (low vs high)	Hand	Age, gender	IRR 1.26 (1.11, 1.42)
						+ obesity	IRR 1.06 (0.93, 1.20)
					Hip	Age, gender	IRR 1.23 (1.17, 1.29)
						+ obesity	IRR 1.04 (0.99, 1.09)
					Knee	Age, gender	IRR 1.51 (1.45, 1.57)
						+ obesity	IRR 1.23 (1.19, 1.28)
Kiadaliri et al (2017)	Sweden	Cross-sectional	1527	Education (high vs low)	Knee	Age, gender	RII 0.56* (0.34, 0.93)
				Occupation (high vs low)	Knee	Age, gender	RII 0.59* (0.37, 0.94)
Putrik et al (2018)	Spain	Cross-sectional	1,923,156	Area-level deprivation (low vs high)	Hand OA	Age, gender	OR 1.12 (1.01,1.25)
					Hip OA	Age, gender	OR 1.33 (1.21, 1.46)
					Knee OA	Age, gender	OR 1.90 (1.78, 2.03)

CI, confidence interval; F, female; IRR, incidence rate ratio; M, male; OR, odds ratio; RII, relative index of inequality. *The paper reported that after adjusting for body mass index, the RII was no longer statistically significant; however, data were not shown.

Part of the relationship between a lower SEP and the development of OA may be explained by work-related physical activity. For example, a meta-analysis reported that compared to sedentary work, occupations with a high physical workload (e.g. construction workers and farm workers) had a higher risk of developing knee OA (OR 1.61 (95% CI 1.45, 1.70))[187]. Other risk factors include frequent bending of the knee, squatting, standing for more than two hours per day, walking more than three km per day, stair climbing and heavy lifting[188]. For hip OA, heavy labour and permanent damage from an injury were predictors[189]. Risk factors for hand OA include tasks involving repetitive movement and vibration[188].

Another explanation for the relationship between a lower SEP and incident OA may be obesity. The studies displayed in Table 5 adjusted for potential confounders, such as age, gender and ethnicity. However, when studies also adjusted for obesity[184] or BMI[183], the strength of the association between SEP and OA reduced or disappeared. As it is unlikely that BMI is a confounder (where BMI causes both a lower SEP and OA), this may indicate that BMI is a mediator for the relationship between a lower SEP and OA.

Mediation is explained in more detail in section 2.1.2.2, but in short: a mediator is an intermediary variable on the causal pathway between an exposure (e.g. SEP) and an outcome (e.g. OA).. Mediation studies are needed to understand whether BMI mediates the relationship between a lower SEP and incident OA. To date, one mediation study has been performed: a Mendelian Randomisation study using data from the UK-Biobank[186]. This study reported that BMI mediated 23% of the relationship between education and incident OA. A limitation of this study was that both BMI and education were genetically predicted; as mentioned in previous sections, BMI and education depend on many more factors than just genes. Moreover, longitudinal studies assessing the mediating effect of BMI on the relationship between a lower SEP and incident OA are needed to limit the possibility for reverse causation (i.e. OA leads to a higher BMI).

1.2.4 Progression of osteoarthritis

OA progresses from a normal joint without symptoms to a joint with loss of cartilage, structural changes (i.e. osteophytes and joint space narrowing), pain, instability and loss of function[147]. Structural changes can be measured using radiographs, MRI and CT[190]. Radiographs are most commonly used to identify structural changes[190]; however, they are only weakly associated with symptoms[144]. Structural changes may not fully capture the impact of OA on patients' day-to-day lives[152]. As such, it is important to measure symptomatic progression of OA, including pain and function.

1.2.4.1 Pain

Pain has been defined by the International Association for the Study of Pain as 'an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage'[191]. Pain is subjective and multifactorial, influenced by biological, psychological and social factors[191]. Pain is the most significant symptom of people with OA, is often chronic and is the main reason to seek medical advice[192, 193]. Pain also significantly contributes to loss of function and reduced quality of life in people with OA[146, 194, 195].

In epidemiological studies, pain is usually measured using the visual analogue scale (VAS) or a numeral rating scale (NRS), which capture the experience of pain intensity over a certain time period. Specific OA questionnaires have also been developed to assess pain in relation to certain activities, such as the Western Ontario and McMaster Universities Arthritis Index (WOMAC)[196], the Hip Disability and Osteoarthritis Outcome Score (HOOS) [197] and the Knee Injury and Osteoarthritis Outcome Score (KOOS)[198].

1.2.4.2 Function/disability

The Global Burden of Disease (GBD) study has shown that globally OA is one of the leading causes for years lived with disability[199]. Research has shown that people with OA have reduced physical capability, quality of life and thus increased dependency on home and hospital care[200-202]. For example, the Disability-Health Survey in France found that, compared to people without OA, people with OA had difficulties in daily-life activities, such as walking (adj OR 1.9 (95% CI 1.7, 2.2)) and lifting and carrying objects (adj OR 1.7 (95% CI 1.5, 2.0)[134].

Physical capability can be measured using objective, performance-based, measures (e.g. gait speed test, balance exercises) and self-reported measures (e.g. activities of daily living)[203]. Although self-reported measures may be subject to recall bias and may not accurately capture the true level of capability[204], they do capture "lived experiences" and the perception of people's capability. These perceptions are important: a person may perform poorly on a performance-based test (i.e. walk slowly on the gait speed test), but this may not be perceived as a problem by that person. Hence, measuring people's perceptions of functional capability and daily tasks may be an important predictor for someone's need for home and hospital care.

A self-reported physical capability questionnaire that is often used in relation to older adults is 'Activities of Daily Living' (ADL); it is used as an indicator to describe basic skills to function independently, such as eating, bathing and mobility[205]. Research has shown that these basic skills are predictors for the requirement of home and hospital care[205] and quality of life. ADL can be classified as basic and instrumental. The basic ADLs are related to self-care and cover skills about someone's basic physical needs, such as dressing, walking and feeding oneself. The instrumental ADLs are related to social participation and include more complex thinking and organisational skills, such as shopping and managing finances. A population-based cross-sectional study of older adults (n=3097) in Austria found that people with OA reported difficulties in performing ADLs, especially bending and/or kneeling down (57.3%), climbing up and down the stairs (32.9%) and walking 500 meters (32.3%)[202]. Understanding factors impacting ADLs in people with OA is important to target interventions with the aim to prevent further worsening of daily functioning.

1.2.4.3 Joint replacement surgery

Joint replacement surgery (JRS) is typically recommended when pain, disability and radiological changes cannot be managed by non-pharmacological and pharmacological approaches[206]. According to the UK-based National Joint Registry, most knee replacement surgeries (97%) and hip replacement surgeries (91.9%) were performed for OA; both types of surgeries were performed more on women than men. The mean age of having knee surgery was 68.9 years (standard deviation (SD) 9.6) and 68.0 years (11.4) for hip surgery[207]. JRS has shown to improve pain, physical activity and quality of life[134]. For example, a Swedish study found that people who had hip or knee JRS had better health status scores (scored 0–3) one year post surgery compared to before the surgery (e.g for knee JRS, the mean score was 0.51 (SD 0.33) before

surgery and 0.73 (SD 0.27) one year after surgery)[208]. Although serious complications after JRS are uncommon, they have a finite life expectancy and revision surgery may carry risks (e.g. infections)[133].

1.2.5 Risk factors for progression of osteoarthritis

1.2.5.1 Demographics: age, gender and ethnicity

A systematic review published in 2015, including 30 studies, indicated that increased age and ethnicity (non-White/non-Western) were strong predictors and gender was a poor predictor for increased disease progression in OA measured by pain, function and JRS[209]. The review noted some limitations: due to large differences in definitions of OA and OA disease progression, it was not possible to pool the results in a meta-analysis and, although pain is the main symptom of OA[192], there are a lack of studies investigating the risk factors for pain progression in knee OA.

The Johnston County Osteoarthritis Project reported that Blacks presented with more bone formation (such as osteophytes) compared with Whites, potentially leading to poorer disease prognosis over time[210]. However, research has also shown that Blacks have lower rates of JRS compared to White Americans[211]. Some suggest that this may be due to cultural factors and an 'unwillingness' of receiving surgery among Black Americans[212]. However, other factors might also be important, such as SEP and having medical health insurance.

In the UK, ethnic differences for JRS also exist. Using data from NJR and HES, researchers compared the observed joint replacement to the expected numbers in different ethnic groups[213]. They found that the observed/expected ratios were significantly lower for knee JRS in Blacks (0.64 (95% CI 0.61, 0.67)) and Asians (0.86 (95% CI 0.84, 0.88)) compared with Whites (1.01 (95% CI 1.01, 1.02)). Similar results for hip JRS were found. The results were adjusted for age, gender and deprivation level. Although healthcare in the UK is accessible for everyone, these results may indicate that there are still inequities regarding access to healthcare in the UK.

1.2.5.2 Obesity

In contrast to the consistent findings on the association between obesity and incident OA, there have been conflicting data in the past about the relationship between BMI and progression of radiographic and symptomatic knee OA in observational studies[209, 214, 215]. This has been called the "risk factor paradox" and may be caused by differential loss of follow-up or index event bias[216]. Differential loss to follow-up is a type of selection bias, where obese people are potentially less likely to visit follow-up appointments for radiographs due to poor health or loss of mobility. This could reduce the effect of obesity on OA progression[217]. Index event bias, also called collider stratification bias, is also a type of selection bias and happens when the occurrence of an event is needed to be selected for the study (for example, having OA). Figure 5 shows a hypothetical observational study investigating the associations between obesity and OA progression. In this example, which is taken and adapted from Zhang et al., 2010[217], pre-existing OA is caused by either obesity or a genetic factor. This means that pre-existing OA is a common effect of obesity

and a genetic factor. By conditioning on the common effect (pre-existing OA), obesity and the genetic factor are no longer independent (see the dotted line in Figure 5): if OA is not caused by obesity, it is caused by the genetic risk factor and vice versa. This opens a path from obesity - - - genetic factor -> OA progression. The genetic factor becomes a confounder for the relationship between obesity and OA progression. In this scenario, the genetic factor was used as an example; however, it could happen with multiple unmeasured risk factors. Unless we can adjust for the genetic factor or other unmeasured risk factors, this will generally bias estimates towards the null and underestimate the contribution of obesity.

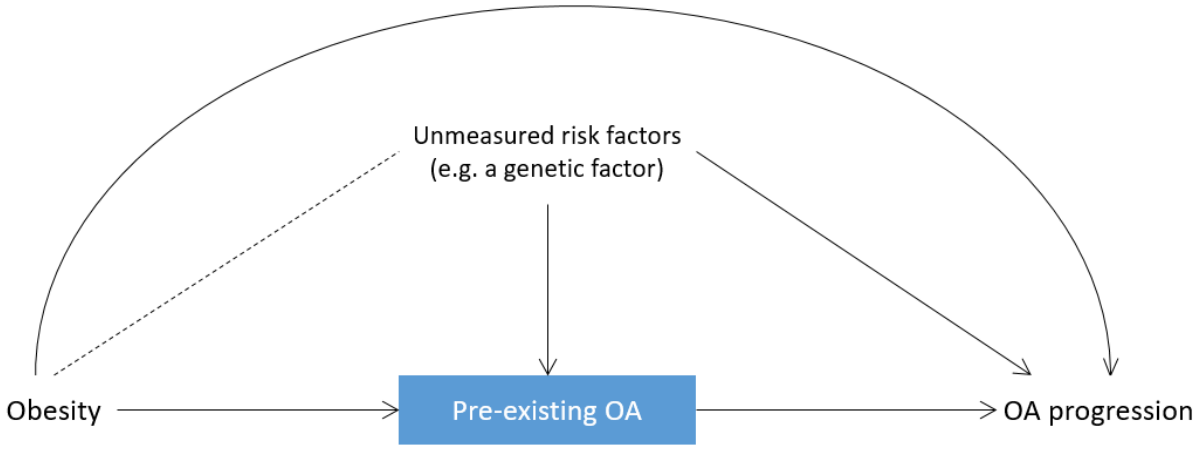


Figure 5: A diagram depicting index event bias in a study assessing the association between obesity and OA progression among people with pre-existing OA. By conditioning on people with OA, its causes (e.g. obesity and other unmeasured risk factors, such as a genetic risk factor) are becoming related even they would be unrelated in a general population (dotted line). This opens a path from obesity - - - genetic factor -> OA progression, which biases the effect of obesity on OA progression towards the null.

Although there are conflicting findings for radiographic progression[209, 214, 215], one study indicated that confining analyses to those with longer follow up indicated BMI is associated with radiographic progression over time[174]. This is supported by a recent review which identified a strong association between BMI and progression of pain and disability over time[209]. Moreover, weight loss is associated with symptomatic improvements[218] and weight gain is associated with increased pain in people with OA[219].

Similarly, studies have shown that obese OA patients have a higher need for JRS[220-222] and at a younger age[223, 224] than non-obese OA patients. For example, the Nurses' Health Study, including only women, reported that being in the highest BMI category (BMI ≥35 kg/m^2) compared to the lowest (BMI <22 kg/m^2) significantly increased the risk of hip JRS in women with OA of 18 years and older (OR 5.2 (95% CI 2.5, 10.7))[221]. Furthermore, weight loss of >7.5% in overweight or obese patients may reduce the risk of knee and hip JRS[225].

1.2.5.3 Socioeconomic position

Evidence suggest that people with OA from a lower SEP experience worse outcomes in terms of pain and function than people from a higher SEP; however, the studies that have been performed to date are mostly cross-sectional[226-229]. The association between a lower SEP and increased pain and function remained after adjusting for BMI (one study did not adjust for BMI[226]). This indicates that other factors may also be important, such as access to healthcare[227].

As previous studies suggest that a lower SEP is associated with increased pain and reduced function in OA, it is expected that a lower SEP is also associated with increased JRS. However, studies have indicated conflicting results. One Swedish prospective cohort study in 2008 (n=204,741) found that compared to white collar workers, construction workers were more likely to undergo JRS due to knee OA[230]. These results were adjusted for age and BMI. However, this study only focussed on occupational factors. Another study from Australia found similar rates of JRS across the highest and lowest SEP groups[231].

By contrast, some research indicates that those from a lower SEP are less likely to undergo JRS. For instance, using data from the English Longitudinal Study of Ageing (ELSA) and Hospital Episode Statistics (HES), researchers have found that people who live in the most deprived areas of England received ~70% fewer hip and knee replacement surgery relative to the need compared to people living in the least deprived areas (equity rate ratios 0.31 (95% CI 0.30, 0.33) for hip replacement and 0.33 (95% CI 0.31, 0.34) for knee replacement)[232]. The association between a lower SEP and lower provision of JRS is confirmed by two subsequent studies in Scandinavia[233 234]. This suggests that there may be under-provision of surgery among the most disadvantaged.

1.2.6 Treatment

There is currently no cure for OA. Hence, treatment focuses on preventing or limiting symptoms[133]. The latest management guidelines were developed in 2019 by the American College of Rheumatology (ACR) and the Arthritis Foundation[235]. Based on a comprehensive systematic literature review, the researchers developed 'strong' or 'conditional' recommendations (Table 6 and 7), where conditional means that the quality or the amount of evidence for efficacy was low and/or the benefits vs harm were balanced and shared decision-making process between patient and clinician is important.

Table 6: Strong recommendations for the management of OA based on the guidelines developed by ACR and the Arthritis Foundation 2019[235]

Management approaches	Type of OA
Non-pharmacological	
Exercise	Hand, knee, hip
Self-efficacy and self-management programmes	Hand, knee, hip
Weight loss	Knee, hip
Tai Chi	Knee, hip
Cane	Knee, hip
1st carpometacarpal orthosis	Hand
Tibiofemoral knee brace	Knee
Pharmacological	
Oral nonsteroidal anti-inflammatory drugs	Hand, knee, hip
Topical nonsteroidal anti-inflammatory drugs	Knee
Intra-articular steroids	Knee, hip

Table 7: Conditional recommendations for the management of OA based on the guidelines developed by ACR and the Arthritis Foundation 2019[235]

Management approaches	Type of OA
Non-pharmacological	
Heat, therapeutic cooling	Hand, knee, hip
Cognitive behavioural therapy	Hand, knee, hip
Acupuncture	Hand, knee, hip
Kinesiotaping	Hand, knee
Balance training	Knee, hip
Other hand orthosis	Hand
Patellofemoral knee brace	Knee
Paraffin	Hand
Yoga	Knee
Radiofrequency ablation	Knee
Pharmacological	
Topical nonsteroidal anti-inflammatory drugs	Hand
Intra-articular steroids	Hand
Acetaminophen (paracetamol)	Hand, knee, hip
Tramadol	Hand, knee, hip
Duloxetine	Hand, knee, hip
Chondroitin	Hand
Topical capsaicin	Knee

In line with the recommendations of ACR and the Arthritis Foundation, the NICE guidelines for the management of OA[206] initial treatment plan includes self-management, exercise, weight management and topical and oral NSAIDs for pain relief. JRS is considered when other interventions do not relieve OA symptoms[206]. It is recommended that JRS is performed after the age of 60 years as the replacement joint may only last for 15–20 years and revision surgery may pose extra risks[133].

1.2.7 Summary

OA can be characterised by degeneration of the joints, leading to significant pain and disability. It can be defined using radiography, clinical assessment (using the EULAR taskforce frameworks), symptoms and self-report. Although radiographic OA was considered the gold standard, research has shown that there is a discordance between radiographic changes and symptoms. Some patients suffer with pain without radiographic changes, whereas others are asymptomatic with severe radiographic changes.

Prevalence rates vary by definition, but the latest estimates in the UK using the clinical definition, suggests that 10.7% of adults aged 20 years and older had OA and this was higher in women (12.8%) than men (8.6%). There is currently no cure for OA, and treatment focusses on managing symptoms. Understanding the risk factors for both the incidence and the progression of disease are therefore important to prevent OA as well as prevent further progression of OA.

The main risk factor for incident OA is obesity, and due to the increase in obesity rates, there are concerns about increasing OA prevalence rates too. Furthermore, there are signs that those from a lower SEP have increased rates of OA. It is uncertain whether this can be explained by higher obesity rates in lower SEP groups.

Progression of OA can be structural, measured using imaging, but it can also be symptomatic, measured by pain, function and disability. JRS is recommended at the end-stage of OA. Understanding risk factors for the progression of disease is important as it allows clinicians to closely monitor patients who are at increased risk for severe OA and potential risk factors may be modified early in the disease process. Evidence suggests that those from a lower SEP experience worse disease outcomes; however, it is unclear whether that can be explained by obesity.

1.3 Rheumatoid arthritis

1.3.1 Definition and classification

Rheumatoid arthritis (RA) is an autoimmune disease in which the immune system attacks the synovial lining of joints and if untreated results in painful and swollen joints, severe disability and premature mortality[236]. It is a major subtype of inflammatory arthritis. There is no single diagnostic test which defines RA, thus the diagnosis is made based on a clinical assessment supported by blood tests (testing for rheumatoid factor (RF); anti-citrullinated protein antibody (ACPA); CRP; and erythrocyte sedimentation rate (ESR)). Classification criteria have been developed for the purpose of selecting homogeneous populations for research studies.

The ACR 1987 classification criteria have been widely used. The classification includes seven criteria: 1) morning stiffness; 2) arthritis/deformity of three of more joints areas; 3) symmetric arthritis/deformity; 4) arthritis/deformity of hand; 5) rheumatoid nodules; 6) serum rheumatoid factor; and 7) radiographic changes. At least four of these criteria need to be present for a patient to be classified as having RA[237]. However, these criteria appeared to miss cases of early onset RA as some of the criteria are only apparent in established RA (e.g. nodules)[238, 239, 240], and treating RA early is essential for beneficial disease outcomes[241]. Since then, new criteria have been developed to identify early RA in patients, with the aim to identify RA patients eligible to receive methotrexate treatment. They were created by the ACR and EULAR in 2010 (Table 8). The criteria apply to patients that have one or more swollen joints that cannot be explained by another disease. A score of six or higher is required to be classified as having RA[242].

Table 8: ACR/EULAR 2010 classification criteria for RA (adapted from Aletaha et al (2010) [242])

	Criteria	Score
A	Joint involvement	
	1 large joint	0
	2–10 large joints	1
	1–3 small joints	2
	4–10 small joints	3
	>10 joints (with at least one small joint)	5
B	Serology*	
	Negative RF *and* negative ACPA	0
	Low positive RF *or* low positive ACPA	2
	High positive RF *or* high positive ACPA	3
C	Acute phase reactants	
	Normal CRP and normal ESR	0
	Abnormal CRP or abnormal ESR	1
D	Duration of symptoms	
	<6 weeks	0
	≥6 weeks	1

*Negative, ≤ upper limit of normal (ULN) for the laboratory values; low-positive, < ULN but ≤3 times the ULN; high-positive, >3 times the ULN. If RF is only available as positive or negative, a positive result becomes low-positive. RF, rheumatoid factor; ACPA, anti-citrullinated protein antibody; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

The above criteria are often used as inclusion criteria in scientific studies that investigate RA patients, such as clinical trials. However, population-based surveys often rely on self-reported RA with answers to questions such as 'Have you ever received a doctor's diagnosis of rheumatoid arthritis?', where respondents can answer 'yes' or 'no'. Although subject to misclassification, a systematic review and meta-analysis studied the sensitivity and specificity of self-reported RA in population-based studies. This study showed a high sensitivity and specificity for RA self-report compared to clinical examination by a rheumatologists or clinical ACR criteria (0.88 and 0.93, respectively)[151]. Moreover, a recent UK Biobank study indicated that 87.7% of self-reported RA diagnoses could be verified with RA codes in linked medical records[243]. Misclassification seems to occur mainly because people classify themselves as having RA, when in fact they only have OA[244]. Asking both RA and OA in the same question may therefore reduce the likelihood of misclassification if people have RA or OA (people can also have both RA and OA[245]).

1.3.2 Epidemiology

Globally, the GBD study estimated that in 2017, 20 million adults suffered from RA, with age-standardised prevalence of 0.25% and a yearly incidence rate of 14.9 per 100,000[246]. From 1990 to 2017, the prevalence and incidence rate has risen by 7.4% and 8.2%, respectively[246]. A possible explanation for the increase in prevalence is the increased life-expectancy of people with RA because of the emergence of new treatments (section 1.3.6). The increase in incidence may be explained by increased awareness and early diagnosis[239] or increased life-expectancy in general (which increases the time to develop RA)[247] .

Age-standardised RA prevalence and incidence rates vary substantially in different regions and countries[246]. The prevalence is generally higher in high-income countries compared to low-income and middle-income countries. In 2017, the highest age-standardised prevalence rates were estimated in North America (0.38%)

and Western Europe (0.35%) and the lowest in South-East Asia (0.10%) and Oceania (0.14%). Incidence rates followed a similar pattern: the highest yearly incidence rates were reported in North America (22.5 per 100,000 population) and South Asia (20.7 per 100,000 population). The lowest yearly incident rates were found in Southeast Asia (6.2 per 100 000 population) and Oceania (7.9 per 100,000 population). These geographical differences could point to variations in genes, lifestyle, climate and age distribution[248], but also the increased number of specialists to diagnose RA in high-income countries[249].

The GBD study also showed that prevalence rates were higher in women compared with men and increased with age. For women, the highest prevalence rates were found in the age group 70–74 years and for men this was 75–79 years. For both men and women, the incidence rates were the highest among the age group of 50–54 years.

Data on prevalence estimates in the UK is limited. Based on CPRD data, Abhishek et al (2017) estimated the prevalence of RA in the UK at 0.67% in 2014 using medical codes[250]. Symmons et al (2002) estimated the prevalence for women to be 1.16% and for men 0.44%, using a stratified random sample in Norwich and the Norfolk Arthritis Register (NOAR)[251].

1.3.3 Risk factors for the development of rheumatoid arthritis

1.3.3.1 Non-modifiable risk factors: genetics, age, gender, ethnicity

RA is recognised as a complex genetic disorder, where environmental factors can trigger disease in individuals that are genetically susceptible[132]. Cross-sectional twin studies from the UK and Finland have suggested that heritability contributes to approximately 60% of RA cases. This heritability estimate was independent of sex, age at disease onset and disease severity[252]. Moreover, GWASs have identified more than 100 loci that are associated with RA; however, effect sizes are generally low[253].

As mentioned in the previous section (1.3.2), prevalence and incidence rates rise with age[246, 254], and more women than men develop RA. Of the RA cases in the USA, England, France, Denmark, Japan, China and Australia, 66–86% were women[255]. Higher incidence rates in women compared to men are seen in auto-immune diseases generally. Although the exact reasons remain unclear, it has been suggested that hormonal changes (such as during post-partum and peri-menopausal periods) are implicated in the immune response and the development of RA, whereas the contraceptive pill (which maintains consistent hormonal levels) may be protective[256, 257].

The risk of developing RA may also depend on ethnic origin. For instance, in the USA, Native Americans are more at risk of developing RA compared to European-Americans[258]. In the UK, there is still insufficient data with regards to RA incidence and prevalence among ethnic minorities[259].

1.3.3.2 Environmental factors

Previous studies have demonstrated that tobacco smoking increases the risk for developing RA[260-263]. The association between smoking and incident RA is stronger for men[262-264]. Gender differences for the

association between smoking and incident RA may be explained by sex hormones, as some studies suggest an association for post-menopausal women[265], but not menstruating women[266]. Indeed, one study found an age-smoking interaction among women (i.e. a stronger association for older compared to younger age), but not men[263]. This could point to a protective effect of menstruation; however, this needs further investigation[263]. Environmental pollutants, such as silica and textile dust, have also been associated with increased risk of developing RA[267-269]. This is especially important for lower SEP groups as they may be at higher risk to be exposed to pollutants.

Diet and nutrients have received increasing attention as possible risk factors for RA[270-272]. The Western diet, consisting of a high intake of red meat, saturated and trans fats, low levels of anti-inflammatory omega-3 and high levels of pro-inflammatory omega-6 and refined carbohydrates, may increase the risk for RA through chronic low-grade inflammation[273] or through obesity (which is also associated with low-grade inflammation)[274]. However, the limited research that has been performed on the Mediterranean diet, which is known for its anti-inflammatory properties, and the onset of RA indicates no significant effect[275, 276]. Nonetheless, a higher intake of fatty fish, a large component of the Mediterranean diet, has been associated with a lower risk of RA[277, 278].

1.3.3.3 Obesity

Obesity is considered a risk factor for RA through the accumulation of pro-inflammatory adipocytokines[279]. Over recent years, several meta-analyses established an association between total obesity and the development of RA among women[274, 280, 281], but not among men[281]. Sex differences may be attributed to an interaction between sex hormones and obesity that specifically put women with obesity at higher risk for RA compared with men with obesity[282]. SEP could be a confounder for the relationship between obesity and incident RA and most studies included in the meta-analyses adjusted their analysis for SEP (education, occupation or income). This indicates that there is an association between obesity and incident RA among women regardless of their SEP.

The relationship between obesity and incident RA may be stronger for early onset RA (diagnosis before the age of 55 years). For example, a study combining data from two large prospective cohorts (the Nurses' Health Study I and II), reported an association between obesity and incident RA among women aged 55 years or younger (HR 1.65 (95% CI 1.34, 2.05)), but this association lost its statistical significance when restricting to RA cases after age 55 years (data not reported)[283]. This may indicate that there are other risk factors for later onset RA, or that BMI is not an ideal measure of fat mass in older adults (because of the decrease in muscle mass and relative increase in fat mass, leading to lower BMI).

In recent years, few studies have focused on the relationship between central obesity and incident RA[284-286]. For example, a case-control study in Sweden in 2016[284], with 379 female RA cases and 178 male RA cases, found that compared to no central obesity, central obesity was associated with RA incidence in men (OR 3.57 (95% CI 1.50, 8.51)) but not among women (OR 1.04 (95% CI 0.63, 1.71), adjusted for education

and smoking. Furthermore, a Danish cohort study in 2019[285] reported that central obesity was not statistically significantly associated with RA incidence among both women HR 1.15 (95% CI 0.93, 1.42) (RA female cases, n=456) and men (HR 1.18 (95% CI 0.86, 1.63)) (RA male cases, n=210), adjusted for multiple covariates (age, smoking, alcohol consumption and education level). From these case-control studies, it is evident that the relationship between central obesity and incident RA among women is less clear than for total obesity.

Most recently, a large prospective cohort study compared the associations of total and central obesity with incident RA (RA cases, n=844) among women participating in the Nurses Health Study I and II[286]. The results showed that BMI was a stronger predictor for incident RA than WC. When the BMI analyses were adjusted for WC, they remained statistically significant. However, when the WC analyses were adjusted for BMI, they lost statistical significance (Table 9). This indicates that WC does not predict incident RA independent of BMI. These results were, however, not adjusted for socioeconomic indicators.

Table 9: The relationships of total and central obesity with incident RA among women in the Nurses Health Study[286]

	Total obesity HR (95% CI)	Central obesity HR (95% CI)
Multivariable model 1*	1.41 (1.18, 1.68)	1.22 (1.06, 1.41)
Multivariable model 2†	1.33 (1.05, 1.68)	1.04 (0.87, 1.24)

CI, confidence interval; HR, hazards ratio. *Adjusted for age, cohort (NHS, NHS II), smoking, diet, physical activity, menopausal status. †Total obesity analysis additionally adjusted for WC; central obesity analyses additionally adjusted for BMI.

To conclude, the association between total obesity and incident RA among women seems to be more established than for central obesity. This is not what we would expect as central obesity is a better measure of visceral fat and has a stronger association with inflammatory cytokines than total obesity. The few studies performed for central obesity are, however, limited by small numbers of RA incident cases (and thus too little power to show the effect) and a case-control design, except for the study by Merchand et al (2021)[286]. Both smoking and SEP could be confounders for this relationship. Although the two case-control studies adjusted their findings for smoking and education level, the study by Merchand et al (2021) did not adjust for any SEP indicators (but did adjust for smoking). In general, there is a lack of data for men.

1.3.3.4 Socioeconomic position

To date, few studies have examined the link between SEP and the development of RA[287]. Cross-sectional and case-control studies have indicated an association between lower SEP (measured through education, occupation and area-level deprivation) and RA[288-290]. However, longitudinal studies, that can study the temporal effects between SEP and incident RA, are limited. One longitudinal study performed in the UK[291], found that a higher occupational class (technical/skilled/managerial worker vs manual worker) and higher education (degree vs no degree) were associated with decreased risk for RA (HR 0.65 (95% CI 0.45, 0.93) and HR 0.17 (95% CI 0.05 to 0.53), respectively).

These studies adjusted their results for smoking, which is a potential mediator for the relationship between a lower SEP and incident RA (SEP -> smoking -> RA). However, other factors, such as obesity, could also

mediate the relationship between SEP and the development of RA: low SEP is associated with obesity and obesity may be a risk factor for RA. To understand whether obesity mediates part of the relationship between a lower SEP and incident RA, longitudinal mediation studies are needed. One recent Mendelian Randomisation study from the UK-Biobank[292] reported that BMI mediated 17% of the relationship between a lower education and incident RA. As mentioned in section 1.2.3.3, there are limitations to using genetically-predicted BMI and education; they are determined by many more factors than just genes. Moreover, UK Biobank is a non-representative sample of the UK population[293], a single indicator as a proxy for SEP (education) was used and the study design was not a prospective longitudinal study. Although education is less prone to reverse causation, other SEP indicators (such as occupation or income) are.

1.3.4 Progression of rheumatoid arthritis

RA is a progressive degenerative disease, which, if untreated, leads to disability, reduced quality of life, comorbidity and mortality. However, with the introduction of early and modern treatments, outcomes have generally improved for RA patients in the last two decades[294]. RA's pathogenesis is complex, and progression of disease is not easily monitored using laboratory measures; instead, disease severity over time is measured using clinical disease activity[132, 295] or measures of disability (section 1.3.4.1), and structural damage through x-rays.

1.3.4.1 Disability, disease activity and quality of life

RA can lead to functional disability, often measured by the Health Assessment Questionnaire (HAQ) score, which measures self-reported functional ability. This questionnaire produces a score from 0–3, where 3 indicates the most severe disability[296]. HAQ is described in more detail in section 2.3.2.3.2. Modern treatment strategies (section 1.3.6) have reduced self-reported disability in patients with RA significantly since 1990[297].

Disease activity is an important predictor of disability over time[298, 299]. Disease activity is usually measured with the Disease Activity Score 28 (DAS28), a composite disease activity measure which incorporates information regarding the number of tender joints, number of swollen joints, inflammation level and patient global assessment[300]. The score of DAS28 ranges from 0.96–10 where a score above 5.1 is considered high disease activity[300] (described in more detail in section 2.3.2.3.2). This measure is often used in the 'treat-to-target' approach mentioned in section 1.3.6; a DAS28 score of <2.6 represents remission and a score of <3.2 represents low disease activity[301]. In addition to DAS28, the latest recommendations for measuring disease activity in RA patients developed by ACR include the Clinical Disease Activity Index (CDAI), Routine Assessment of Patient Index Data 3 (RAPID3) and Simplified Disease Activity Index (SDAI)[302].

1.3.5 Risk factors for progression of rheumatoid arthritis

1.3.5.1 Demographics: age, gender, ethnicity

Studies that investigated gender differences in RA disease progression found no differences in terms of radiographic joint damage between men and women[303], but did find that women had significantly worse scores of DAS28, HAQ, pain and fatigue compared to men[304]. The researchers of the latter study suggested that gender differences in those outcomes may be a result of women having generally less muscle strength and, therefore, RA might be more burdensome for women compared with men[304]. It may also be possible that women are more willing to report physical limitations compared with men[305].

With respect to ethnic differences, a longitudinal study in the USA investigated ethnic differences of RA disease activity and remission rates[306]. They found that mean disease activity measured by the CDAI (score ranges from 0–17) was higher in Hispanics compared to Whites: 11.6 (95% CI 10.4, 12.8) and 10.7 (95% CI 9.6, 11.7), respectively. Ethnic differences were also observed for remission rates, where 27.4% (95% CI 24.9, 29.8) of Whites compared to 22.7% (95% CI 19.5, 25.8) of Hispanics achieved remission. A possible explanation may be disparities in treatment prescription, where those from non-white ethnic background are less often prescribed the relatively new and effective biologic agents[307].

In the UK, there is a paucity of research regarding ethnicity and the progression of RA. However, Allison et al (2002)[308] researched the prevalence of musculoskeletal pain (not specific to RA) in different ethnic groups in Greater Manchester; they found that compared to Whites, people from ethnic minorities experienced more widespread musculoskeletal pain: ORs were 1.5 (95% CI 1.2, 1.8), 2.6 (95% CI 2.2, 2.9), 2.1 (95% CI 1.6, 2.5) and 1.5 (95% CI 1.1, 1.8) for Afro-Caribbean, Indian, Pakistani and Bangladeshi, respectively[308]. These differences within different ethnic groups may be due to a complex interaction of genetic and environmental factors[309].

1.3.5.2 Environmental factors

Although smoking is an established risk factor for incident RA, conflicting results are reported about the effect of smoking on RA disease progression[310]. This may again be explained by index event bias[216], which was discussed in detail in section 1.2.5.2. In a study performed in the USA among Veterans, smokers had significantly higher cytokine levels and DAS28 scores compared to former or never smokers[311]. However, another longitudinal study performed in Switzerland concluded that there was no significant difference in radiographic joint damage progression in smokers compared to non-smokers after 3.1 years (radiographic damage progression in non-smokers was 2.79% (95% CI 2.59%, 3.02%) and in smokers 2.51% (95% CI 2.14%, 2.89%), p=0.26), suggesting that smoking does not necessarily accelerate progression of radiographic joint damage in RA[312]. However, it is questionable whether 3.1 years is enough time to see radiographic changes. Further studies in Sweden also did not find an association between smoking and HAQ scores in patients with RA[313-315]. In addition to index event bias, these conflicting results may be due to differences in adjusting for possible confounders (e.g. rheumatic factor, ACPA and BMI) that also contribute to disease

progression[316] and potential differential loss to follow-up (where smokers are less likely to visit follow-up appointments due to poor health).

A EULAR taskforce conducted a SLR of the effect of different dietary factors (such as animal products, experimental diets, fruit and vegetables interventions and supplements) on RA[317]. It was concluded that the evidence was low due to the limited amount of studies performed and low sample size. As mentioned in section 1.3.3.2, the Mediterranean diet has anti-inflammatory properties, which may be particularly of interest in RA as RA is an inflammatory disease. Two small clinical trials to date have reported on the effects of the Mediterranean diet on the progression of RA[318, 319]. In a deprived area in Glasgow researchers demonstrated in females with RA that active promotion of a Mediterranean style diet with community meetings and cooking classes (n=75) statistically significantly improved pain scores after three and six months, early morning stiffness at six months and HAQ scores at three months compared to the control group, who only received written information about the Mediterranean diet (n=55)[318]. In Sweden, RA patients who ate a Mediterranean diet (n=25) showed a reduced DAS28 score of 0.56 ($p<0.001$) and HAQ of 0.15 ($p=0.020$) after 12 weeks, with controls (n=25), who were on an ordinary Western diet, seeing no significant changes during this period[319]. Although both studies were small, these studies highlight the potential of dietary intervention to be an affordable and accessible way to improve outcomes in RA patients[320].

1.3.5.3 Obesity

Although research points towards an association between obesity and the development of RA (section 1.3.3.3), the association between obesity and RA disease progression is less clear. A 2017 systematic review and meta-analysis, including 20 longitudinal studies, found that obesity was associated with reduced chance of achieving remission (pooled OR 0.57 (95% CI 0.45, 0.72)) compared with non-obese patients. Moreover, obese patients had worse disease activity scores but did not have increased mortality compared with non-obese RA patients[321]. Since the publication of this systematic review, other studies[322-324] and a EULAR taskforce systematic review[325] have also indicated an association between obesity and worse disease activity outcomes in patients with RA. One of these studies indicated that the relationship between BMI and disease activity was a linear relationship: the higher the BMI the higher the disease activity[324].

By contrast, some studies reported that radiographic prognosis of RA was better in obese compared with non-obese RA patients[326, 327]. There are several potential explanations for this. Firstly, it has been suggested that adipokines produced by fat tissue may be protective of joints[328]; however, this is still an ongoing area of investigation. Secondly, low BMI may be the result of weight loss due to having severe disease, which is associated with increased joint damage[326]. Thirdly, a higher BMI (including a greater muscle mass) has positive effects on bone remodelling and support cartilage, reducing joint damage[323]. Fourthly, some studies do not adjust for relevant confounders, such as smoking, that may contribute to joint damage.

Nonetheless, obese patients do experience worse symptoms (pain, disability); this may be because of comorbidities and immobility related to having a high BMI[322].

Studies have also linked central obesity to worse progression of RA (measured through HAQ and DAS)[329-331], of which one was a longitudinal study[331]. For example, after a follow-up of 9.5 years, central obesity at baseline was associated with reduced chance of remission (<2.6 DAS28) (OR 0.73 (0.53, 0.98))[331]; however, this study failed to adjust for SEP and smoking which could also contribute to worse disease progression.

1.3.5.4 Socioeconomic position

Sufficient evidence in cross-sectional[332-335] and longitudinal[336-339] studies suggests that a lower SEP is associated with worse disease activity and self-reported health outcomes in people with RA. In the UK, Camacho et al (2012) researched the association between SEP and disease outcomes in patients with early onset of inflammatory polyarthritis in NOAR. Patients from the most deprived areas experienced significantly worse HAQ scores compared to those from the least deprived areas; the median difference in HAQ score was 0.42 (95% CI 0.08, 0.75)[335]. Another study in the West of Scotland found that RA patients from the most deprived areas had a higher risk of excess mortality compared to RA patients from the most affluent areas (RR adjusted for sex and age 1.66 (95% CI 0.74, 3.69))[340], potentially due to lifestyle factors and higher rates of chronic diseases among socioeconomically disadvantaged groups[340]. Both these studies did not adjust for BMI. It is possible that the association between a lower SEP and worse disease progression in RA are mediated by BMI; however, this has not yet been investigated.

Management of RA requires active patient participation. In the UK, although healthcare is free for everyone at the point of use regardless of SEP, it has been suggested that differences in disease progression could be due to lower patient participation of people with lower SEP in their healthcare process[341]. However, a recent longitudinal study in the USA of 83,965 RA patients who use rheumatology care found that a lower SEP (defined by area-level deprivation) was associated with more disability (measured through HAQ score) compared with people from a higher SEP, regardless of the number of visits to the rheumatology clinic[339].

1.3.6 Treatment

The current treatment strategy for RA is based on a 'treat-to-target' approach, with the aim to achieve remission or low disease activity. Subsequently, clinicians monitor disease activity closely with regular follow-ups and adapt treatments where necessary to maintain disease control. This strategy began to be adopted in the 2000s in the UK[342], and has since then been proven successful[343].

Treating the patient at the earliest stages of the disease has shown to be beneficial in RA disease outcomes[344, 345]. RA patients are primarily treated with 'disease modifying anti-rheumatic drugs' (DAMRDs). These types of agents not only suppress symptoms, but also influence the disease process by inhibiting joint damage and decreasing levels of the inflammatory markers ESR and CRP. Subsequently, they have been shown to improve patient outcomes[346].

The latest recommendations by EULAR for the management of RA[347] include methotrexate (MTX), a conventional disease-modifying antirheumatic drug (DMARD), as a first strategy. It is suggested to add another conventional DMARDs or glucocorticoids if there is not enough improvement in three months. If the treatment target is not reached after 6 months, a biological DMARDs (e.g. tumour necrosis factor (TNF)-inhibitors) should be added to the treatment protocol. If this fails, another biological DMARDs or targeted DMARDs (e.g. janus kinase inhibitors) is recommended. In the UK, biological and targeted DMARDs are considered high-cost drugs[348] and their use is limited to patients whose disease remains active (DAS28>3.6) despite treatment with at least two conventional DMARDs in combination.

It is not yet clear whether these treatment advances have benefitted different population groups equally. The aforementioned association between a lower SEP and worse disease activity could potentially be explained by unequal access to treatments. Although healthcare in the UK is free and everyone should have equal access to care, people from a lower SEP may have a delayed diagnosis and start treatment later, leading to more severe disease. This is seen in the US[339], but needs further investigation in the UK. Moreover, obesity may influence the efficacy of medication; potentially due to underdosing (if medications are not dosed by weight) or its association with comorbidities and discontinuation of RA treatment[323]. However, this not yet clearly understood.

1.3.7 Summary

RA is an autoimmune disease, leading to painful and swollen joints, severe disability and premature mortality if untreated. Global prevalence and incidence rates have risen since 1990 and the latest estimates (which was in 2014) suggest that 0.67% of people in the UK have RA. It is a multifactorial disease, with risk factors including a higher age, being a woman, certain genes, smoking, obesity and a lower SEP. There is evidence for the relationship between total obesity and the development of RA, but there are conflicting results for central obesity. Few studies found a relationship between a lower SEP and RA and adjusted their results for smoking, a known risk factor of RA and a lifestyle factor that is more prevalent among socioeconomically disadvantaged groups. However, it is uncertain whether obesity contributes to the relationship between SEP and incident RA.

With the introduction of modern treatments, outcomes of RA patients have improved in the last two decades. Outcomes are usually measured by disease activity (e.g. DAS28) and functional disability (e.g. HAQ). Conflicting results about the relationship between obesity and disease progression in RA are reported, indicating that further research is needed. There is also evidence to suggest a relationship between a lower SEP and worse outcomes in RA; however, it is unclear what the reasons for these disparities are and whether higher obesity rates in people with lower SEP may potentially play a role.

1.4 Conclusion, aims and hypotheses

This chapter provided an extensive background of the epidemiology and risk factors of obesity, OA and RA. Specifically in the era of widening health inequalities and increasing rates of obesity, it is of interest to understand how both SEP and obesity are associated with the development and progression of common RMDs, such as OA and RA. Over the years, research has concluded that those from a lower SEP are more likely to be obese. Although research points towards social inequalities in OA and RA, they were mostly cross-sectional and cannot conclude the direction of the relationship (i.e. whether lower SEP leads to arthritis or whether arthritis leads to lower SEP). Furthermore, various studies investigated aspects of the complex relationships between SEP, obesity and RA and OA; however, studies bringing together all these factors that might explain some of the underlying relationships in more detail are lacking. This interdisciplinary thesis brings together sociology, epidemiology, public health and rheumatology and aims to contribute to the understanding of the complex relationships between SEP, obesity and RA and OA. Below, I will outline the gaps in the literature and my hypotheses based on existing literature per study aim.

1. **To perform a systematic literature review and meta-analysis assessing the association between educational attainment and different definitions of obesity in OECD countries (Chapter 3)**

Gap in the literature: Extensive research has shown a relationship between a lower SEP and total obesity, defined by BMI. However, central obesity, measured with WC, has received increased attention because of the additional prognostic information it may provide for some health outcomes, such as cardiovascular disease and type 2 diabetes. However, a comparison of the relationships between educational attainment and total obesity and central obesity among men and women has yet to be carried out.

Hypothesis: It is hypothesised that a lower education is associated with both total and central obesity and that there is no significant difference between the two obesity types. In line with the existing literature about a lower SEP and total obesity, it is thought that the association between a lower education and central obesity is also gender specific, where the association is stronger for women than men.

2. **To understand the associations between obesity, socioeconomic position and incident OA and RA (Chapter 4)**

Gap in the literature: Understanding risk factors for the incidence of disease is important for the prevention of disease. There is evidence for the relationship between total obesity and incident RA; however, few studies have investigated the relationship between central obesity and RA and they report conflicting results. A small number of studies (mostly cross-sectional and case-control studies) have investigated the link between SEP and the development of RA. These studies found a relationship between a lower SEP and RA and adjusted their results for smoking, a known risk factor of RA and a lifestyle factor that is more

prevalent among socioeconomically disadvantaged groups. However, other factors, such as obesity, could explain the relationship between SEP and the development of RA as a lower SEP is associated with obesity and obesity may be a risk factor for RA. Obesity is the main risk factor for incident OA, evidenced by many longitudinal studies. However, there are also signs that those from a lower SEP have increased rates of OA. It is uncertain whether this can be explained by higher obesity rates in lower SEP groups.

Hypothesis: It is hypothesised that there is a longitudinal association between a lower SEP at baseline and the development of both OA and RA. It is further thought that both total and central obesity are associated with incident OA and RA. Lastly, it is hypothesised that the relationships between a lower SEP and incident OA and RA are mediated by both BMI and WC.

3. **To understand the associations between obesity, socioeconomic position and the progression of OA (Chapter 5)**

Gap in the literature: Understanding risk factors for the progression of disease is important as it allows clinicians to closely monitor patients who are at increased risk for severe disease and potential risk factors may be modified early in the disease process. Evidence suggests that those from a lower SEP experience worse disease outcomes in OA; however, it is uncertain whether this can be explained by obesity.

Hypothesis: It is hypothesised that a lower SEP is associated with worse disease progression in OA; however, in line with previous studies, this may not lead to increased rates in JRS among the lower SEP. It is thought that obesity is associated with worse disease progression and increased rates of JRS. Further, it is thought that the relationship between a lower SEP and worse disease progression may partly be explained by obesity.

4. **To understand the associations between socioeconomic position, obesity and the progression of RA (Chapter 6)**

Gap in the literature: There is also evidence to suggest a relationship between a lower SEP and worse outcomes in RA; however, it is unclear what the reasons for these disparities are and whether higher obesity rates in people with lower SEP may potentially play a role. Moreover, conflicting results about the relationship between obesity and RA disease progression are reported.

Hypothesis: It is hypothesised that both a lower SEP and obesity are associated with worse outcomes in RA. It is also thought that BMI may mediate part of the relationship between having a lower SEP and worse outcomes in RA.

The next chapter will outline the methodologies used in this thesis to answer the above research questions.

Chapter 2

2. Methodology

This chapter provides a detailed overview of the methodology used in this PhD project. First, concepts in epidemiology that are relevant for this PhD will be explained. Subsequently, the methods of Chapter 3, the systematic literature review (SLR), will be described. For Chapters 4, 5 and 6, secondary data were used from two national longitudinal observational studies: the English Longitudinal Study of Ageing (ELSA) and UK Rheumatoid Arthritis Medication Study (RAMS). A brief background of ELSA and RAMS, their study designs, the study populations and the variables used in the analyses of this PhD will be described as well as how the study samples were constructed. Finally, the statistical methods of this PhD will be described.

2.1 Concepts of epidemiology important to my PhD thesis

2.1.1 Bias

For research results to have meaning and the correct interpretation, it is important to take into account *internal validity*, the ability of a study to measure what it aimed to measure, as well as *external validity*, the ability of study results to be generalisable to the wider population[349]. To increase internal and external validity of scientific studies, it is important to limit sources of *bias* as much as possible. In research, bias refers to "any deviation from the truth", potentially leading to false conclusions[350]. However, not all sources of bias are avoidable. Below I will set out different sources of bias related to this PhD project, and methods of dealing with such biases.

2.1.1.1 Selection bias

Selection bias occurs when the study sample is not a true reflection of the target population. Participation in a population-based cohort study may depend on an individual's social or health status; for example, transportation, linguistic and health barriers may reduce the opportunity for some population groups to participate in studies. It is also possible that if recruitment of a study takes place in a hospital, potentially a more severe disease population will be recruited. If the characteristics of the studied sample are systematically different from the target population, this will impact the external validity and generalisability to the target population. Although it is challenging to fully address the effects of selection bias, it may be reduced by the use of survey weights (which is explained in more detail in section 2.4.1) and adjusting for covariates that are associated with selection (e.g. socioeconomic factors)[351].

2.1.1.2 Information bias

Information bias occurs when study variables are measured inaccurately[352]. There are different types of information bias. *Self-reporting bias* is a common challenge in surveys, where data is often self-reported. This can lead to measurement error where self-reported values deviate from the actual values. From self-reported data, *social desirability bias* can arise. For example, for sensitive questions (e.g. weight or income) answers can be affected by social desirability or external approval. To illustrate, people tend to underestimate their weight and overestimate their height[353]. *Recall bias* can also arise, where answers depend on the ability to recall events in the past. Depending on the type of recall error, it can lead to underestimation or overestimation of the association. For example, if participants underestimate their weight and overestimate their height (and thus report a lower BMI than they actually have), the association between BMI and disease may be underestimated[352].

Another type of information bias is *measurement error bias*, which may happen when using inaccurate devices, poor questionnaire design or inaccurate interviewing[352]. This will lead to the measured value being different from the actual value. They can be systematic, where errors are consistently higher or lower than the actual value (e.g. a device is not calibrated correctly). They can also be random, where there is random

variation between the measured and actual measurement. Having standardised data collection protocols may reduce some of these biases[352].

Information bias can be non-differential, when 1) the misclassification of the exposure is equal among those experiencing the outcome and those who do not or 2) the misclassification of the outcome is equal among the exposed versus the non-exposed. Non-differential misclassification underestimates the effect. Information bias can also be differential, which happens when the misclassification of the exposure is not equal among those with the health outcome or not, or when the misclassification of the outcome is not equal among those who are exposed or not. Differential misclassification may underestimate or overestimate the effect. If there are fewer people with the health outcome recorded as exposed or fewer exposed people are recorded to have the health outcome in the study, then the effect will be underestimated. On the other hand, the effect will be overestimated if there are more people with health outcome recorded as exposed or more exposed people are recorded to have the health outcome[354].

2.1.1.3 Attrition

Attrition is one of the most common issues in longitudinal observational studies. Attrition refers to participants dropping out of the study before the study ends. There are different reasons for participants to discontinue with a study, including death, illness, moving house or barriers to attend the study site (e.g. transport or financial barriers). If the characteristics of participants dropping out of the study are different than those remaining in the study (i.e. differential attrition), attrition may lead to biased estimates. For example, differential loss of follow-up may partly explain the risk factor paradox mentioned in section 1.2.5.2, where obesity is associated with incident OA but not consistently with radiographic progression of OA. It is possible that obese people with OA are less likely to visit follow-up appointments for radiographs because of poor health or loss of mobility; this could reduce the effect of obesity on OA progression[217]. The use of survey weights (section 2.4.1) may correct for some of the bias due to differential attrition. However, non-differential attrition is also concerning as it may also lead to loss of statistical power.

2.1.1.4 Missing data

Missing data indicates that some information is missing, which may lead to bias[355]. When only complete cases are used, it may lead to the exclusion of a substantial amount of data, leading to loss in precision. There are different mechanisms whereby data can become missing. These mechanisms can be grouped into three different categories[355]:

- *Missing completely at random (MCAR)*: the probability that an observation is missing is unrelated both to the unobserved value itself and to the values of any other variables in the dataset. Thus, there are no systematic differences between the missing and observed values, and the missing value was just as likely to be observed. For example, a weight measurement is missing due to a broken scale. This type of missing data results in minimal bias, but will still affect statistical power.

However, in reality, considering your missing data to be MCAR is a strong assumption and relatively rare.

- *Missing at random (MAR)*: the probability that a missing observation is related to the observed data in your sample. In this instance, the missing value can be explained by differences in observed data. This is a common assumption. For example, missing income in lower educated individuals (lower educated individuals might be less inclined to report income, but you have data on education within your dataset and can therefore infer information about the missing income from the education data).
- *Missing not at random (MNAR)*: even when accounting for all observed variables, there are still systematic differences between the missing and observed values. The reason for the values being missed depend on the missing observations themselves. For example, people with a high alcohol consumption might be more likely to not answer the question about alcohol consumption.

These mechanisms of missing data will inform the methods of dealing with missing data, described below.

Commonly used approaches to deal with missing data include listwise deletion (deleting participants who have missing data on any of the variables in the analysis; the analysis is only performed on participants who have complete data) and pairwise deletion (only deletes cells with missing values, but still uses variables with non-missing data). If data is MCAR, these methods will not lead to bias; however, excluding a substantial amount of data will lead to loss in statistical power.

Missing values can also be imputed from observed data; for example, last observation carried forward (can be used in longitudinal data, where the missing value is replaced with the last available value), imputation of single mean (replace a missing value with the mean of the observed values) and imputation of regression mean (use a regression model to estimate missing value). However, these methods often lead to bias and underestimation of standard errors, as they do not account for the uncertainty of the imputed values[355].

Another method is multiple random imputation using chained equations (MICE), where multiple copies of the dataset are created and missing values are imputed based on the distribution of the observed variables. This improves the variability of the imputed values. Statistical analyses are performed in each dataset and estimates averaged together to generate an overall estimate using Rubin's rules[356]. If the data are MAR, multiple random imputation may lead to unbiased results. In most epidemiological studies, missing data are considered MAR (i.e. the values of the missing data can be predicted by the observed data)[357]. However, in some cases it is difficult to distinguish the pattern of the missing data from MAR and MNAR; this means that in reality MICE may be performed when data is actually MNAR. This may produce biased results[356].

2.1.2 Confounders, mediators and moderators

When analysing the association between an exposure variable and an outcome variable, a third variable may influence or interact with this association by being a confounder, mediator or moderator. Directed acyclic graphs (DAGs) can be used to identify the presence of confounding, mediating or moderating

variables. DAGs are a visual overview of causal relationships between variables based on prior knowledge and review of the literature[358]. DAGs give a clear overview of the minimum amount of variables to adjust for in the analysis to remove confounding.

2.1.2.1 Confounder

Confounding is a common risk in observational studies as opposed to RCTs. In RCTs people's characteristics (i.e. potential confounding variables) should be equally distributed between different intervention groups due to randomisation procedures[79]. Therefore, any difference in results between the intervention and control group can be attributed to the intervention, and not due to potential differences in groups. This is why results from RCTs, if well-conducted, generally have a causal interpretation[79].

In contrast, in observational studies, characteristics between the exposed and the non-exposed are usually not equally distributed. Therefore, it may be the case that a third variable (a confounder) distorts the relationship between an exposure variable and an outcome variable. A confounder must fulfil three criteria: 1) it is associated to both the exposure and the outcome; 2) it must be distributed unequally between exposed and non-exposed groups; 3) it cannot be a path variable (Figure 6)[349].

A classic example is that smoking is a confounder for the relationship between drinking coffee and lung cancer, as smoking is associated with both drinking coffee and lung cancer. Failing to adjust for smoking would lead to a conclusion that drinking coffee is associated with lung cancer, while in reality this may not be the case (i.e. there would be no association between drinking coffee and lung cancer when adjusting for smoking).

Possible confounders can be identified through an understanding of the existing literature about variables that are associated with the outcome. If the variable is also associated with the exposure variable, it is a possible confounder. In this PhD thesis, a DAG was used to create an overview of possible confounders for each analysis (Appendix B). For the relationships between SEP and the development and progression of arthritis, very few confounders were identified; instead, most variables were thought to be on the causal pathway (e.g. smoking, alcohol, obesity). Adjusting for variables on the causal pathway may lead to overadjustment bias[359]. However, for the relationships between obesity and the development and progression of arthritis, multiple variables were associated with both obesity and arthritis (e.g. SEP, physical activity, alcohol). Statistical testing can further be used to assess whether the confounding variable has an effect on the association by changing the strength of the association between an exposure and an outcome when the confounder is adjusted for. A common rule of thumb is when the difference between the unadjusted and adjusted estimates are greater than 10%, it may be concluded that there was confounding[360].

Confounding can be addressed using different statistical methods, including stratification (sub group analysis according to potential confounders), multivariable analysis (a regression analysis with multiple dependent variables, including the exposure of interest) and weighting (see section 2.4.1). In this PhD,

multiple confounders were identified and therefore multivariable regression analysis was used to adjust for confounders.

However, these methods are limited to confounders that are known and available in the dataset. Residual confounding may occur when the confounding variable is not perfectly measured; for example, it is challenging to perfectly determine the exposure of cigarette smoking or alcohol consumption. Moreover, there is a possibility of unmeasured confounding of variables that are not available in the dataset and can therefore not be adjusted for. The risk of both residual and unmeasured confounding limit the causal interpretation of associations found in observational studies.

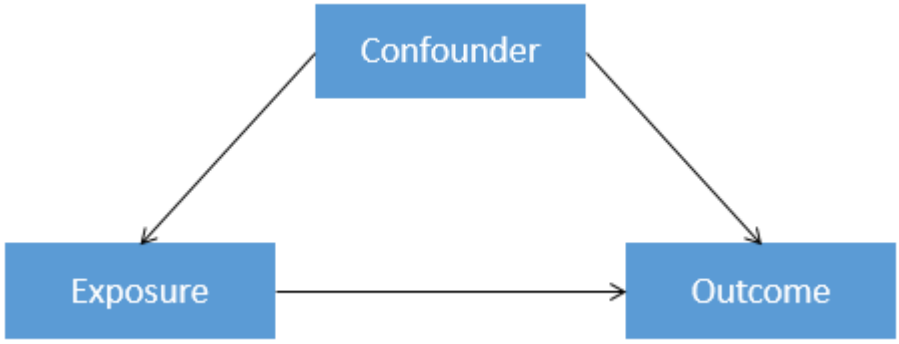


Figure 6: The relationship between an exposure, outcome and a confounder

2.1.2.2 Mediator

A *mediator* is an intermediate variable between an exposure and the outcome (Figure 7), where the exposure causes the mediator which then causes the outcome[361]. Mediation is important in epidemiological studies to disentangle the different pathways between exposure and outcome[362]. For example, in studies of socioeconomic health inequalities it is unlikely that having a lower SEP has a direct impact on health; rather, intermediate variables (e.g. lifestyle, environment, access to healthcare) may explain the process by which SEP influences health. Studying mediators helps to explain and understand why there is a relationship between a certain exposure and an outcome. If a mediator explains a large proportion of a relationship, mediators can be a desirable target for interventions. This is especially helpful when the exposure is difficult (or even impossible) to change with an intervention, such as SEP or ethnicity[363]. In contrast, if the proposed mediator is found to not explain a relationship, interventions should be focussed elsewhere.

Understanding the influence of these intermediate variables on the relationship between exposure and outcome is possible with the help of mediation analyses (explained in more detail in sections 2.4.4 and 2.4.5). Using mediation analyses, the extent to which an effect of the exposure on an outcome is explained by a hypothesised mediator can be estimated through calculating the total effect (i.e. the total effect of

the exposure on the outcome), the indirect effect (i.e. the effect of the mediator) and the direct effect (i.e. the effect not explained by the mediator).

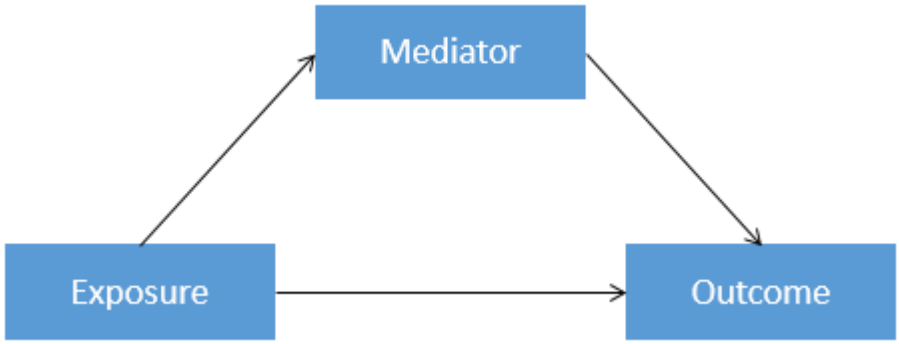


Figure 7: The relationship between an exposure, mediator and an outcome

2.1.2.3 Moderator

A *moderator* is a variable influencing the relationship between an exposure and outcome and impacting its strength or direction (Figure 8). An example mentioned by Rothman (2012) is that alcohol is a moderator for the relationship between driving and injury: driving and drinking alcohol increases the risk for injury compared to driving and not drinking any alcohol[354]. As you can see from this example, understanding moderators is important for public health interventions as it allows us to understand which subgroups are most at risk for health/disease (or injury). It may therefore help to understand for which subgroups interventions may be most beneficial.

Moderation can be assessed by investigating whether interactions between an exposure variable and a third variable are statistically significant in a regression analysis. If the interaction term is statistically significant ($p<0.05$), there is evidence of moderation and the analysis and reporting of results should be stratified by different groups. However, there are some limitations of using significance testing, described in the next section.

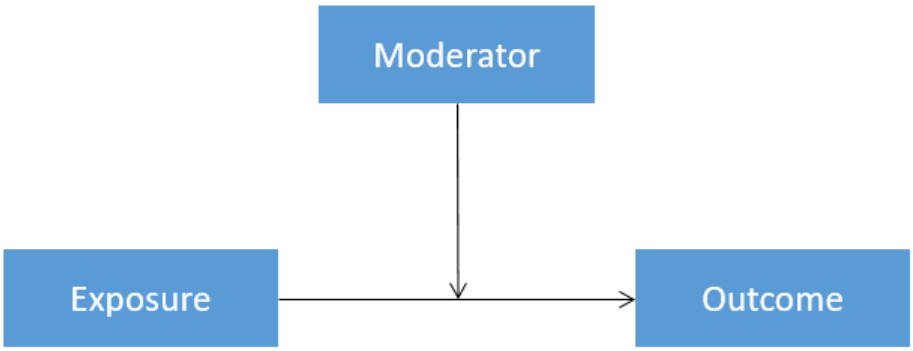


Figure 8: The relationship between an exposure, moderator and an outcome

2.1.3 Limitations of statistical significance

In research, a p-value of ≤0.05 is commonly used to indicate "significance". P stands for statistical probability and it describes the likelihood that the result would have occurred by random chance. A p-value of ≤0.05 means that there is a less than 5% chance that the result is due to chance. A positive results due to chance is also called a type 1 error (i.e. a false positive). Type 2 error happens when the researcher fails to find an effect when in reality there is (i.e. a false negative); this is often related to having not enough statistical power.

It is important to note that the 5% threshold is arbitrary and there may not be a clinical difference with a p-value of 0.045 and 0.055[364]. It has also been argued that it is too simplistic to explain clinical or societal significance; for example, a p-value of 0.05 may indicate that a drug has a statistically significant effect on disease outcomes, but this may not be a therapeutic effect[365]. Moreover, the p-value depends on the sample size; with a larger sample, you might get a significant p-value for a very small effect[364]. Lastly, p-values do not measure the size of an effect[364]. Therefore, the clinical importance of results should not be determined by how low the p-value is.

It is preferable to look at effect sizes with associated confidence intervals, as these are able to determine the strength of the effect and the precision of the results. The effect sizes show us the magnitude of the effect and allow us to understand whether the effect is clinically important in each specific context. Confidence intervals give information about both the effect size and the precision of the results. They are also based on sample size; the larger the sample size, the smaller the range of the confidence interval and the more precise the result.

In this PhD thesis, p-values will only be used to assess effect-moderation discussed in the previous section. However, the focus will not be strictly on the 5% threshold; if the p-value is slightly above this, stratified analyses will also be performed to observe any differences between groups.

2.2 Systematic literature review and meta-analysis

The first study of this thesis was a systematic literature review (SLR) and meta-analysis (Chapter 3). The aim of the SLR was to: 1) understand whether the associations between educational attainment and obesity are different depending on the measures used to identify obesity (BMI and WC), and 2) explore whether these relationships differ by gender and region. The specific methodology and search strategy are outlined in the published manuscript found in Chapter 3. The review employed some key methodological approaches, such as meta-analyses, meta-regression analyses and the quality assessment of studies, which are described in more detail here.

2.2.1 Meta-analyses

A meta-analysis is a subset of a systematic literature review, and integrates the results of multiple individual studies with the same research question. It calculates a weighted average of the effect sizes of each of the individual studies, with the weights dependent on the precision of the estimates of each study (with the higher precision studies having more weight). It may therefore create a more precise outcome than any of the individual studies[366]. Meta-analyses can either use a fixed or a random-effects model. In a fixed-effects model, the assumption is that all effect sizes from the studies are from one homogeneous population and that all studies measure exactly the same thing (e.g. there is no variation on how an outcome is measured). It therefore assumes that all included studies have the same true effect size. This true effect size will be estimated in the meta-analysis. According to this type of model, heterogeneity between studies is due to sampling variability. However, these assumptions are often unrealistic in real-world settings; it is likely that studies vary based on target population or how the outcome was measured. A random-effects model takes this between study heterogeneity into account. In this model, it is assumed that effect sizes may vary between studies[367]. In the systematic review in this thesis, effect sizes may differ per country or per age of the study population; therefore, the meta-analyses are based on random-effects models.

Although studies may have the same or a similar research question, studies may use different measures of exposures and outcomes depending on what is available in their respective data sources. For example, studies may use different definitions of education; to make studies still comparable, comparing the lowest versus the highest educational level is a solution. Moreover, studies may present the results in different effect measures (i.e. RR, OR, RII). In that case, it is possible to group studies based on which measure they used.

2.2.1.1 Publication bias

Publication bias occurs when the results of a study determine whether the results are published or not; for example, studies that do not find an association between a lower education and obesity may be less likely to be published than studies that do find an association. This could lead to an overestimation of the effect between a lower education and obesity when performing meta-analysis.

One way to detect publication bias is through a funnel plot (Figure 9), which visualises the effect size of a study in relation to its precision. When there is no publication bias, the funnel plot will look like a symmetrical pyramid: wide at the bottom and narrow at the top. The wide part at the bottom represents the smaller studies with less precision, whereas the narrow part at the top represent the larger studies with more precision. The outer dotted lines represent the region in which 95% of the studies are expected to fall within when biases and heterogeneity are not present[368].

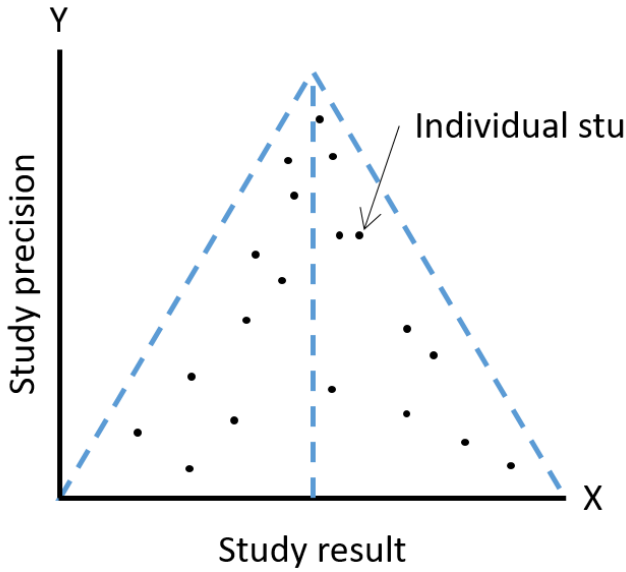


Figure 9: Generic funnel plot

When there is a high risk of publication bias, the funnel plot will be asymmetrical; this may indicate that there is a systematic difference between studies that are published or not. For example, if studies are missing on the bottom left, it may indicate that small studies with an effect estimate lower than the aggregate effect are missing. To formally test whether the asymmetry of a funnel plot is statistically significant, the Egger's test can be used[369]. The Egger's test is a regression of the standardised effect estimate (effect/SE) on precision (1/SE). If this relationship is statistically significant, this often indicates asymmetry in the funnel plot and potential publication bias. However, this test only works with a sufficient amount of studies included in the meta-analysis (at least 10 is advised by the Cochrane Handbook) to ensure there is enough power to distinguish chance from asymmetry[370].

2.2.1.2 Quality assessment

An outcome of a meta-analysis may be misleading if the studies that are included are biased or invalid. Therefore, an essential part of a systematic review and meta-analysis is to assess the validity and reliability of the included studies. There are a variety of quality assessment tools based on whether studies are interventional or observational. However, generally, quality assessment tools include the assessment of internal validity (i.e. whether the design and conduct of the study is able to measure what it is meant to

measure) and external validity (i.e. whether results of the study can be generalised to the population it is meant to study).

This PhD thesis followed the recommendation by the Cochrane Prognosis Methods Group and used the Quality In Prognosis Studies (QUIPS) tool[371]. This tool is specifically developed to evaluate the risk of bias in studies of prognostic factors, and has proven to be effective[371]. Six domains were evaluated for each study: study participation, study attrition, prognostic factor measurement, outcome measurement, confounding and statistical analysis and reporting. Each domain consists of different prompts that can help evaluate the study with regards to bias. Using these prompts, each domain can be rated as a risk of bias of 'low', 'moderate' or 'high'. The results of the QUIPS are taken into account when interpreting the results; however, it did not determine whether a study was included in the systematic review or meta-analysis or not.

2.2.2 Meta-regression

Meta-regression analyses are an extension to meta-analyses and can be used to understand whether certain study characteristics (e.g. type of obesity measurement used) or population characteristics (e.g. gender, region) influence the size of the effect of a meta-analysis[370]. Meta-regression analyses follow the principles of a simple regression analysis, where an outcome variable is predicted by one or multiple dependent variables. In addition, meta-regression analyses incorporate information about the size and precision of included studies; the larger and more precise studies get a higher weight in the analyses. Moreover, in the same way as in a meta-analyses (section 2.2.1), heterogeneity between studies are taken into account when choosing a random-effect meta-regression model[370].

2.3 Description of datasets

This thesis used two observational longitudinal studies to address objectives 2–4. To address objectives 2 (to understand the associations between socioeconomic position, obesity and incident arthritis, Chapter 4) and 3 (to understand the associations between socioeconomic position, obesity and the progression of OA, Chapter 5), the English Longitudinal Study of Ageing (ELSA) was used. To address objective 4 (to understand the associations between socioeconomic position, obesity and the progression of RA, Chapter 6), the Rheumatoid Arthritis Medication Study (RAMS) was used. Both datasets are explained in detail in the next sections.

2.3.1 English Longitudinal Study of Ageing

ELSA (https://www.elsa-project.ac.uk/) was established in 2002 and provides a source of longitudinal information about health, wellbeing and socioeconomic factors in the English population of 50 years and older and their partners in England. ELSA is funded by the National Institute on Aging and various UK Government Departments, and it is conducted by University College London, the Institute for Fiscal Studies, the University of Manchester and NatCen Social Research[372]. It was initially created as a sister study to the Health and Retirement Study in the US; however, now there are also sister studies in Australia, Brazil,

Canada, China, Costa Rica, South Africa, Scotland, Ireland, Japan, Korea, Malaysia, Mexico, New Zealand, Northern Ireland, Thailand, Europe, Indonesia and India. This allows for cross-national comparisons.

Written informed consent was obtained from all participants and ethical approval was acquired from the NHS Research Ethics Committees under the National Research and Ethics Service. The UK Data Service provided anonymized data for this study[373].

2.3.1.1 Study design

ELSA has an observational longitudinal study design. The original sample in 2002 and refreshment samples in 2006, 2008, 2012 and 2014 (to keep the sample representative of the general population) were derived from the Health Survey of England (HSE). The HSE is an annual cross-sectional study aiming to monitor the health of the general population in England, with a multi-stage stratified probability sampling design. The first stage includes a random selection of primary sampling units based on postcodes. In the second stage, a random sample of postal addresses were drawn from the primary sample units. Participants of HSE who were 50 years or older and who agreed to take part in future studies were invited to participate in ELSA.

There were 16,983 eligible participants and 11,391 responded, leading to a response rate of 67%. These are defined as 'core members'. Cohabiting partners, who may be younger than 50 years, were also invited to participate to understand behaviours within a couple or household. An extra 708 cohabiting partners were included, resulting in a total sample of 12,099 who completed the first interview in 2002[372]. However, this PhD thesis will only use data from core members.

Data collection cycles are referred to as 'waves', and were every two years from 2002–2019 (currently nine waves are published). If participants moved house, or to an institution (e.g. care home), within Great Britain (GB), they remained eligible. In contrast, they became ineligible if they moved outside GB or passed away[372].

Over time, as expected, the core sample became older, leaving the younger age groups underrepresented; for example, those who are 50 years old in one wave will be 52 in the next. Therefore, refreshment samples were included in waves 3, 4, 6, 7 and 9 to make the study sample representative for the English population aged 50 and older (Table 10)[372].

Table 10: An overview of the core members per cohort (refreshment samples in waves 3, 4, 6, 7 and 9) per wave

Wave	Date	Cohort 1	Refreshment w 3	Refreshment w 4	Refreshment w 6	Refreshment w 7	Refreshment w 9	Total sample
1	2002/3	11,391	-	-	-	-	-	11,391
2	2004/5	8,781	-	-	-	-	-	8,780
3	2006/7	7,535	1,276	-	-	-	-	8,811
4	2008/9	6,623	972	2,291	-	-	-	9,886
5	2010/11	6,242	936	1,912	-	-	-	9,090
6	2012/13	5,659	888	1,796	826	-	-	9,169
7	2014/15	4,894	787	1,606	661	301	-	8,249
8	2016/17	4,219	723	1,470	582	229	-	7,223
9	2018/19	3,660	688	1,307	523	212	899	7,289

W, wave.

2.3.1.2 Data collection

Data were collected from study participants via a face-to-face Computer-Assisted Personal Interview (CAPI) and a self-completion questionnaire by trained interviewers. The questions from both assessments contained information about a broad range of topics including socioeconomic factors, social participation and physical and mental health[372]. Appendix C details example topics of the CAPI interview and the self-completion questionnaire[374].

2.3.1.2.1 Nurse visits

At the end of the main interview of waves 2, 4 and 6, all core members were asked whether they would be willing to participate in a nurse visit in the weeks after the main interview[375]. In waves 8 and 9, only a subset of the sample was offered a nurse visit. For wave 8, purposive sampling was used to prioritise participants who participated in all of the previous nurse visits they were invited to. For wave 9, the remaining participants (if they were not asked for a nurse visit in wave 8) were eligible for a nurse visit if they completed the wave 9 main interview. This ensured that all members were either eligible for a nurse visit in wave 8 or 9. Response rates for the nurse visits in waves 2, 4, 6, 8 and 9 were 87.3%, 85.7%, 84.3%, 93.7%, 83.8% respectively[375].

During the nurse visit, a trained registered nurse carried out a range of measurements, including blood pressure, weight, height and waist measurements. Blood samples were collected for biomarker information, such as CRP levels[372] (Appendix D[374]). The next section will describe the variables used in this PhD thesis in more detail.

2.3.1.3 Variables of interest in this thesis

2.3.1.3.1 Obesity

In both objective 2 and 3, total and central obesity were predictors of interest. Total obesity was defined by BMI ≥30kg/m^2 and central obesity was defined by WC ≥102 cm for men or ≥88 cm for women[376]. Height, weight and WC are measured in waves 2, 4 and 6 by a registered nurse. In certain circumstances height or weight could not be measured; for example, if a participant was chair-bound or if the participant was

thought to exceed the limit of 130 kg of the scale. In these circumstances, an estimate was obtained from the participant. In waves 8 and 9, weight was collected according to the same procedure by trained interviewers in the main interview in order to collect weight from the full sample. Waist measurements were taken on all participants, except if they were chair-bound or had a colostomy or ileostomy. The waist was measured at the midpoint between the lower rib and the upper margin of the iliac crest. WC was measured twice; if there was a difference of 3 cm or more, another measurement was taken.

2.3.1.3.2 Socioeconomic position

SEP was defined using multiple indicators in objectives 2 and 3, including education, occupation, income, wealth and area-level deprivation. These were measured at baseline (how baseline is defined is mentioned in section 2.3.1.4) and included:

Education – Participants were asked what their highest educational qualification was, with seven categories: 1) national vocational qualification (NVQ)4/NVQ5/university degree or equivalent, 2) higher education below university degree, 3) NVQ3/ general certificate of education (GCE) A-level equivalent, 4) NVQ2/GCE O-level equivalent, 5) NVQ1/ certificate of secondary education (CSE) other grade equivalents, 6) foreign/other, and 7) no qualifications. Qualifications that did not fit in any of the categories were classed as foreign or other; as mentioned in section 1.2.3.3.1, this impacts the ordinal nature of this variable and the results of this category is difficult to interpret[93]. In this PhD, whilst the results for the category 'foreign/other' are presented, usually the other categories (2, 3, 4, 5 and 7) are compared to the highest category (1).

Occupation – Current or most recent occupational status was measured using the UK National Statistics Socioeconomic Classification (NS-SEC)[377]. The NS-SEC is used in all official statistics and surveys in the UK. It is based on people's employment conditions and relations, and it takes into account whether people have a fixed salary or an hour-dependent wage, opportunities for promotion and levels of autonomy. This classification system organises occupations in 7, 5 or 3 groups with an additional category of 'never worked and long term unemployed' (Table 11). This thesis used the NS-SEC with five classes (NS-SEC5), those who were never in paid work were excluded.

Table 11: Different classes of the NS-SEC[377]

Eight classes	Five classes	Three classes
1. Higher managerial, administrative and professional occupations	1. Higher managerial, administrative and professional occupations	1. Higher managerial, administrative and professional occupations
1.1 Large employers and higher managerial and administrative occupations		
1.2 Higher professional occupations		
2. Lower managerial, administrative and professional occupations		
3. Intermediate occupations	2. Intermediate occupations	2. Intermediate occupations
4. Small employers and own account workers	3. Small employers and own account workers	
5. Lower supervisory and technical occupations	4. Lower supervisory and technical occupations	3. Routine and manual occupations
6. Semi-routine occupations	5. Semi-routine and routine occupations	
7. Routine occupations		
8. Never worked and long-term unemployed	*Never worked and long-term unemployed	*Never worked and long-term unemployed

NS-SEC, National Statistics Socioeconomic Classification.

Income quintiles – This measure includes the total net income of the household in the last month, including: employment income, self-employment income, state benefit income, state pension income, private pension income, asset income and any other income.

Wealth quintiles – This measure includes the net total wealth of the household, including savings, investments, physical wealth and housing wealth minus any debts.

Deprivation – Area-level deprivation was measured through the Index of Multiple Deprivation (IMD). This was described in more detail in section 1.1.3.3.5. In short, IMD is a measure of relative deprivation of small areas in England based on 39 indicators across seven domains of deprivation: income; employment; education; skills and training; health deprivation and disability; crime; barriers to housing and services; and living environment[378]. Areas are ranked by scores and classified into five quintiles: 1) least deprived, 2) 2nd quintile, 3) 3rd quintile, 4th quintile, and 5) most deprived. The IMD2004 was used for waves 1–3, the IMD2010 for waves 5–7 and IMD2015 for wave 8.

2.3.1.3.3 Incident arthritis

For objective 2, the outcomes of interest were incident RA and OA in waves 3–9. At each wave, participants were asked 'Has a doctor ever told you that you have (or had) any of the following conditions on this card?'. If 'Arthritis' was chosen, participants were then asked 'Which type or types of arthritis do you have?', with as answer options 'osteoarthritis', 'rheumatoid arthritis' or 'some other kind of arthritis'. Participants who indicated diagnosis of RA or OA were asked for updates on their condition in subsequent waves, but could not report the same diagnosis again; however, they were able to report diagnoses of other types of

arthritis. Participants who did not indicate an arthritis diagnosis in previous waves or newly recruited participants were asked the original question.

However, after investigating incident RA cases, it became clear that there was a problem of significant misclassification; the incidence rate of self-reported RA in ELSA (1417 per 100,000 persons years) was markedly higher than would be anticipated in a similar population of older adults (not higher than 100 per 100,000[239]). Potential reasons and implications are elaborated in the Discussion (section 7.2.6). Incident rates of OA in ELSA (3622 per 100,000 persons years) were similar to rates in a UK adult population (3150 per 100,000 persons years)[379]; hence, misclassification of self-reported OA was thought to be minimal. It was subsequently decided to focus on the OA analyses in the publication of Chapter 4; however, the results of RA are still included in Appendix F.

2.3.1.3.4 Progression of osteoarthritis

For objective 3, the outcome of interest was the progression of knee OA, measured through functional disability and knee joint replacement surgery (JRS). Functional disability was measured through the Activities of Daily Living (ADL), a self-reported physical capability questionnaire[205], and different mobility indicators in waves 2–9. ADL comprises six activities, including dressing, walking across a room, bathing/showering, eating, getting in or out of bed, and using the toilet. For each ADL, participants answered the question "because of a health or memory problem, do you have difficulty doing any of the activities on this card?", where participants could respond with yes or no. For this study, a continuous indicator of the number of ADLs where a participants reported 'yes' was used. This resulted in a score from 0–6, where 0 is no difficulties and 6 is all difficulties present. Five further self-reported mobility indicators were recorded as binary variables (ability to perform the activity, yes/no), including: 1) walking 100 yards, 2) getting up from a chair after sitting for long periods, 3) climbing several flights of stairs without resting, 4) climbing one flight of stairs without resting , and 5) stooping, kneeling or crouching. Unlike ADL, which creates a validated score[205], the mobility indicators were not summed to avoid loss of information of specific mobility indicators.

The second outcome measure was the first self-reported knee JRS due to arthritis at follow-up (waves 3–9). If participants answered 'yes' to the question 'whether right/left knee joint was replaced', they were further asked what the reason for the knee replacement was (arthritis, fracture, other reason). If the answer was 'arthritis', it was recorded as knee JRS due to arthritis.

2.3.1.3.5 Covariates / additional variables

In both objectives 2 and 3, the following variables were included as covariates: gender (male, female), age (in years, continuous variable), ethnicity (recoded by ELSA into white or non-white), alcohol consumption (less than monthly, 1x/month–4x/week, (almost) every day), smoking status (never smoked, ex-smoker, current smoker), and physical activity (sedentary, low, moderate, high). Physical activity level was determined based on the level of self-reported work activity (sedentary, standing, physical work or heavy

manual work) and three questions about leisure time physical activity, which measure the frequency of participation in vigorous (e.g. running, swimming, cycling, gym workout, tennis, digging with a spade), moderate (gardening, cleaning the car, walking at moderate pace, dancing) and light (laundry and home repairs) physical activities, with answer options: more than once per week, once per week, one to three times per months, hardly ever. A variable was created that closely follows the classification used in the Allied Dunbar Survey of Fitness[380]. The categories are as follows:

- Sedentary: Not working or sedentary occupation, engages in mild exercise 1–3 times a month or less, with no moderate or vigorous activity.
- Low: Standing occupation, engages in moderate leisure-time exercise once a week or less and no vigorous activity; OR engages in mild leisure-time activity at least 1–3 times a month, moderate once a week or less and no vigorous; OR has a sedentary or no occupation and engages in moderate leisure-time activity once a week or 1–3 times a month, with no vigorous activity.
- Moderate: Does physical work; OR engages in moderate leisure-time activity more than once a week; OR engages in vigorous activity once a week to 1–3 times a month.
- High: Heavy manual work or vigorous leisure activity more than once a week.

For objective 3, we additionally accounted for comorbidity and glycated haemoglobin (HbA1c). Comorbidity was defined using an adapted version of the rheumatic disease comorbidity index (RDCI)[381]. All comorbid diseases comprising the RDCI were used (i.e. lung disease, cardiovascular disease, fracture, depression and cancer), except for stomach ulcers, which are not recorded in ELSA. This resulted in a score from 0–8 (where 0 is no comorbidities and 8 the highest comorbidity score). Moreover, HbA1c is a measures of average blood sugar over two to three months. Peri-operative complications are more common in people with high blood sugar levels[382] and NHS Diabetes guidelines indicate that blood sugar levels need to be stable before surgery[383]. Hence, it was decided to account for time-varying HbA1c levels. HbA1c values were measured using nurse-collected blood samples in waves 2, 4, 6 and 8.

2.3.1.4 Study samples of ELSA used for this PhD thesis

2.3.1.4.1 Sample for objective 2

For objective 2 (Chapter 4), longitudinal data was used from wave 2 (2004/05) to wave 9 (2018/19). The baseline cohort was constructed based on having had a nurse visit at least once where nurse-measured height and weight and waist circumference was collected. These data were available in the nurse visit in waves 2, 4 and 6. Each participant's baseline assessment was defined at the time of first anthropometric measurements. Participants who gave a self-reported diagnosis of RA or OA at or before their baseline assessment were excluded (917 RA cases and 2,567 OA cases were excluded). Follow-up data were collected in the core interview at every wave, and therefore were collected from waves 3–9. Figures 10 and 11 detail the data selection process and their follow-up measurements for the OA and RA cohorts,

respectively. The baseline samples included 9,281 for the OA analyses and 10,931 participants for the RA analyses.

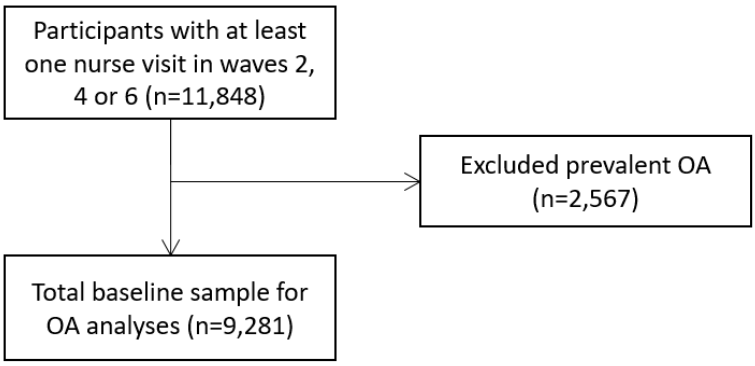


Figure 10: Flowchart of eligible participants for Chapter 4 – OA analysis (total baseline sample = 9,281)

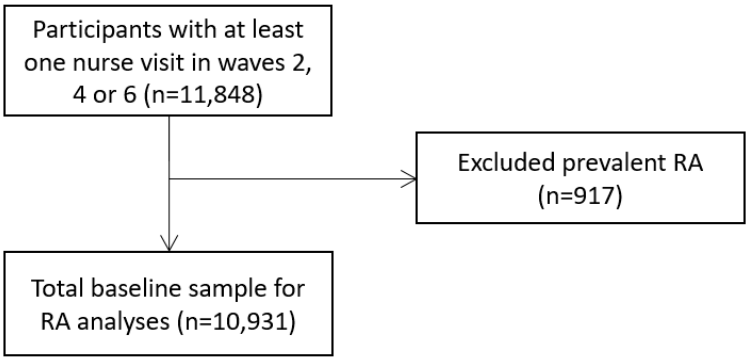


Figure 11: Flowchart of eligible participants for Chapter 4 – RA analysis (total baseline sample = 10,931)

2.3.1.4.2 Sample for objective 3

For objective 3 (Chapter 5), people with knee OA were included. Participants who self-reported an OA diagnosis for the first time in waves 2–8 and answered 'yes' to the question 'Do you feel knee pain?' in the same or previous wave of a self-reported diagnosis of OA were defined as having knee OA. Prevalent OA cases from wave 1 were excluded as we could not ascertain the date of diagnosis. Participants with at least one BMI measurement were included. The BMI measurement closest to OA diagnosis was used. Baseline assessment was defined at the time of OA diagnosis; this could be at waves 2–8. Figure 12 shows the flowchart of sample selection for this study.

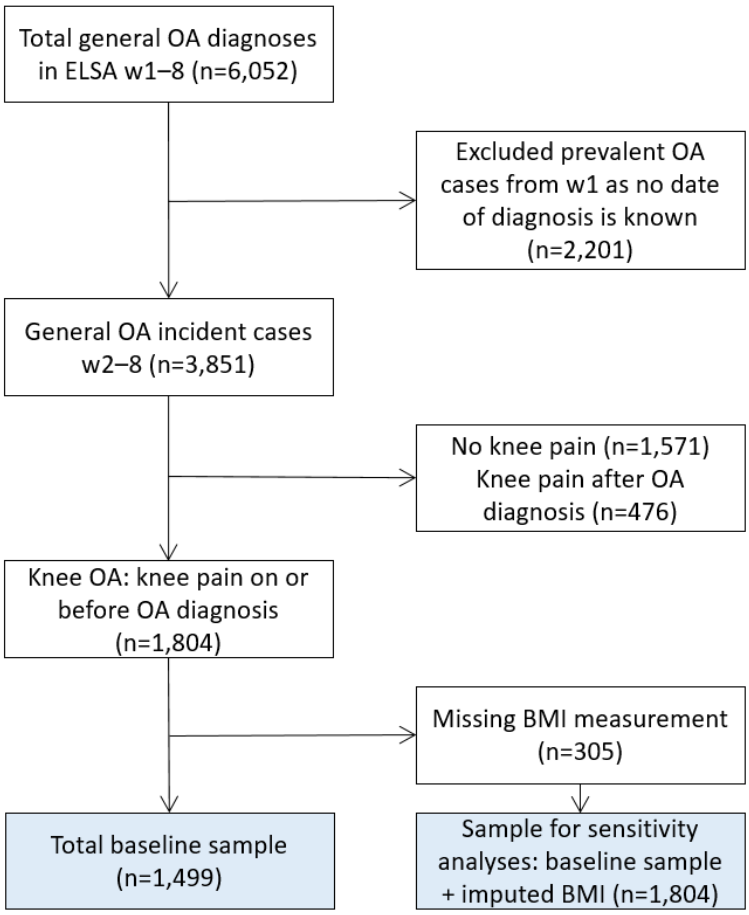


Figure 12: Flowchart of eligible participants for Chapter 5

2.3.2 Rheumatoid Arthritis Medication Study

2.3.2.1 Study design

RAMS is a prospective observational cohort of people with RA who are about to start MTX for the first time. The main objective of RAMS was to identify predictors of response and adverse events to MTX in patients with RA. Participants are recruited from 38 rheumatology centres in the UK and were included if they were 18 years or older, had a physician diagnosis of RA and were about to start with MTX for the first time. People were excluded if they had known contradictions to MTX (e.g. women of childbearing age not taking contraception; excess alcohol consumption; abnormal liver function tests), if they were previously treated with biological DMARDs and if they were participating in a blinded clinical trial (as medication intake needed to be known).

RAMS was approved by the Central Manchester NHS Research Ethics Committee (reference 08/H1008/25) and all patients provided written informed consent.

2.3.2.2 Data collection

Patients were recruited for RAMS between August 2008 and July 2019 by rheumatologists or rheumatology nurses at the time patients were about to start MTX. Participants who agreed to participate in the study had a baseline assessment, and were then followed up at 4 weeks, 3 months, 6 months and 12 months. This PhD thesis only used data from the follow-up visits at 6 months and 12 months.

A research nurse completed a case report form (CRF) at baseline and follow-up visits, which included information about patient's characteristics, medical history, co-morbidities, medication use, and disease activity. The CRF included an interview with the patient, laboratory data and data extraction from participants' medical records. Blood samples were collected for the measurement of C-reactive protein (CRP) (BLOSR6X99 05, mg/mL) and rheumatoid factor (RF) (BLOSR6X105 06, lU/mL). They were stored at –80°C and posted to the UK Biobank in Stockport for analysis. If blood samples were not available, CRP and RF were taken from participants' clinical records. Information from the CRF were entered in the database by a research nurse.

In addition, patients completed a patient questionnaire at baseline, 6 months and 12 months. The patient questionnaire at baseline can be found in Appendix E; it consists of information about demographic characteristics, symptoms, physical activity, HAQ (explained further in section 2.3.2.3.2) and self-reported health status. The completed patient questionnaires were sent to the co-ordinating centre in Manchester in a pre-paid envelope by either the study nurse or participants, where data was entered in a secure database.

The next section will describe in more detail which variables were used in this PhD study.

2.3.2.3 Variables of interest in this thesis

2.3.2.3.1 Exposure variables: obesity and SEP

Self-reported height and weight were recorded in the CRF at baseline, 6 months and 12 months. BMI was calculated by dividing the weight in kilograms by height in meters squared. Obesity was defined as having a BMI of 30 or higher.

SEP was defined using area-level deprivation, measured through the IMD. Using the patients' postcode, which was recorded at baseline, the most recent IMD was used after the date of the baseline assessment (either 2010, 2015 or 2019). As mentioned previously (section 1.1.3.3.5), the IMD is a measure of small-area deprivation based on seven indicators of deprivation (income, employment, education, skills and training, health deprivation and disability, crime, barriers to housing and services, and living environment)[60].

2.3.2.3.2 Outcome variables: HAQ-DI and DAS28

In the patient questionnaire, participants completed the HAQ Disability Index (HAQ-DI), which measures self-reported disability, at every visit. The questionnaire produces a score from 0–3, where 3 indicates the most severe disability[296]. The HAQ-DI includes 20 questions across eight categories: dressing, rising, eating, hygiene, walking, reach, grip, everyday activities. With each item, the participants report how RA affects their ability to perform the specified task (answer options: without any difficulty (0); with some difficulty (1); with much difficulty (2); unable to do (3)). Each of the eight categories are then given an overall score of 0–3, based on the highest score of the items within that category. A score of two is given when the participant reports using a device (e.g. a bath rail) with a specific category. The final score of the HAQ-DI is calculated by adding the scores of all eight categories and dividing it by eight, producing a final score from 0–3, where 3 indicates the most severe disability[296]. In this study, HAQ-DI was treated as a continuous variable.

DAS28 was further calculated at every visit, incorporating information from the CRF regarding the number of tender joints out of 28 joints, the number of swollen joints out of 28 joints, CRP levels (mg/L) and self-reported general wellbeing using the visual analogue scale (VAS) (0–100 mm, where 100 is the worst score)[300]. DAS28 score ranges from 0.96–10, where a score above 5.1 is considered high disease activity[300].

2.3.2.3.3 Covariates

Demographic and lifestyle covariates were recorded at baseline; the variables that were relevant to this analysis included age, gender, ethnicity (white, non-white), smoking status (never, current, ex-smoker), alcohol intake (yes/no) and physical activity (compared to people your own age – much more, more, the same, less, much less).

Further clinical variables were also collected. Factors relating to the 1987 ACR classification criteria were recorded, including: 1) morning stiffness; 2) arthritis/deformity of three of more joints areas; 3) symmetric arthritis/deformity; 4) arthritis/deformity of hand; 5) rheumatoid nodules; 6) serum rheumatoid factor;

and 7) radiographic changes. If four or more of these criteria were present, the patient complied to the 1987 ACR criteria of RA[237]. Symptom duration (in years), MTX starting dose (mg/wk) and history of comorbidities were also recorded. Comorbidities were collected from a pre-defined table of diseases, including: hypertension, diabetes, cardiovascular disease, asthma, chronic obstructive pulmonary disease, peptic ulcer disease, liver disease, renal disease, depression and cancer. Comorbidities were categorised into: no comorbidities; one comorbidity; two or more comorbidities).

All covariates were collected in the CRF, with the exception of physical activity which was captured in the patient questionnaire.

2.3.2.4 Study sample for objective 4

Study samples for objective 4 (Chapter 6) were created for the HAQ-DI and DAS28 analyses separately. Participants were included if they had a baseline assessment with at least one follow-up assessment (either at 6 or 12 months) of HAQ-DI or DAS28. They also had to have a valid BMI measurement at baseline. The flowchart is shown in Figure 13.

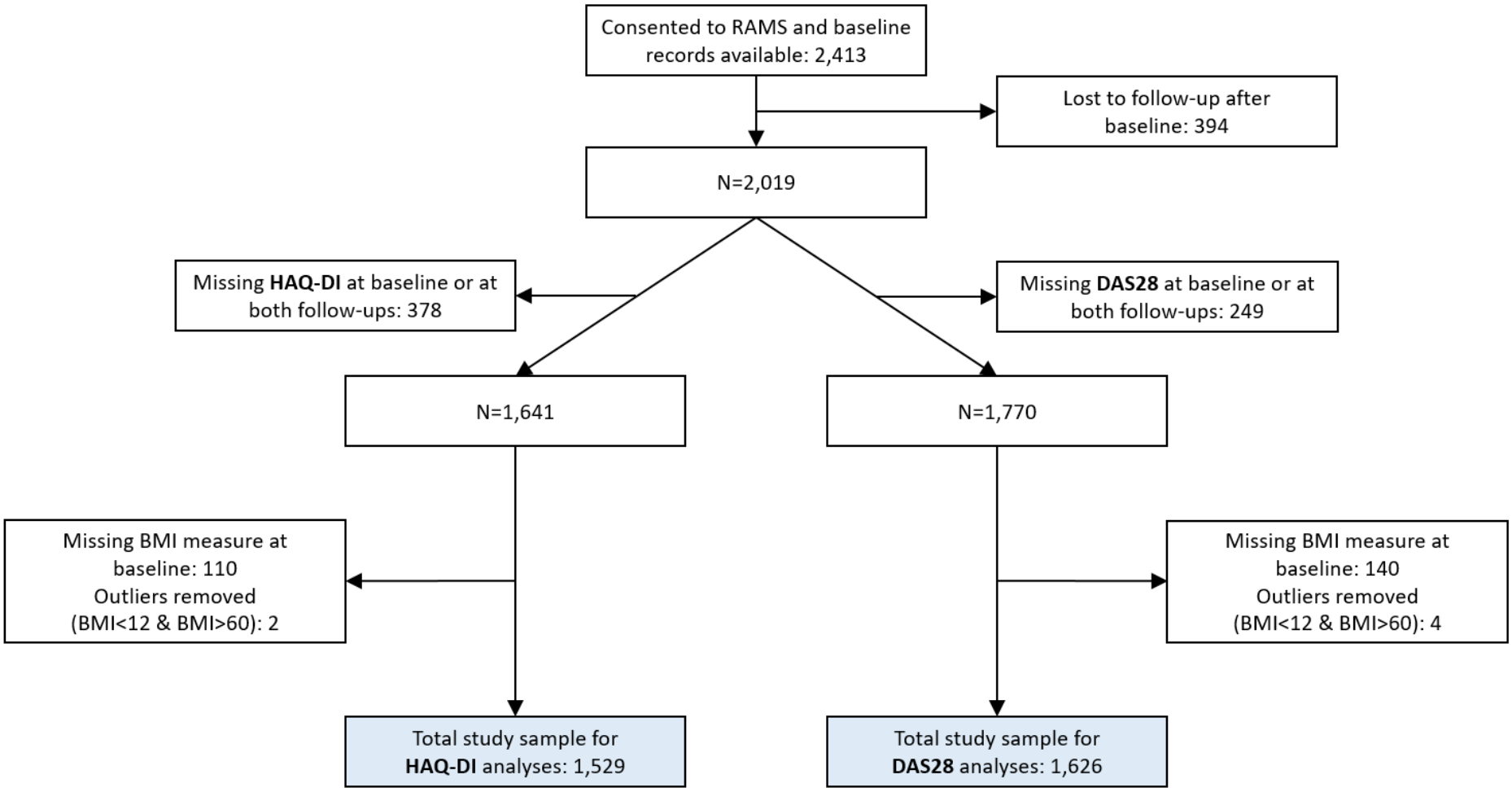


Figure 13: Flowchart of eligible participants for Chapter 6

2.4 Statistical analyses

2.4.1 Survey weights

Survey weighting can be used to bring a study sample more in line with the aimed population to be studied based on certain characteristics. A larger weight is given to those who are underrepresented and a smaller weight is given to those who are overrepresented. For example, if females are overrepresented in the study sample, they will get a smaller weight than men. Survey weighting simply means that an individual's outcome is multiplied by a particular weight.

Although ELSA aims to be representative of the older population in England, there may be some selection bias as very few ethnic minority participants have been recruited[384]. Survey weights attempted to adjust for the difference in the propensity to respond to the survey request among sub groups (based on age, gender, IMD quintiles, urban/rural, education, ethnicity and NS-SEC) and aimed to scale the sample to the general population based on estimates of the ONS[385]. Cross-sectional and longitudinal weights have been developed per wave. The longitudinal weights are also designed to adjust for historical non-response; this means that the wave 9 weight adjusts for non-response in each previous wave of ELSA. They are assigned to core members only. The weight needed for each participants is dependent on when the participant was lost to follow-up (i.e. if a person was lost to follow-up at wave 5, the weight of wave 5 needs to be used). In this PhD, longitudinal weights were used for the analyses in Chapter 4 so the results could be extrapolated to the older general population of England. Weights were not used in Chapter 5 as only people with OA were included and the weights were calculated for the whole population.

2.4.2 Cox proportional hazards regression analysis

Cox proportional hazards regression analysis is used in Chapters 4 and 5. The Cox proportional hazards regression model is a regression model that investigates the relationship between a predictor and the survival time of a sample. The Cox model is a type of survival analysis that allows both continuous and categorical variables as predictors and that can assess multiple predictors at once. It investigates how certain predictors influence the rate of an event (e.g. incidence of disease or death) happening at a specific point in time; this is called the 'hazard ratio (HR)'. A HR of 1 indicates no effect; >1 indicates increased hazard per unit increase in the predictor; and <1 indicates reduced hazard per unit increase in the predictor.

In this PhD thesis, Cox proportional hazards regression was used to estimate the associations between baseline exposures (e.g. SEP and obesity) and outcomes at follow-up (e.g. arthritis incidence and knee JRS). It allows the hazard (arthritis incidence / knee JRS) to fluctuate over time; however, it assumes that the ratio of the hazard between groups (e.g. obese vs normal weight) is proportional, which means that the hazard ratio (HR) (e.g. hazard for obesity/hazard for normal weight) is constant over time. Person year follow up was calculated from baseline to either a) date of self-reported arthritis diagnosis / knee JRS, b) loss to follow-up, c) end of follow-up (Wave 9). The proportional hazard assumption was tested using the

Schoenfeld residuals test[386], where a p-value of <0.05 means that the proportional hazard assumption holds.

2.4.3 Longitudinal data analysis

Longitudinal analysis was used to address objectives 3 and 4 in Chapters 5 and 6, respectively. Whereas a diagnosis of arthritis or knee JRS can be classed as a one-time (or a maximum of two times for knee JRS) event at follow-up, some outcomes are measured at several time points, such as disability, HAQ and DAS28. It is important to note that individual's observations at different time points are not independent from each other: the observation at time point two is correlated with the observation at time point one, etc. The correlation between repeated measures on the same individual needs to be taken account in the analysis.

Fixed-effects models assume that the exposure variable has a fixed relationship with the outcome variable across all observations. It only takes into account one source of random variability, namely the variability across individuals of the sample. Random-effects models assume that the exposure variable has a fixed relationship with the outcome variable across all observations, but that these fixed effects may differ across observations. Therefore, random-effects models also take into account variability across observations. Mixed models incorporate both fixed-effects and random-effects.

Linear mixed models are an extension of the standard linear regression analysis. An assumption of the standard linear regression model is that each observation is independent; therefore, this model would lead to over-precise estimates when using longitudinal data. Linear mixed models take into account both fixed- and random-effects, as explained before, and are therefore used in this PhD thesis. Linear mixed models were used for continuous outcomes and generalised linear mixed models were used for binary outcomes.

2.4.4 Structural equation modelling

Structural equation modelling (SEM) was used in objectives 2 and 3, described in Chapters 4 and 5. SEM is a statistical method used for the analysis of complex relationships. SEM was used to test the hypothesis that BMI mediates the relationship between having a lower SEP and arthritis incidence and progression.

SEM combines two statistical methods: confirmatory factor analysis (CFA) and path analysis[387]. CFA is used for the measurement of 'latent variables'. Latent variables are variables that are unobserved (i.e. not included in the dataset) and are derived from several observed variables in the dataset. The latent variable is first specified based on theory and prior knowledge, and then tested statistically. The most common method to estimate the latent construct is maximum likelihood (ML) and it is often the default method in SEM software. The purpose of ML is to find an optimal way to fit a distribution to the data (i.e. fitting a normal distribution to maximise the likelihood of observing the variables in the dataset). This method assumes that the observed variables are continuous and follow a normal distribution. If the observed variables are ordinal or non-normally distributed (i.e. when responses are more frequent at one side of the scale), diagonally weighted least squares (WLMSV in Lavaan) should be used[388].

Path analysis aims to find a relationship between two or more exposure variables and one outcome variable, and estimates the magnitude and statistical significance of each relationship[387]. SEM includes path analysis with latent variables. This also includes mediation (explained in more detail in section 2.1.2.2), where direct and indirect effects are measured simultaneously. Figure 14 shows an example of a structural equation model, combining latent variables and path analysis. Variable A has both a *direct effect* (β2) and an *indirect effect* via variable B (β1 and β3) on variable C. The mediation effect of variable B can be calculated by taking the product of the effect from A to B (β1) and the effect from B to C (β3). This method of estimating mediation is based on the "traditional" approach first described by Baron & Kenny (1986)[389].

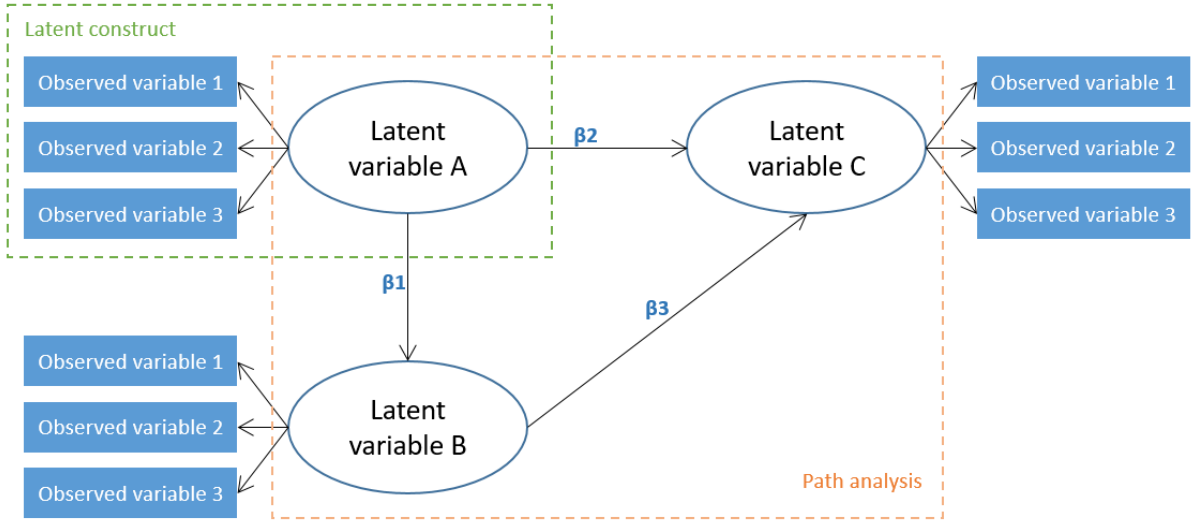


Figure 14: A structural equation model with latent variables A, B and C and the path analysis showing the relationships between latent variables A, B and C (adapted from Nachtigall et al., 2003[390]).

SEM compares the hypothesised model to the empirical data. Several fit statistics can assess whether the model fits the data; if the fit statistics are acceptable, the model will not be rejected. Instead, the constructed latent variable and the proposed relationships between them are supported by the data[390]. Many fit statistics have been developed to date and there is ongoing debate on which fit statistics are best to use[391]. Commonly used measures are:

- **Chi-square (χ2)** – regarded as the "traditional" measure of overall model fit. It assesses the 'the magnitude of discrepancy between the sample and fitted covariance matrices'[392]. A statistically non-significant result (p>0.05) would indicate a good model fit. However, because the Chi-square is based on significance testing, using a large sample will almost always result in a statistically significant p-value and the rejection of the model[393].
- **Standardised root mean square residual (SRMSR)** – is the square root of the difference between the observed correlation in the sample and the predicted correlation in the hypothesized model. Values range from 0 to 1; a value of less than 0.08 is considered a good fit.

- **Root mean square error of approximation (RMSEA)** – compares the observed correlation in the sample per degree of freedom with the hypothesised correlations in the model. Values range from 0 to 1; a value of 0.08 or lower indicates a good fit.
- **Normed-fit index (NFI)** – compares the χ2 of the model with the χ2 of the 'null' model (where all variables are uncorrelated). Values range from 0 to 1; a value of 0.90 or greater is considered a good fit.
- **Comparative fit index (CFI)** – an updated form of NFI and also considers sample size. Values range from 0 to 1; a value of 0.95 or closer to 1 is considered good fit.

This PhD will use the SRMSR, RMSEA and CFI to assess model fit of the CFA and the structural equation models as these have been found to be the least sensitive to sample size[391].

2.4.4.1 Advantages and limitations of structural equation modelling

The main advantage of using SEM is that it allows the use of latent variables. As described before, latent variables are able to capture multiple observed indicators into one unobserved construct. Some variables cannot be measured using one observed indicator. For example, for the definition of SEP (section 1.1.3.3), different indicators can be used (i.e. education, occupation, income, wealth, deprivation); however, none provide an optimal definition of SEP on their own. Therefore, a latent variable (using multiple indicators) may provide more valid conclusions. However, it is important to note that the latent variable may not be a perfect representation of the underlying construct; it depends on the quality of the observed indicators and there may be other indicators important for the construct that are not available in the dataset.

Another advantage of using a latent variable is that it reduces measurement error. The CFA takes measurement error of the different observed variables into account; the weight of the observed variables given to the latent variable depends on its measurement error (i.e. variability that is not shared among other observed indicators). This reduces measurement error bias and increases the reliability of the findings[387].

Although SEM analysis has sometimes be referred to causal modelling, there needs to be caution when interpreting the SEM results as such. The SEM approach is based on the traditional mediation approach, and has been criticised as associations between variables and represent descriptive rather than causal relationships[394]. Causal mediation analysis, explained in the next section, is an alternative approach.

2.4.5 Causal mediation analysis

Causal mediation analysis is an alternative approach to investigate mediation. This method is used as a sensitivity analysis in objective 2 (Chapter 4) and as the main mediation analysis in objective 4 (Chapter 6). Causal effects are defined as the difference between two "counterfactual" outcomes. A counterfactual outcome is an outcome based on whether an individual has been exposed or not. Causal mediation assigns all participants first as exposed and then unexposed; the causal/total effect is then defined as the

difference between the two outcomes[395, 396]. If a mediator is continuous (i.e. BMI), the mediator takes the value that would result under different exposure values using linear regression methods[397]. It has been said that this method has a causal interpretation when there is no unmeasured confounding[398]. However, in practice, this is a strong assumption[398]. A limitation of this method is that it does not support the use of latent variables; therefore, in the sensitivity analysis of Chapter 4, the different SEP indicators were modelled separately. As the SEP data in RAMS was limited to IMD and no latent variable could be constructed, causal mediation analysis was also used in Chapter 6. The R package for Causal Mediation Analysis[399] was used to perform these analyses.

Chapter 3

3. The relationship between educational attainment and obesity

Publications

Witkam, R., Gwinnutt, J. M., Humphreys, J., Gandrup, J., Cooper, R., & Verstappen, S. M. (2021). Do associations between education and obesity vary depending on the measure of obesity used? A systematic literature review and meta-analysis. SSM-population health, 15, 100884.

3.1 Abstract

Background: Consistent evidence suggests a relationship between lower educational attainment and total obesity defined using body mass index (BMI); however, a comparison of the relationships between educational attainment and total obesity (BMI ≥30kg/m^2) and central obesity (waist circumference (WC) >102cm for men and WC >88cm for women) has yet to be carried out. This systematic literature review (SLR) and meta-analyses aimed to understand whether i) the associations between education and obesity are different depending on the measures of obesity used (BMI and WC), and ii) to explore whether these relationships differ by gender and region.

Methods: Medline, Embase and Web of Science were searched to identify studies investigating the associations between education and total and central obesity among adults in the general population of countries in the Organisation for Economic Co-operation and Development (OECD). Meta-analyses and meta-regression were performed in a subset of comparable studies (n=36 studies; 724,992 participants).

Results: 86 eligible studies (78 cross-sectional and eight longitudinal) were identified. Among women, most studies reported an association between a lower education and total and central obesity. Among men, there was a weaker association between lower education and central than total obesity (OR central vs total obesity in men 0.79 (95% CI 0.60, 1.03)). The association between lower education and obesity was stronger in women compared with men (OR women vs men 1.66 (95% CI 1.32, 2.08)). The relationship between lower education and obesity was less strong in women from Northern than Southern Europe (OR Northern vs Southern Europe in women 0.37 (95% CI 0.27, 0.51)), but not among men.

Conclusions: Associations between education and obesity differ depending on whether total or central obesity is used among men, but not in women. These associations are stronger among women than men, particularly in Southern European countries.

3.2 Introduction

The most recent global estimates for adults suggest that 11.6% (95% confidence interval (CI) 10.6%–12.6%) of males and 15.7% (95% CI 14.6%–16.8%) of females were obese in 2016[1]. The prevalence is highest among high income countries[2], with a mean prevalence of 19.5% (95% CI not reported) in OECD countries in 2015[3]. This poses enormous individual and public health risks as obesity is associated with increased all-cause mortality and significant morbidity[4-7]. Total obesity is usually identified using body mass index (BMI), where a BMI ≥30kg/m^2 is classed as obese in both men and women[8]. However, central obesity has received increased attention because of the additional prognostic information it may provide for some health outcomes, such as cardiovascular disease and type 2 diabetes[9, 10]. Central obesity is usually identified measuring waist circumference (WC) (>102cm for men and >88cm for women). Although there are more precise measures of adiposity, such as body fat mass derived from skinfold thickness or dual energy X-ray absorptiometry (DXA), BMI and WC are the most commonly utilised measures as they are inexpensive and practical to use in epidemiological studies and routine clinical practice[11].

The complex factors that play a role in the development of obesity can be described by the 'social determinants of health' model[12], which describes the multiple socioeconomic circumstances that can together influence a person's behaviour and health. Previous reviews have shown that lower socioeconomic position (SEP) is associated with obesity in high-income countries[13-19], but not in low-income countries[15], suggesting that region (or more specifically economic status of a country) may modify the relationship between SEP and obesity. In studies examining SEP-obesity associations in high income countries, this was reported more consistently among women than men, suggesting that gender may modify the relationship between SEP and obesity[13-16, 18, 19]. Importantly, most of these studies focussed on BMI and few compared the associations of indicators of SEP with total and central adiposity. One review indicated that men and women with cumulative exposure to lower SEP across life had a higher mean BMI compared with those with a higher SEP across life; however, men with a lower SEP across life had lower mean WC compared with men with a higher SEP across life[13]. Therefore, associations between SEP and obesity may differ depending on whether the outcome is total or central obesity, but this has not been investigated.

Most reviews about SEP and obesity use multiple indicators of SEP including educational attainment, occupation, income or deprivation[13, 14, 16, 19]. However, McLaren (2007) reported that adiposity outcomes vary by SEP indicator and thus they cannot be used interchangeably. This review focuses on educational attainment (numbers of years at school / highest qualifications obtained), because more so than occupation or income, it is an important indicator of SEP in early life, reflecting a family's lifestyle, material and intellectual resources, and it is also a strong predictor of SEP and life chances across adulthood[20, 21]. It has been proposed that increased health literacy and material and financial resources among people with higher levels of educational attainment lead to healthier lifestyles and reduced obesity rates[22, 23]. Other advantages of studying educational attainment over other SEP indicators is that it is easy to measure,

usually has a high response rate when measured in studies and can be assessed in all people regardless of age or working circumstances[24]. Understanding the link between educational attainment and different definitions of obesity may lead to the development of targeted education-based policy interventions that help to prevent obesity and related chronic diseases[25].

We therefore aimed to conduct a systematic literature review (SLR) and meta-analysis to: 1) understand whether the associations between educational attainment and obesity are different depending on the measures used to identify obesity (BMI and WC), and 2) explore whether these relationships differ by gender and region.

3.3 Methods

The review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[26]. The following PICO model defined the search strategy (Table S1): Population (P), adults (aged ≥16 years) from the Organisation for Economic Co-operation and Development (OECD) countries (as of 2020[27]); Intervention/exposure (I), educational attainment/years of education; Comparison (C), none (limited to observational studies); and Outcome (O), total obesity (BMI ≥30kg/m^2) and central obesity (WC >102cm for men and WC >88cm for women).

3.3.1 Inclusion and exclusion criteria

Medline, Embase and Web of Science were searched for studies from 1/1/2000 until 28/02/2021 to summarise the literature most relevant to today's social environment. The inclusion criteria were 1) peer-reviewed articles including statistical analysis with an effect size for the association between educational status and obesity in the total study population and/or by gender, 2) total obesity or central obesity defined by BMI ≥30 or WC >102cm for men and WC >88cm for women[8], 3) participants aged ≥16 years, 4) cross-sectional or prospective observational cohort studies, 5) OECD countries as of March 2020[27], and 6) English language articles only. Conference abstracts were excluded.

We focussed specifically on the state of total obesity or central obesity as weight change is not a definite proxy for excess adiposity. Only studies with participants aged ≥16 years were included in this review as children and younger adolescents were unlikely to have completed their education. Lastly, Cohen et al (2013) reported that the direction of the association between education and obesity depends on a country's economic status; therefore, only countries within the OECD as of 2020 were included to minimise sources of heterogeneity between studies.

3.3.2 Screening

Titles and abstracts were independently screened by RW and JG, and disagreements were solved through consensus discussion. Subsequently, full texts were screened by one reviewer (RW) and a random sample of 10% by a second reviewer (JMG) to confirm agreement. Disagreements of inclusion and exclusion of articles were resolved with an independent reviewer (SV). Reference lists of two previously conducted systematic literature reviews[15, 18] and of the included studies were also screened.

3.3.3 Data abstraction

Descriptive data on study population and design were extracted from all manuscripts using a standard pro forma. If a study presented results from unadjusted and adjusted models, only the independent effect sizes from the adjusted models were included in this review. If different countries, ethnicities or multiple time points were assessed in one article, estimates from each country, ethnicity or time point were reported as separate 'data points' where possible, though some studies pooled multiple time points into one data point. Countries were grouped by geographic region using the United Nations 'M49 standard'[28].

3.3.4 Data synthesis

For both BMI and WC, meta-analyses were performed if studies stratified results based on gender and if they reported an odds ratio (OR) with three or four educational categories. For BMI, an additional meta-analysis was performed for studies that estimated the effect of education with the relative index of inequality (RII) separately for men and women. RII is a regression based measure that compares the risk of obesity between those with the lowest and the highest education in a sample[29]. For the meta-analyses, pooled ORs were calculated using random-effect models. The lowest with the highest educational category was compared; if studies did not report in this order, an inverse of the OR and 95% CI was calculated. All meta-analyses were checked for publication bias using the Egger's test for asymmetry. Moreover, random-effect meta-regression analyses were performed to investigate differences between measures (BMI vs WC), gender (women vs men) and regions. Only the different regions in Europe were included in the meta-regression as there was a lack of data on the other regions. All statistical analyses were performed using Stata version 14, with Metan and Metareg packages. Studies that did not meet the above criteria for the meta-analyses and meta-regression are reported in a narrative summary.

3.3.5 Quality assessment

Study quality was assessed by RW using the Quality In Prognosis Studies (QUIPS) tool[30], recommended by the Cochrane Prognosis Methods Group[31]. Six domains were evaluated for each study: study participation, study attrition, prognostic factor measurement, outcome measurement, confounding and statistical analysis and reporting. For each domain, the risk of bias was rated 'low', 'moderate' or 'high'.

3.4 Results

The initial database search identified 3,230 articles of which 2,506 were unique records (Figure 1). After full-text review and reference list screening, 86 studies were included.

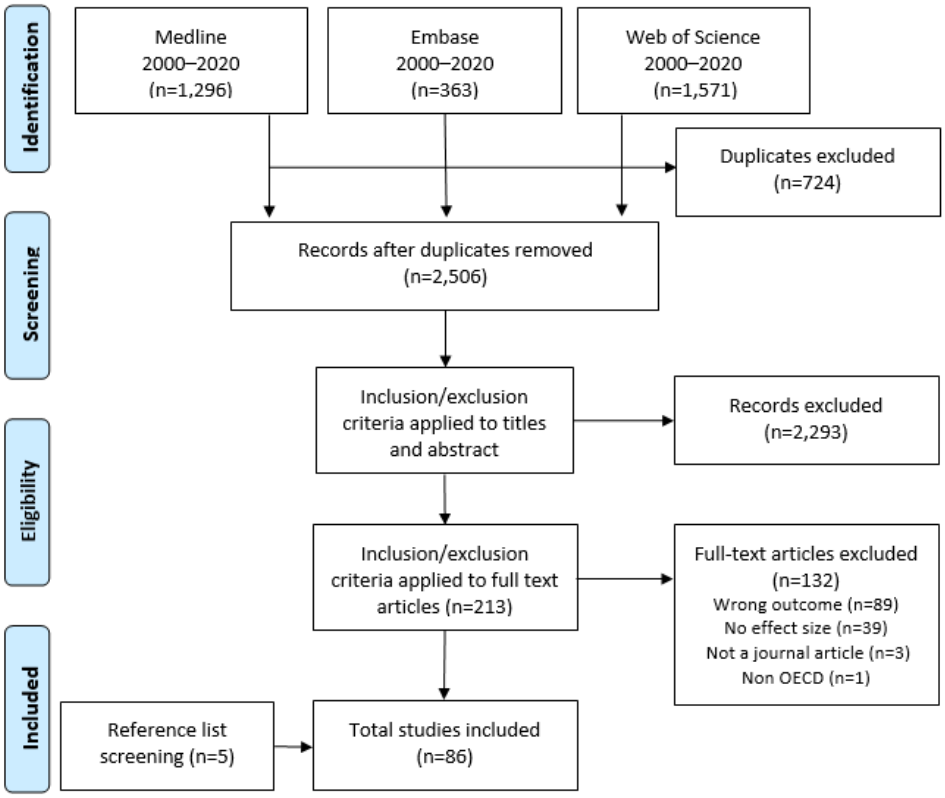


Figure 1: PRISMA flowchart of the selection of studies

3.4.1 Description of included studies

Studies from thirty-two OECD countries were included in this review, representing all geographic regions of the M49 standard, except for South America. Of the 86 studies, the majority were cross-sectional (n=78), which means that the exposure (educational attainment) and outcome (obesity) were measured at the same time point. The median sample size of all studies was 6,548 (interquartile range (IQR): 3,410, 11,497). Mean age ranged from 18 years (SD: not reported (NR)) (a sample of 18 year old Portuguese conscripts)[32] to 68.7 years (SD: 0.2 [sic])[33], but the majority of studies (n=78, 90.7%) reported a mean age of above 40 years. Overall, studies were of good quality (Table S6). The domains 'attrition/response rate', 'outcome measurement' and 'statistical analysis' received the most moderate to high bias ratings due to, respectively, no information about missing data, self-reported instead of measured height and weight data and no reporting of the obesity reference category (healthy weight or non-obese). The measurement of educational attainment and categorisation of educational level varied across studies (Table S3). Tables 1 and 3 report estimates comparing the lowest and highest educational categories.

Total and central obesity prevalence in different study samples are shown in Table S2. In studies that reported estimates separately for men and women, total obesity prevalence was similar in men and women (mean prevalence 16.9% in women vs 17.0% in men), whereas prevalence of central obesity was often higher in women than men (mean prevalence 34.3% in women vs 23.8% in men). In studies presenting both measures (BMI and WC), central obesity prevalence was generally higher than total obesity prevalence. Obesity prevalence varied across countries and within countries: generally, the highest total and central obesity prevalence estimates were found in Northern America (survey years range 1993–2016) and Spain (survey years range 1997–2013) (ranges from 7.0–44.1% for total obesity and 21.8–59.7% for central obesity), and the lowest were found in Italy (survey years 2000, 2005), France (survey years range 1996–2008) and Denmark (survey years range 1994–2003) (ranges from 4.8–12% for total obesity and 13.6–15.4% for central obesity) (Table S2).

3.4.2 Association between educational attainment and obesity defined by BMI

In total, 85 studies reported on associations between education and obesity defined using BMI (Table S3). There were eight longitudinal studies (follow-ups were five[34], 10[35], 13[36], 14[37], 23[38], 29[39], 33[40] and 36 years[41]). Six studies reported results of multiple countries[42-47]. Another six studies, all performed in the USA, reported on multiple ethnicities[38, 39, 48-51]. Therefore, the 85 studies included 101 data points for women, 91 for men and 35 data points for studies that combined men and women. 82 of the 85 studies reported results adjusted for covariates, and for three studies it was not clear[52-54]. 65 studies reported stratified results for men and women (Table 1). Five studies were eligible for the meta-analysis for studies that reported on the association of education modelled as RII, and 31 studies were included in the meta-analysis of studies that compared three or four educational categories. In both these meta-analyses, there was no evidence of publication bias using Egger's test (p=0.217 and p=0.686, respectively) (funnel plots are shown in Figures S1 and S2).

Of the data points including women, 86.1% (87/101) found an association between lower levels of education (for example, fewer years of schooling or no qualifications) and higher odds of total obesity. This was 65.9% (60/91) for men. Subgroup meta-analysis of data points that reported on the association of education modelled as RII and odds of obesity showed higher pooled ORs for women (2.95 (95% CI 2.37, 3.68), I^2=89.9% and 2.02 (95% CI 1.78, 2.31), I^2=92.7%) compared with men (2.12 (95% CI 1.80, 2.48), I^2=63.2% and 1.46 (95% CI 1.16, 1.83), I^2=98.6%). These gender differences were tested in meta-regression analyses (Table 2a) and were found to be statistically significant: adjusted for region and number of educational categories the ORs were 1.66 (95% CI 1.32, 2.08), I^2=58.9% for the RII subset of studies and 1.40 (95% CI 1.09, 1.81), I^2=94.46%) for the OR subset of studies. Statistical heterogeneity was higher in studies that looked at the odds of obesity with three and four educational categories compared with RII, and subgroup meta-analysis indicate high statistical heterogeneity particularly in Western and Southern Europe (Table 1).

The association between a lower education and total obesity was more consistent in women than men in Northern America and Eastern, Western and Southern Europe compared with Northern Europe and Oceania, where effect sizes differed less between genders. These differences were confirmed by the meta-regression analyses in a subset of RII and studies with three or four educational categories respectively, which showed that there was a stronger association between a lower education and total obesity in women in Southern compared with Northern Europe (ORs for Northern vs Southern Europe: 0.37 (95% CI 0.27, 0.51), I^2=20.31% and 0.59 (95% CI 0.40, 0.88), I^2=91.81%), but this was not the case for men (ORs for Northern vs Southern Europe 0.77 (95% CI 0.40, 1.51), I^2=67.05% and 0.88 (95% CI 0.66, 1.16), I^2=74.0%) (Table 2b). There were no statistically significant differences between other regions in Europe (Table S5), and due to a small amount of studies it was not possible to formally test differences between the other regions.

3.4.3 Association between educational attainment and central obesity defined by WC

16 studies reported on WC (Table S4), of which 12 stratified results based on gender and eight studies were included in the meta-analysis (Table 3). In 81.8% (9/11)[33, 34, 54-60] of studies of women, a relationship between lower education and central obesity was found, with a pooled OR of 1.7 (95% CI 1.3, 2.1), I^2= 82.5%. This was 50.0% (6/12)[33, 54-57, 60] for studies of men, with a pooled OR of 1.3 (95% CI 1.1, 1.6), I^2= 74.4%. Similar to the results for BMI, among women there was more likely to be an association between lower levels of education and increased odds of central obesity than among men (OR women vs men 1.63 (95% CI 1.05, 2.54)) (Table 4). At least one study of every region reported on WC, except for Western Asia, Northern America and Southern America. There were no clear differences in the effect sizes or the direction of the association between different regions; however, it was not possible to formally test this due to a small amount of studies. There was no evidence of publication bias in the meta-analysis using Egger's test (p=0.652) (funnel plot is shown in Figure S3).

3.4.4 Comparing the results for BMI and WC

15 studies reported on both BMI and WC in the same sample. Eight of these reported on both men and women and had comparable educational categories and were included in the meta-analysis (Figure 2). The pooled ORs of total obesity were larger for both men and women (respectively, 1.66 (95% CI 1.31, 2.10) and 2.52 (95% CI 2.04, 3.11)) than for central obesity (1.32 (95% CI 1.09, 1.59) for men and 2.15 (95% CI 1.60, 2.88) for women). Meta-regression indicated that men were less likely to have an association between lower education and central obesity compared with total obesity (OR central vs total obesity 0.79 (95% CI 0.60, 1.03)) (Table 4). This was less so the case among women (OR central vs total obesity 0.84 (95% CI 0.48, 1.47)).

Table 1: Association between education and total obesity defined by BMI ≥30 kg/m^2 lowest vs highest educational categories

Country (year(s) of survey)	N	Association with obesity (effect size (95% CI))	
		Women	Men
Eastern Europe (total inverse associations)		*6 out of 6 (100%)*	*4 out of 6 (66.7%)*
Czech Republic[42] (2002) ‖	789	RII 5.3 (1.5, 18.2)†	RII 3.6 (1.1, 12.2)†
Hungary[45] (2000, 2003)	8,543	RII 2.9 (95% CI NR)†	RII 1.8 (95% CI NR)†
Hungary[42] (2000, 2003) ‖	3,618	RII 2.3 (1.6, 3.3)†	RII 1.4 (1.0, 2.2)
Hungary[54] (2013) ‖	40,331	OR 2.4 (2.2, 2.7)†	OR 1.5 (1.4, 1.7)†
Poland[53] (2011)	3,854	OR 2.1 (1.7, 2.5)†	OR 1.5 (1.2, 1.9)†
Slovak Republic[42] (2002) ‖	635	RII 5.9 (1.4, 24.2)†	RII 1.6 (0.5, 4.8)
Meta-analysis pooled RII	***5,042***	***3.14 (1.67, 5.90), I^2=33.3%***	***1.59 (1.09, 2.31), I^2=0.0%***
Meta-analysis pooled OR	***40,331***	***2.44 (2.21, 2.69), I^2=-****	***1.52 (1.36, 1.70), I^2=-****
Northern Europe (total inverse associations)		*21 out of 26 (80.8%)*	*19 out of 27 (70.4%)*
Denmark[43] (1994) ‖	3,081	OR 2.8 (1.5, 5.2)†	OR 2.3 (1.3, 3.9)†
Denmark[42] (2000) ‖	5,821	RII 2.7 (1.7, 4.3)†	RII 3.1 (1.9, 5.2)†
Denmark[61] (2002)	2,013	OR 6.5 (2.3, 18.7)†	OR 2.9 (1.4, 5.9)†
Denmark[62] (2003)	783	NR	OR 1.9 (1.1, 3.3)†
England[45] (Annually 1995–2007)	144,807	RII 1.9 (95% CI NR) †	RII 1.4 (95% CI NR)†
England[63] (1996)	15,061	OR 1.8 (1.4, 2.4)†	OR 1.8 (1.3, 2.4)†
England[42] (2001) ‖	5,583	RII 2.2 (1.7, 2.9)†	RII 1.7 (1.3, 2.3)†
Estonia[46] (1994, 1996, 1998) ‖	3,759	OR 2.3 (1.6, 3.2)†	OR 0.9 (0.6, 1.5)
Estonia[42] (2002, 2004) ‖	1,740	RII 3.3 (1.7, 6.7)†	RII 1.7 (0.8, 3.4)
Finland[64](Biannually 1993–2003)	11,486	OR 1.5 (1.3, 1.8)†	OR 1.4 (1.2, 1.8)†
Finland[43] (1994) ‖	6,474	OR 2.7 (1.8, 3.9)†	OR 1.7 (1.3, 2.3)†
Finland[46] (1994, 1996, 1998) ‖	9,488	OR 1.8 (1.4, 2.3)†	OR 1.7 (1.3, 2.2)†
Finland[42] (Biannually 1994–2004) ‖	8,223	RII 1.6 (1.1, 2.4)†	RII 1.5 (1.0, 2.3)†
Finland[65] (2000, 2001) ‖	6,227	OR 1.1 (0.7, 1.6)	OR 1.2 (0.6, 2.3)
Finland[66] (2001) ‖	6,300	OR 1.7 (1.3, 2.2)†	OR 1.8 (1.3, 2.3)†
Finland[40] (2004) ‖	2,003	OR 1.4 (0.9, 2.1)	OR 1.3 (0.7, 2.0)
Latvia[42] (1998, 2000, 2002, 2004) ‖	3,537	RII 1.5 (0.9, 2.5)	RII 0.9 (0.5, 1.6)
Lithuania[46] (1994, 1996, 1998) ‖	5,635	OR 1.4 (1.1, 1.9)†	OR 1.2 (0.8, 1.7)
Lithuania[42] (Biannually 1994–2004) ‖	5,465	RII 2.7 (1.8, 3.9)†	RII 1.0 (0.6, 1.6)
Northern Ireland[44] (2011)	3,239	RII 2.1 (95%CI NR)†	RII 1.1 (95%CI NR)†
Norway[42] (2002) ‖	2,529	RII 1.8 (0.8, 4.0)	RII 3.4 (1.7, 6.9)†
Republic of Ireland[42] (1995, 2002)	2,064	RII 2.0 (0.9, 4.2)	RII 1.3 (0.7, 2.7)
Republic of Ireland[44] (2007)	8,707	RII 1.7 (95%CI NR)†	RII 1.5 (95%CI NR)†
Sweden[67] (1994) ‖	3,788	OR 2.3 (1.4, 3.8)†	OR 2.3 (1.5, 3.5)†
Sweden[68] (2000) ‖	6,394	OR 2.3 (1.3, 4.2)†	OR 2.5 (1.3, 4.8)†
Sweden[45] (2000)	4,350	RII 3.3 (95% CI NR)†	RII 2.8 (95% CI NR)†
Sweden[42] (2000, 2001) ‖	3,990	RII 3.9 (2.1, 7.0)†	RII 4.3 (2.4, 7.8)†
Meta-analysis pooled RII	***90,037***	***2.25 (1.85, 2.74), I^2=32.1%***	***1.81 (1.30, 2.52), I^2=72.4%***
Meta-analysis pooled OR	***53,149***	***1.82 (1.52, 2.17), I^2=56.5%***	***1.61 (1.35, 1.91), I^2=45.2%***
Western Europe (total inverse associations)		*18 out of 18 (100%)*	*16 out of 18 (88.9%)*
Austria[45] (1999, 2007)	42,059	RII 2.0 (95% CI NR)†	RII 2.3 (95% CI NR)†
Belgium[42] (1997, 2001) ‖	6,932	RII 6.3 (4.1, 9.7)†	RII 2.2 (1.5, 3.2)†
Belgium[69] (2004)	9,709	RR 3.3 (2.4, 4.6)†	RR 2.6 (1.9, 3.7)†
France[70] (1996) ‖	6,705	OR 1.8 (1.3, 2.6)†	OR 1.6 (1.2, 2.1)†
France[45] (Annually 1995–98, 2000, 2002, 2004, 2006)	67,780	RII 4.8 (95% CI NR)†	RII 3.2 (95% CI NR)†
France[71] (2003) ‖	14,727	RII 4.8 (3.6, 6.4)†	RII 2.5 (1.9, 3.3)†
France[42] (2004) ‖	6,048	RII 4.2 (2.5, 7.2)†	RII 3.3 (1.7, 6.2)†
Germany[72] (1992, 1998) ‖	13,049	OR 4.8 (3.3, 6.9)†	OR 2.6 (1.8, 3.8)†
Germany[42] (1998) ‖	2,786	RII 5.1 (3.0, 8.7)†	RII 1.7 (1.1, 2.6)†
Germany[73] (2003) ‖	8,318	OR 1.7 (1.3, 2.2)†	OR 1.5 (1.2, 2.0)†
Luxembourg[74] (2007) ‖	7,768	OR 2.1 (1.4, 3.0)†	OR 0.8 (0.5, 1.1)
Luxembourg[75] (2015) ‖	1,484	OR 3.0 (1.5, 6.3)†	OR 1.2 (0.6, 2.4)
Netherlands[42] (2003, 2004) ‖	5,607	RII 2.9 (1.9, 4.3)†	RII 3.6 (2.3, 5.7)†
Switzerland[76] (1993, 1997, 2002, 2007) ‖	53,588	OR 3.0 (2.3, 3.9)†	OR 1.9 (1.5, 2.5)†
Switzerland[77] (1993, 1997, 2002, 2007) ‖	63,782	OR 3.0 (2.3, 3.6)†	OR 1.9 (1.5, 2.5)†
Switzerland[55] (2003) ‖	6,186	OR 2.9 (2.4, 3.3)†	OR 2.3 (2.0, 2.7)†

Switzerland[56] (2006) ‖	6,303	RII 4.8 (3.2, 7.2)†	RII 3.0 (2.1, 4.2)†
Switzerland[78] (2015) ‖	2,057	OR 1.9 (1.7, 2.2)†	OR 0.8 (0.7, 0.8)†
Meta-analysis pooled RII	***42,403***	***4.54 (3.69, 5.57), I²=30.3%***	***2.56 (2.09, 3.14), I²=34.7%***
Meta-analysis pooled OR	***162,937***	***2.54 (2.05, 3.15), I²=82.8%***	***1.59 (1.00, 2.53), I²=98.7%***
Southern Europe (total inverse associations)		*17 out of 17 (100%)*	*12 out of 18 (66.7%)*
Greece[79] (2003) ‖	16,073	OR 1.6 (1.2, 2.0)†	OR 1.3 (1.0, 1.7)
Italy[45] (1995, 2000, 2003, 2005)	215,664	RII 6.8 (95% CI NR)†	RII 2.2 (95% CI NR)†
Italy[42] (1999, 2000) ‖	41,613	RII 6.0 (4.7, 7.7)†	RII 2.3 (1.9, 2.8)†
Portugal[32] (Annually 1986–2000)	850,081	NR	OR 2.7 (2.7, 2.7)
Portugal[80] (1996, 1999, 2005) ‖	102,540	OR 3.8 (3.3, 4.4)†	OR 1.8 (1.6, 2.1)†
Portugal[81] (1998) ‖	39,640	OR 5.3 (3.7, 7.1)†	OR 2.5 (1.9, 3.3)†
Portugal[42] (1998, 1999) ‖	12,297	RII 5.1 (3.1, 8.4)†	RII 2.7 (1.9, 3.9)†
Portugal[34] (2008)	1,621	RR 2.3 (1.2, 4.5)†	RR 1.6 (0.6, 4.5)
Portugal[57] (2009) ‖	6,908	OR 3.6 (2.7, 4.9)†	OR 2.0 (1.4, 2.7)†
Portugal[82] (2015)	4,819	PR 2.8 (2.0, 3.8)†	PR 1.9 (1.4, 2.5)
Portugal[83] (NR) ‖	1,436	OR 5.3 (3.7, 7.1)†	OR 2.5 (1.9, 3.3)
Spain[84] (1993) ‖	3,091	OR 3.5 (1.4, 4.8)†	OR 1.2 (0.7, 2.0)
Spain[85] (1994) ‖	5,388	OR 1.8 (1.8, 1.8)†	OR 2.4 (2.3, 2.4)†
Spain[86] (1995, 1997)	2,880	PR 3.5 (1.5, 8.2)†	PR 1.5 (1.0, 2.3)
Spain[45] (1995, 1997, 2001, 2003)	39,826	RII 18 (95% CI NR)†	RII 2.2 (95% CI NR)†
Spain[42] (2001) ‖	7,741	RII 5.1 (3.1, 8.4)†	RII 2.7 (1.9, 3.9)†
Spain[33] (2010) ‖	2,699	OR 3.6 (2.2, 5.6)†	OR 1.7 (1.2, 2.3)†
Spain[87] (NR)	2,833	OR 2.5 (1.5, 4.2)†	OR 1.5 (1.0, 2.3)†
Meta-analysis pooled RII	***61,651***	***6.05 (4.98, 7.34), I²=0.0%***	***2.32 (1.99, 2.70), I²=0.0%***
Meta-analysis pooled ORs	***177,775***	***3.19 (2.20, 3.20), I²=96.0%***	***1.82 (1.50, 2.21), I²=84.5%***
Eastern Asia (total inverse associations)		*5 out of 5 (100%)*	*0 out of 5 (0%)*
Japan[88] (2018)	5,425	OR 1.69 (1.29, 2.22)	OR 1.16 (0.96, 1.40)
South Korea[58] (1998) ‖	7,962	OR 2.6 (1.9, 3.7)†	OR 0.8 (0.6, 1.1)
South Korea[45] (1998, 2001, 2005)	19,113	RII 17 (95% CI NR)†	RII 0.8 (95% CI NR)
South Korea[89] (2012) ‖	17,245	OR 1.7 (1.3, 2.2)†	OR 0.7 (0.6, 0.9)
South Korea[35] (2016) ‖	9,991	OR 3.03 (1.79, 5.26)	OR 0.75 (0.54, 1.04)
Meta-analysis pooled OR	***25,207***	***2.27 (1.57, 3.29), I²=68.7%***	***0.74 (0.63, 0.87), I²=0.0%***
Western Asia (total inverse associations)		*4 out of 4 (100%)*	*0 out of 1 (0%)*
Turkey[90] (1993)	2,401	OR 2.2 (95% CI NR), p<0.001†	NR
Turkey[91] (Biannually 2008–16)	13,546	OLS estimate h vs l –0.051 (SE 0.008)‡, p<0.001†	OLS estimate h vs l 0.014 (0.010), not sig
Turkey[92] (2015)	833	OR 9.7 (5.6, 16.6)†	NR
Turkey[52] (NR) ‖	1,500	OR 1.4 (1.4, 9.1)† [sic]	NR
Meta-analysis pooled OR	***1,500***	***1.41 (0.56, 3.58), I²=0.0%****	***Not enough data***
Northern America (total inverse associations)		*8 out of 16 (50%)*	*6 out of 11 (54.5%)*
Canada[93] (1993, 1997) ‖	10,014	OR 2.6 (1.6, 4.0)†	OR 1.6 (1.1, 2.3)†
Canada[94] (1997)	5,980	OR 1.5 (1.2, 1.8)†	OR 2.2 (1.8, 2.6)†
Canada[45] (1995, 2001, 2003, 2005)	266,782	RII 2.2 (95% CI NR)†	RII 1.6 (95% CI NR)†
Canada[48] (2004)	Ab 334; Non -ab 6,259	OR Ab 0.6§ (95% CI NR), p=0.005; Non-abh 1.4§ (95% CI NR) p=0.024†	OR Ab 2.0§(95% CI NR), p=0.019†; Non-ab 1.7§(95% CI NR), p=0.001†
USA[90] (1988–94, NR how many cross-sectional surveys included)	5,219	OR 0.8 (95% CI NR), not sig	NR
USA[49] (1999)	2,657	OR l W 1.2 (0.7, 1.9) B 0.6 (0.3, 1.5) vs m	OR l W 0.9 (0.5, 1.7) B 1.7 (0.7, 3.9) vs m
USA[45] (Biannually 2000–2008)	24,243	RII 1.6 (95% CI NR)†	RII 1.0 (95% CI NR)
USA[38] (2002)	NR	OR M-A: 0.4 (0.2, 0.7); W: 1.4 (0.9, 2.2); A-A: 1.4 (0.9, 2.2)	NR
USA[95] (2003) ‖	5,078	OR 1.5 (1.0, 2.2)	OR 1.8 (1.0, 3.1)
USA[37] (2009)	21,457	RR 1.7 (1.5, 1.9)†	NR
USA[36] (2010)	8,665	OR 1.3 (SD 0.1)†	OR 1.1 (SD 0.1)†
USA[96] (2014, 2016)	10,792	PR 1.5 (1.3, 1.6)†	PR 1.1 (0.95, 1.3)
Meta-analysis pooled ORs	***15,092***	***1.28 (0.78, 2.11), I²=82.2%***	***1.64 (1.19, 2.25), I²=0.0%***
Central America (total inverse associations)		*4 out of 5 (100%)*	*0 out of 2 (0%)*
Mexico[90] (1987)	3,681	OR 1.7 (95% CI NR), P<0.001†	NR
Mexico[97] (2000)	38,901	OR U 2.0 (1.4, 2.5)†; R 1.4 (1.0, 2.0)†	OR U 1.3 (0.7, 2.0); R 0.8 (0.5, 1.3)
Mexico[98] (2012) ‖	U 9,588 R 4,943	RII U 1.6 (1.3,1.8)†; R 1.1 (0.9, 1.4)	NR
Meta-analysis pooled RII	***14,531***	***1.34 (0.97, 1.83), I²=78.9%****	***Not enough data***
Oceania (total inverse associations)		*4 out of 4 (100%)*	*3 out of 3 (100%)*

Australia[99] (1996) ‖	14,099	RII 0.3 (0.3, 0.4)†	NR
Australia[60] (2000) ‖	11,247	OR 2.1 (1.2, 3.8)†	OR 2.4 (1.6, 3.6)†
Australia[100] (2001)	26,863	RR 1.4 (1.2, 1.7)†	RR 2.1 (1.7, 2.6)†
Australia[45] (1995, 2001, 2005)	80,215	RII 1.9 (95% CI NR)†	RII 1.6 (95% CI NR)†
Meta-analysis pooled RII	***14,099***	***2.20 (1.59, 3.04), I^2=-****	***Not enough data***
Meta-analysis pooled OR	***11,247***	***2.12 (1.18, 3.80), I^2=-****	***2.40 (1.59, 3.62) I^2=-****
Total inverse associations of all studies		*87 out of 101 (86.1%)*	*60 out of 91 (65.9%)*
Meta-analysis of all studies RII	***227,763***	***2.95 (2.37, 3.68), I^2=89.9%***	***2.12 (1.80, 2.48), I^2=63.2%***
Meta-analysis of all studies OR	***497,229***	***2.02 (1.78, 2.31), I^2=92.7%***	***1.46 (1.16, 1.83), I^2=98.6%***

N, sample size; CI, confidence interval; RII, relative index of inequality; NR, not reported; OR, odds ratio; RR, risk ratio; PR, prevalence ratio; SE, standard error; SD, standard deviation; USA, United States of America; U, urban; R, rural; B, Black; W, White; M-A, Mexican-American; A-A, African American. Only the estimate of the most recent year and of the lowest vs the highest or the highest vs the lowest education categories are shown here; however, all estimates are shown in Table S3. *Subgroup meta-analysis based on one study †Indicate an inverse association (i.e. an association between lower education and obesity) based on statistical significance. ‡Estimates from linear probability models. §Regression coefficients from multivariable logistic regression models converted to ORs. ‖Included in meta-analyses and meta-regression analyses (Tables 2a and 2b)

Table 2a: Meta-regression to confirm gender differences for the association between education and total obesity defined by BMI ≥30 kg/m^2, in a subset of studies modelling RII (n=5 studies) and OR with three to four educational categories (n=30 studies)

Gender	**OR (95% CI) not adjusted**	**OR (95% CI) adjusted for region (and for OR also number of educational categories)**
Women vs men RII subset of studies	1.39 (1.03, 1.87) I^2=85.07%	1.66 (1.32, 2.08), I^2=58.92%
Women vs men OR subset of studies	1.39 (1.07, 1.79) I^2=97.59%	1.40 (1.09, 1.81), I^2=94.46%

OR, odds ratio; CI, confidence interval; RII, relative index of inequality.

Table 2b: Meta-regression to confirm regional differences for the association between education and total obesity defined by BMI ≥30 kg/m^2, in a subset of studies modelling RII (n=5 studies) and OR with three to four educational categories (n=30 studies)

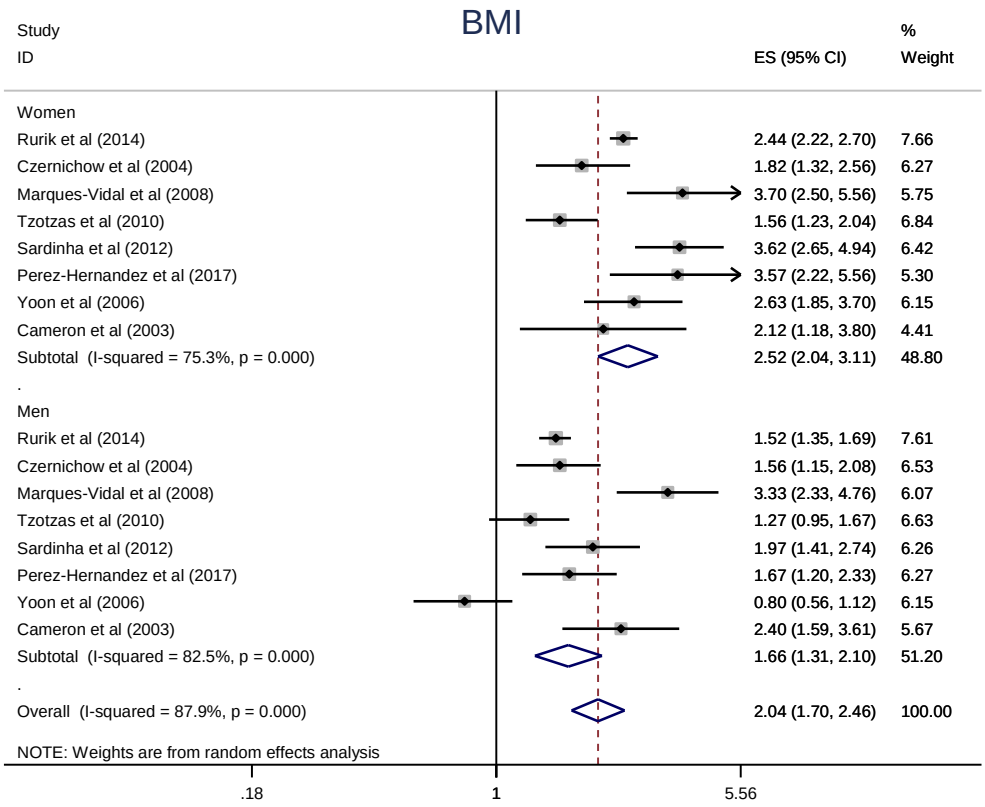
	Subset of RII studies included in meta-analysis OR (95% CI)	**Subset of OR studies with three or four educational categories included in meta-analysis OR (95% CI)**
Women		
Northern vs Western Europe	0.50 (0.36, 0.68), I^2=31.42%	0.72 (0.52, 1.00), I^2=74.75%
Northern vs Southern Europe	0.37 (0.27, 0.51), I^2=20.31%	0.59 (0.40, 0.88), I^2=91.81%
Men		
Northern vs Eastern Europe	1.00 (0.41, 2.42), I^2=67.83%	1.06 (0.64, 1.75), I^2=45.21%
Northern vs Southern Europe	0.77 (0.40, 1.51), I^2=67.05%	0.88 (0.66, 1.16), I^2=74.00%

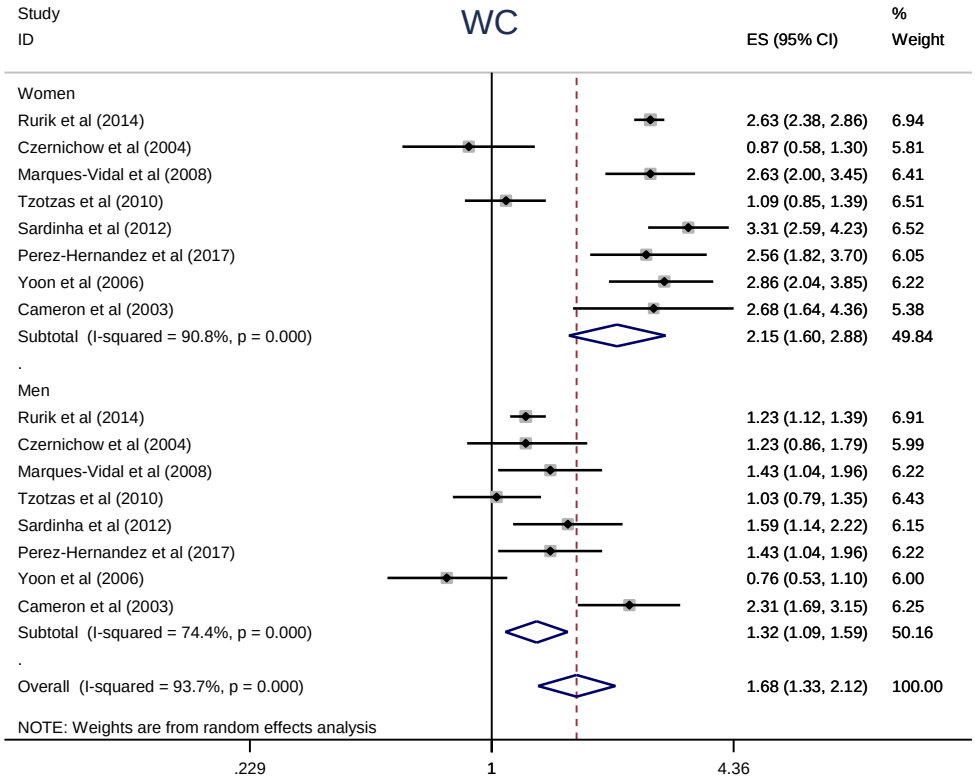
OR, odds ratio; CI, confidence interval. Only the estimates of statistically significant differences between regions are shown here; however, comparisons of all regions that have enough data points are shown in Table S5.

Table 3: Association between education and central obesity defined by WC>102cm for men and WC>88cm for women for the lowest vs the highest educational categories

Country (year of survey)	N	Association with central obesity (effect size (95% CI))	
		Women	Men
Eastern Europe (total inverse associations)		*1 out of 1 (100%)*	*1 out of 1 (0%)*
Hungary[54] (2013) ‖	40,331	OR 2.6 (2.4, 2.9)†	OR 1.2 (1.1, 1.4)†
Northern Europe (total inverse associations)		*–*	*0 out of 1 (0%)*
Denmark[62] (2003)	783	NR	OR 1.0 (0.6, 1.7)
Western Europe (total inverse associations)		*2 out of 3 (66.7%)*	*2 out of 3 (66.7%)*
France[70] (1996) ‖	6,705	OR 0.9 (0.6, 1.3)	OR 1.2 (0.9, 1.8)
Switzerland[55] (2003) ‖	6,186	OR 2.6 (2.0, 3.5)†	OR 1.4 (1.0, 2.0)†
Switzerland[56] (2006)	6,303	RII 2.6 (2.1, 3.3)†	RII 1.5 (1.2, 1.9)†
Southern Europe (total inverse associations)		*3 out of 4 (75%)*	*2 out of 4 (50%)*
Greece[79] (2003) ‖	16,073	OR 1.1 (0.9, 1.4)	OR 1.0 (0.8, 1.4)
Portugal[34] (2008)	1,621	RR 2.0 (1.4, 3.3)†	RR 0.8 (0.6, 5.0)
Portugal[57] (2009) ‖	6,908	OR 3.3 (2.6, 4.2)†	OR 1.6 (1.1, 2.2)†
Spain[33] (2010) ‖	2,699	OR 2.6 (1.8, 3.7)†	OR 1.4 (1.0, 2.0) vs l†
Eastern Asia (total inverse associations)		*2 out of 2 (100%)*	*0 out of 2 (0%)*
South Korea[58] (1998) ‖	7,962	OR 2.9 (2.0, 3.9)†	OR 0.8 (0.5, 1.1)
South Korea[59] (2010)	6,178	PR 2.5 (1.7, 3.3)†	PR 0.8 (0.6, 1.0)
Oceania (total inverse associations)		*1 out of 1 (100%)*	*1 out of 1 (100%)*
Australia[60] (2000) ‖	11,247	OR 2.7 (1.6, 4.4)†	OR 2.3 (1.7, 3.2)†
Total inverse associations of all studies		*9 out of 11 (81.8%)*	*6 out of 12 (50.0%)*
Meta-analysis	**98,111**	***1.7 (1.3, 2.1), I^2= 82.5%***	***1.3 (1.1, 1.6), I^2= 74.4%***

N, sample size; CI, confidence interval; OR, odds ratio; h, highest education; l, lowest education; NR, not reported; RII, relative index of inequality; RR, risk ratio; PR, prevalence ratio. Only the estimate of the most recent year and of the lowest vs the highest or the highest vs the lowest education categories are shown here; however, all estimates are shown in Table S4. †Results that show an inverse association (i.e. an association between lower education and obesity) based on statistical significance. ‖Included in meta-analyses and meta-regression analyses (Figure 2 and Table 4)





*Studies are ordered in the same way as Tables 1 and 3, based on region and date of survey.

Figure 2: Meta-analyses of studies reporting an OR for both BMI and WC for the association between education and obesity, stratified by measure and gender.

Table 4: Meta-regression of a subset of studies reporting an OR for both BMI and WC for the association between education and obesity stratified by gender and obesity measure

Meta-regression WC vs BMI	**Women (pooled OR (95% CI))**	**Men (pooled OR (95% CI))**
Not adjusted	0.84 (0.54, 1.33), I^2=86.61%	0.79 (0.53, 1.18), I^2=79.23%
Adjusted for region and number of educational categories of the studies	0.84 (0.48, 1.47), I^2=90.34%	0.79 (0.60, 1.03), I^2=58.22%
Meta-regression women vs men	**BMI (OR (95% CI))**	**WC (OR (95% CI))**
Not adjusted	1.52 (1.02, 2.29), I^2=79.55%	1.63 (1.05, 2.54) , I^2=86.47%
Adjusted for region and number of educational categories of the studies	1.53 (0.96, 2.44), I^2=82.43%	1.64 (0.97, 2.76) , I^2=88.29%

OR, odds ratio; CI, confidence interval. Based on eight studies that reported OR and that used three or four educational categories. Only the effect sizes of the lowest vs the highest education categories were included in the meta-analysis and meta-regression.

3.5 Discussion

This SLR investigated how the association between education and obesity varies depending on the measure used to identify obesity, for men and women and between different regions of the OECD. The results show that, in OECD countries, the association between lower education levels and total and central obesity is stronger among women than men. Among men, more studies reported an association between lower education and total obesity compared with central obesity. Moreover, the association between lower education and total obesity was stronger among Southern compared with Northern European women.

The results of this SLR are similar to those found in a previous SLR, published in 2017, looking at the associations between multiple measures of SEP across life (e.g. parents or own occupation, income, education or material possessions) and obesity. Men and women with a lower life course SEP had a higher mean BMI; however, mean WC was lower among men with a lower compared to a higher life course SEP, whereas the opposite was seen for women[13]. This may suggest that educational inequalities manifest differently in men and women due to occupational differences. Research has shown that lower SEP was linked to increased occupational physical activity among men (i.e. manual occupations), but not among females (i.e. administrative or caring occupations)[101 102] Increased occupational physical activity in men with lower education levels may lead to increased lean muscle mass[103], resulting in higher BMI but normal WC. By contrast, this happens less often in women[63].

In general, the relationship between a lower SEP and obesity defined by BMI in high income countries have been confirmed by other SLRs among women, whereas more inconsistent results were found among men[13-16, 18, 19]; two of these focussed specifically on education[15, 18]. Mechanisms through which education and SEP may affect obesity are outlined in the 'social determinants of health' model[12], where education influences living and working conditions and social and community networks which, in turn, influence individual lifestyle factors and health. This has been supported by studies that show that in high-income countries higher educated individuals eat healthier diets[104] and perform more leisure time physical activity[101], presumably due to increased health literacy[22] and having better financial and emotional support[105]. The 'health belief model' might help us to understand the stronger association between education and obesity observed among women compared with men, where perceived severity, susceptibility, benefits and barriers influence weight control practices[106]. Compared with men, women experience increased weight-related ideals, where a lower weight is seen as healthier and more attractive (perceived benefit of weight control practices). These weight-related ideals might be more difficult to sustain for women with a lower SEP[107] (perceived barrier for weight control practices). Because of this, education may influence weight to a greater extent in women; however, this needs further investigation.

Our review also indicated geographical variation regarding the influence of gender on the relationship between education and obesity defined by BMI; in women, the association between lower education and obesity was stronger in Southern compared with Northern Europe. This difference was not seen in men.

This might be explained by the fact that Northern European countries (compared to other OECD countries) have had a longstanding progressive agenda for gender equality, with concrete policies to ensure women and men from all educational backgrounds are equally represented in the workforce[108, 109]. This has proven effective as figures show that compared to other OECD countries, Northern European countries have smaller gender gaps in labour market participation and working hours, and mothers are more likely to work[103]. In contrast, women with lower levels of education in Southern Europe often have a more 'traditional' role and participate less in the workforce, which might be reinforced by limited opportunities to work part-time and less financial support for child care[110]. Participating in the workforce increases social support, which may lead to increased empowerment to access health care services, and increase income levels to support a healthy lifestyle[105].

There are some disadvantages to using education as an indicator for SEP. Firstly, the meaning of education differs for different birth cohorts; trends of improving educational opportunities have resulted in increased educational attainment for women and ethnic minorities in recent decades, which means that people with lower levels of education are overrepresented in older birth cohorts[24]. These effects have not been accounted for in the included studies. Although using a publication cut-off of the year 2000 might have reduced these effects, there were still studies that included data from 1987 (Table 1) and, thus, there will be some generational differences unaccounted for. One of the inclusion criteria was participants aged ≥16 years; as some included participants might not have finished their formal education yet, in some studies the highest levels of educational attainment may be underrepresented. Nonetheless, the results of four studies that included participants aged ≥16 years[45, 74, 90, 111] do not differ substantially from the rest of the studies that included participants aged ≥18 years. Furthermore, qualifications and quality of education are not standardised across different countries and therefore makes comparisons across countries challenging[112]. However, the advantages of using education as an indicator in observational studies is that it is easy to measure and usually has a high response rate when assessed in clinical and epidemiological studies[24]. Although BMI and WC are the most commonly used measures of obesity in research and clinical settings, it is recognised that these measures lack some precision and do not directly measure fat mass. The relationship between life course SEP and body composition using more sophisticated, but more expensive, measures, such as DXA, computer tomography and magnetic resonance imaging, is assessed in another SLR[113].

Most studies presented low or moderate risk of bias in most of the domains of the QUIPS tool (Table S6). When studies relied on self-reported height and weight to calculate BMI, they scored a 'moderate risk of bias' in the outcome measurement domain, as self-reported height and weight data are prone to social desirability bias and consequently measurement error bias (i.e. underreporting of weight and over reporting of height)[114]. Moreover, many studies presented no information about the reference category of obesity (healthy weight or non-obese), which impacted the score on the 'statistical analysis' domain. Despite these variabilities, the results were mostly consistent between studies and, therefore, unlikely to

influence our conclusions. Most studies were cross-sectional and reverse causality cannot be ruled out (i.e. childhood obesity leads to lower education), a possibility that is supported by previous studies that showed that a proportion of the association is accounted by the reverse causation[18, 115]. Because some studies have pooled data from multiple years, the survey years range from 1987–2016; in this time period, obesity has increased substantially[2]. Variability in obesity prevalence (Table S2) across and within countries may partly be due to variations in survey years. Sample selection bias may also play a role; for example, the national prevalence of obesity in France was estimated to be 11.9% (95% CI 11.5%, 12.3%) in 2003[116] whereas Roskam et al. (2010) reported an obesity prevalence of 6.0% in 2004, indicating that the study sample is not generalizable to the whole population of France at that time. Lastly, the Egger's test has been criticised because type 1 errors are likely to occur, leading to an overestimation of the presence of publication bias[117-119]. However, as none of the results from our Egger's tests were statistically significant, i.e. they did not indicate publication bias, this was not a concern in our review. Nonetheless, it is important to note that we only included formally published data in English language journals, and may therefore have missed some studies that were published in other languages.

A strength of this systematic literature review is that established protocols were followed and a large number of studies were synthesised. Furthermore, meta-analyses and meta-regression were performed in a subset of studies to formally test differences between measures, gender and region. To take into account the heterogeneity in definitions of education, it was decided to perform subgroup meta-analysis in studies with a similar education definition, where studies were combined based on the number of educational categories. This means that studies that did not define education based on three or four categories or did not estimate the relationship between education and obesity using RII were omitted for the meta-analyses; as a result, it is important to interpret the findings of the meta-analysis with some caution. Statistical heterogeneity was slightly reduced when adjusting for region or educational categories; the high degree of the remaining statistical heterogeneity might be caused by other factors, such as the inconsistent reporting of the obesity reference category. Moreover, only studies from OECD countries were included so that we could compare results of countries of a similar economic status. However, this does limit generalisability of our findings to countries outside the OECD. Although OECD countries are all considered high-income countries, there are still large differences socioeconomically, with the highest gross domestic product (GDP) of US$ 118,582 in Luxembourg and the lowest GDP of US$ 14,994 in Colombia[120] in 2020 and in income inequality, with a Gini coefficient (an indicator of income inequality, where zero would represent an equal income for everyone) of 0.37 in the UK in 2019 and 0.26 in Belgium in 2018[121]. Moreover, there are institutional and cultural differences between OECD countries, such as costs of further education, equal opportunities for men and women and compulsory military service (e.g. in South Korea and Israel) that may reflect educational attainment differences in different countries[112]. This means that direct comparison between countries may be problematic. Lastly, the majority of studies adjusted their

analyses for relevant covariates such as age, gender (if applicable), other socioeconomic indicators and lifestyle factors.

This SLR has shown that both BMI and WC are important when researching obesity inequalities, particularly when examining gender differences. This might also be the case for other more accurate indicators (i.e. body fat percentage); therefore, there is a need to ensure a wide range of indicators of obesity are included in population surveys and public health interventions.

When devising strategies to prevent and treat obesity, it is important to take into account educational differences. A previous SLR indicated that targeted weight loss interventions for low SEP individuals delivered at schools, communities and primary care settings were effective in reducing weight in the short term[123]. Further research should also investigate whether interventions such as raising the compulsory education age reduces obesity levels over time.

In conclusion, this review strengthened the knowledge that lower educational attainment is associated with obesity, particularly for women. In addition, this study found that the association differed depending on the measure of obesity used: among men, there was more consistent evidence of the association between lower educational attainment and total obesity than central obesity, indicating the importance of using multiple measures of adiposity in future research and public health interventions.

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3.7 Supplementary material

Table S1: Search strategy

Database	Search terms	Results
Medline	(Educational status [Mesh] or "educational attainment.mp") and (Obesity[Mesh] or Abdominal Obesity [Mesh] or Overweight [Mesh]) *Limits: English, Humans, yr 2000–current, Adults*	1,296
Embase	(Educational status [Mesh] or "educational attainment.mp") and (Obesity[Mesh] or Abdominal Obesity [Mesh]) *Limits: English, Humans, yr 2000–current, Adults, Not Medline*	363
Web of Science	(TS="Educational Status" OR TS="Educational Attainment" OR TS="Educational level") AND (TS=overweight TS=obes*) *Limits: English, yr 2000–current, Social Science Citation Index*	1,571

Mesh, medical subject heading; TS, topic.

Table S2: Description of studies (studies are ordered based on region and survey date)

Reference	Country	Study design	Inclusion criteria of population	Sample size (n)	Year of data collection / final follow-up year	Baseline gender (% women)	Baseline age in years (mean (SD) unless otherwise reported)	Proportion of people normal weight, overweight, obese (%)
Eastern Europe								
Roskam et al (2010)	Czech Republic	Cross-sectional	Health Interview Survey of the Czech Republic; adults aged 25–44 years	789	2002	NR	NR	Obese: 11.1
Devaux & Sassi (2013)	Hungary	Cross-sectional	Nationally representative; adults 16–65 years	8,543	2000, 2003	NR	NR	Obese: F: 16.9; M: 18.10
Roskam et al (2010)	Hungary	Cross-sectional	National Health Interview Survey Hungary, Budapest; adults aged 25–44 years	3,618	2000, 2003	NR	NR	Obese: 17.7
Nedo & Paulik (2012)	Hungary	Cross-sectional	A small area of County Békés, including six settlements; adults aged ≥18 years	1,099	2007	52.30	48.23 (18.49)	Healthy weight: 39.0 Overweight: 36.0 Obese: 22.0
Rurik et al (2014)	Hungary	Cross-sectional	All geographical regions in Hungary; non-institutionalised adults aged >18 years	40,331	2013	58.98	NR	Overweight: F: 31.3; M: 40.4 Obese: F: 31.5; M: 32.0 Abdominal obesity: F: 60.9; M: 37.1
Zatonska et al (2011)	Poland	Cross-sectional	Population of the Świętokrzyskie province, Poland; adults aged 45–64 years	3,854	2011	66.60	Range: 45–64 Mean (SD):NR	45–54 years Normal: F: 31; M: 16 Overweight: F: 42; M:52 Obese: F: 26; M: 32 55–64 years: Normal: F: 19; M: 11 Overweight: F: 42; M: 52 Obese: F: 40; M: 37
Roskam et al (2010)	Slovak Republic	Cross-sectional	Health Monitor Survey Public Health Institute of Slovak Republic, Bratislava; adults aged 25–44 years	635	2002	NR	NR	Obese: 10.3

Reference	Country	Study design	Inclusion criteria of population	Sample size (n)	Year of data collection / final follow-up year	Baseline gender (% women)	Baseline age in years (mean (SD) unless otherwise reported)	Proportion of people normal weight, overweight, obese (%)
Northern Europe								
Sarlio-Lahteenkorva et al (2006)	Denmark	Cross-sectional	Danish Health and Morbidity Survey; adults aged 25–64 years	3,081	1994	52.06	NR	Underweight: F: 4.5; M: 0.5 Normal weight: F: 68; M: 50 Overweight: F: 21; M: 40 Obesity: F: 7; M: 10
Roskam et al (2010)	Denmark	Cross-sectional	Danish Health and Morbidity Survey; adults aged 25–44 years	5,821	2000	NR	NR	Obese: 9.7
Groth et al (2009)	Denmark	Cross-sectional	Danish National Dietary Survey; random sample of non-institutionalised Danish citizens from the civil registration system; adults aged 20–75 years	2,013	2002	52.6	Men: 45 (14) Women: 44 (14)	Overweight: F: 23; M: 40 Obese: F: 10; M: 11
Nielsen et al (2006)	Denmark	Cross-sectional	Men in the county of Funen; representative 9% of the total Danish population; aged 20–29 years	783	2003	0	20–21: 18.0% 22–23: 19.4% 24–25: 20.1% 26–27: 21.3% 28–29: 21.2% Mean (SD):NR	Underweight: 0.7 Normal weight: 66.5 Overweight: 28.0 Obese: 4.8
Devaux & Sassi (2013)	England	Cross-sectional	Nationally representative; adults 16–65 years	144,807	Annually 1995–2007	NR	NR	Obese: F: 22.5; M: 21.6
Wardle, Waller & Jarvis (2002)	England	Cross-sectional	Health Survey for England; nationally representative; adults >16 years	15,061	1996	53.54	16–24 y: F: 12.6%; M: 13.0% 25–34 y: F: 18.6%; M: 18.4% 35–44 y: F: 18.5%; M: 19.3% 45–54 y: F: 17.2%; M: 17.8% 55–64 y: F: 12.5%; M: 13.4% 65–74 y: F: 12.2%; M: 11.9% ≥75 y: F: 8.4%; M: 6.2% Mean (SD):NR	Obese: F: 18.7; M: 16.5
Roskam et al (2010)	England	Cross-sectional	Health Survey for England; adults aged 25–44 years	5,583	2001	NR	NR	Obese: 21.6
Klumbiene et al (2004)	Estonia	Cross-sectional	Finbalt surveys; nationally representative; adults aged 20–64 years	3,759	1994, 1996, 1998	57.00	20–34 y: 32% 35–49 y: 37% 50–64 y: 31% Mean (SD):NR	Obese: F: 15.3; M: 9.9

Reference	Country	Study design	Inclusion criteria of population	Sample size (n)	Year of data collection / final follow-up year	Baseline gender (% women)	Baseline age in years (mean (SD) unless otherwise reported)	Proportion of people normal weight, overweight, obese (%)
Roskam et al (2010)	Estonia	Cross-sectional	Health Behavior among Estonian Adult Population National Institute for Health Development, Tallinn; adults aged 25–44 years	1,740	2002, 2004	NR	NR	Obese: 13.3
Sulander & Uutela (2007)	Finland	Cross-sectional	Random sample of national population; adults aged 65–84 years	11,486	Biannually 1993–2003	50.03	NR	Obese: F: 12.8; M: 19.9
Sarlio-Lahteenkorva et al (2006)	Finland	Cross-sectional	Finnish Survey on Living Conditions; adults aged 25–64 years	6,474	1994	49.32	NR	Underweight: F: 1.9; M: 0.3 Normal weight: F:57; M: 43 Overweight: F: 29; M: 45 Obese: F: 12; M: 12
Klumbiene et al (2004)	Finland	Cross-sectional	Finbalt surveys; nationally representative; adults aged 20–65 years	9,488	1994, 1996, 1998	52.00	20–34 y: 32% 35–49 y: 38% 50–64 y: 31% Mean (SD):NR	Obese: F: 10.4; M: 10.9
Roskam et al (2010)	Finland	Cross-sectional	Finbalt Health Monitor and National Public Health Institute, Helsinki; adults aged 25–44 years	8,223	Biannually 1994–2004	NR	NR	Obese: 8.8
Laaksonen et al (2004)	Finland	Cross-sectional	The Helsinki Health Study; middle-aged women and men employed by the City of Helsinki; age 40, 45, 50, 55 or 60 years	6,227	2000, 2001	79.89	NR	Obese: F: 14; M: 15
Seppanen-Nuijten et al (2009)	Finland	Cross-sectional	National representative; adults aged 30–64 years	6,300	2001	54.50	NR	Obese: F: 18.0; M: 19.7
Salonen et al (2009)	Finland	Prospective	Helsinki Birth Cohort Study; participants born in Helsinki during 1934–1944, who attended child welfare clinics and who were still resident in Finland in 1971	2,003	2004	53.67	61.5	Underweight/normal: F: 32.3; M: 26.1 Overweight: F: 40.4; M: 51.5 Obese: F: 27.1; M: 22.3

Reference	Country	Study design	Inclusion criteria of population	Sample size (n)	Year of data collection / final follow-up year	Baseline gender (% women)	Baseline age in years (mean (SD) unless otherwise reported)	Proportion of people normal weight, overweight, obese (%)
Roskam et al (2010)	Latvia	Cross-sectional	Finbalt Health Monitor; adults aged 25–44 years	3,537	1998, 2000, 2002, 2004	NR	NR	Obese: 8.6
Klumbiene et al (2004)	Lithuania	Cross-sectional	Finbalt surveys; nationally representative; adults aged 20–66 years	5,635	1994, 1996, 1998	56.00	20–34 y: 35% 35–49 y: 34% 50–64 y: 31% Mean (SD):NR	Obese: F: 18.3; M: 10.3
Roskam et al (2010)	Lithuania	Cross-sectional	Finbalt Health Monitor (see under Finland); adults aged 25–44 years	5,465	Biannually 1994–2004	NR	NR	Obese: 8.6
Hughes et al (2017)	Northern Ireland	Cross-sectional	Nationally representative; adults aged 20–69 years	3,375	1997	57.50	NR	Non-obese: 30.6 Obese: 7.8
	Northern Ireland	Cross-sectional	Nationally representative; adults aged 20–69 years	3,374	2006	58.60	NR	Non-obese: 57.1 Obese: 20.4
	Northern Ireland	Cross-sectional	Nationally representative; adults aged 20–69 years	3,239	2011	59.30	NR	Non-obese: 47.5 Obese: 16.0
Roskam et al (2010)	Norway	Cross-sectional	Norwegian Survey of Living Conditions Statistics Norway; adults aged 25–44 years	2,529	2002	NR	NR	Obese: 10.1
Roskam et al (2010)	Republic of Ireland	Cross-sectional	Living in Ireland Panel Survey Economic and Social Research Institute; adults aged 25–44 years	2,064	1995, 2002	NR	NR	Obese: 10.6
Hughes et al (2017)	Republic of Ireland	Cross-sectional	Nationally representative; adults aged 20–69 years	5,104	1998	53.00	NR	Non-obese: 83.9 Obese: 10.2
	Republic of Ireland	Cross-sectional	Nationally representative; adults aged 20–69 years	4,627	2002	59.10	NR	Non-obese: 79.8 Obese: 13.3
	Republic of Ireland	Cross-sectional	Nationally representative; adults aged 20–69 years	8,707	2007	58.10	NR	Non-obese: 70.4 Obese: 13.0
Lindstrom et al (2003)	Sweden	Cross-sectional	Random selection of the population in Malmö; adults aged 20–80 years	3,428	1986	54.93	NR	Underweight/normal: F: 74.3; M: 61.5 Overweight: F: 19.6; M: 33.9 Obese: F: 6.1 M: 4.6

Reference	Country	Study design	Inclusion criteria of population	Sample size (n)	Year of data collection / final follow-up year	Baseline gender (% women)	Baseline age in years (mean (SD) unless otherwise reported)	Proportion of people normal weight, overweight, obese (%)
Lindstrom et al (2003)	Sweden	Cross-sectional	Random selection of the population in Malmö; adults aged 20–80 years	3,788	1994	50.58	NR	Underweight/normal: F: 61.1; M: 43.3 Overweight: F: 29.1; M: 45.2 Obesity: F: 9.8; M: 11.4
Molarius (2003)	Sweden	Cross-sectional	Random sample of the adult population aged 25–79 years in Varmland County, Western Sweden	6,394	2000	52.63	25–44:35.4% 45–64:37.7% 65–74:26.9% Mean (SD):NR	Obese 25–44 y: F: 10.6; M: 10.9 45–64 y: F: 14.2; M: 13.2 65–74 y: F: 17.5; M: 12.7
Devaux & Sassi (2013)	Sweden	Cross-sectional	Nationally representative; adults 16–65 years	4,350	2000	NR	NR	Obese: F: 7.4; M: 7.8
Roskam et al (2010)	Sweden	Cross-sectional	Swedish Survey of Living Conditions Statistics Sweden; adults aged 25–44 years	3,990	2000, 2001	NR	NR	Obese: 11.6
Western Europe								
Devaux & Sassi (2013)	Austria	Cross-sectional	Nationally representative; adults aged 16–65 years	42,059	1999, 2007	NR	NR	Obese: F: 10.7; M: 10.9
Roskam et al (2010)	Belgium	Cross-sectional	Health Interview Survey Institute of Public Health; adults aged 25–44 years	6,932	1997, 2001	NR	NR	Obese: 10.1
Charafeddine et al (2009)	Belgium	Cross-sectional	Non-institutionalized Belgian population; adults aged ≥18 years	7,953	1997	51.23	15–24 y: F: 10.31%; M: 9.90% 25–44 y: F: 38.88%; M: 40.94% 45–64 y: F: 27.86%; M: 30.39% ≥65 y: F: 22.95%; M: 18.77% Mean (SD):NR	Obese: F: 11.02; M: 11.01
	Belgium	Cross-sectional	Non-institutionalized Belgian population; adults aged ≥18 years	8,887	2001	51.23	15–24 y: F: 8.61%; M: 9.04% 25–44 y: F: 37.38%; M: 39.04% 45–64 y: F: 31.21%; M: 32.42% ≥65 y: F: 22.80%; M: 19.50% Mean (SD):NR	Obese: F: 12.67; M: 12.69
	Belgium	Cross-sectional	Non-institutionalized Belgian population; adults aged ≥18 years	9,709	2004	53.10	15–24 y: F: 7.78%; M: 8.98% 25–44 y: F: 30.49%; M: 33.44% 45–64 y: F: 28.48%; M: 30.28% ≥65 y: F: 33.25%; M: 27.29% Mean (SD):NR	Obese: F: 13.23; M: 12.27

Reference	Country	Study design	Inclusion criteria of population	Sample size (n)	Year of data collection / final follow-up year	Baseline gender (% women)	Baseline age in years (mean (SD) unless otherwise reported)	Proportion of people normal weight, overweight, obese (%)
Czernichow et al (2004)	France	Cross-sectional	Adults aged ≥45 years from all over France	6,705	1996	48.05	45–50 y: F: 45.2%; M: 35.8% 50–55 y: F: 28.6%; M: 31.3% ≥55 y: F: 26.2%; M: 33.0% Mean (SD):NR	Obese: F: 8.3; M: 8.7 Abdominal obesity: F: 15.4; M: 13.6
Singh-Manoux et al (2009)	France	Cross-sectional	Nationally representative; adults aged 25–54 years	7,651	1970	51.20	NR	Obese: F: 6.5; M: 6.3
	France	Cross-sectional	Nationally representative; adults aged 25–54 years	7,666	1980	50.60	NR	Obese: F: 5.3; M: 5.8
	France	Cross-sectional	Nationally representative; adults aged 25–54 years	7,811	1991	51.60	NR	Obese: F: 6.0; M: 5.0
	France	Cross-sectional	Nationally representative; adults aged 25–54 years	14,727	2003	52.50	NR	Obese: F: 10.2; M: 10.0
Devaux & Sassi (2013)	France	Cross-sectional	Nationally representative; 16–65 years	67,780	Annually 1995–98, 2000, 2002, 2004, 2006	NR	NR	Obese: F: 9.9; M: 9.9
Roskam et al (2010)	France	Cross-sectional	French Health, Health Care and Insurance Survey; adults aged 25–44 years	6,048	2004	NR	NR	Obese: 6.0
Drewnowski et al (2014)	France	Cross-sectional	Adults aged 30–79 years in central Paris and suburbs	7,131	2008	35.00	18–44 y: 35% 45–64 y: 53% ≥65 y: 12% Mean (SD):NR	Obese: 12
Icks et al (2007)	Germany	Cross-sectional	National health surveys; adults aged 25–69 years	13,049	1992, 1998	51.42	1990-92: F: 45 (13); M: 45 (12) 1998: F: 46 (12); M: 46 (12)	Obese: 1992: F: 20.9; M: 18.1 1998: F: 21.6; M: 19.9
Nocon et al (2007)	Germany	Cross-sectional	Nationally representative; adults aged 18–79 years	7,124	1998	52.00%	F: 46 (16); M: 45 (15)	Obese: 21
Roskam et al (2010)	Germany	Cross-sectional	German National Health Examination and Interview Survey; adults aged 25–44 years	2,786	1998	NR	NR	Obese: 14.5
Kuntz & Lampert (2010)	Germany	Cross-sectional	Representative population of Germany; adults aged ≥18 years	8,318	2003	52.58	NR	Obese: F: 20; M: 17
Maier et al (2014)	Germany	Cross-sectional	Private households in Germany; adults aged ≥18 years	33,690	2009, 2010	57.25	30–49 y: 47.3% 50–64 y: 29.9% ≥65 y: 22.8%	Underweight/normal weight: 47.9 Overweight: 37.0 Obese: 15.2

Reference	Country	Study design	Inclusion criteria of population	Sample size (n)	Year of data collection / final follow-up year	Baseline gender (% women)	Baseline age in years (mean (SD) unless otherwise reported)	Proportion of people normal weight, overweight, obese (%)
Tchicaya & Lorentz (2012)	Luxembourg	Cross-sectional	Private households in Luxembourg; adults aged >16 years	5,117	1995	51.70	16-24 y: F: 6.80%; M: 7.20% 25-34 y: F: 21.99%; M: 23.67% 35-44 y: F: 19.90%; M: 22.65% 45-54 y: F: 15.26%; M: 17.44% 55-64 y: F: 13.68%; M: 13.92% ≥65 y: F: 22.36%; M: 15.13% Mean (SD):NR	Overweight: F: 28.9; M: 46.3 Obese: F: 13.6; M: 15.1
	Luxembourg	Cross-sectional	Private households in Luxembourg; adults aged >16 years	7,768	2007	50.80	16-24 y: F: 11.88%; M: 13.58% 25-34 y: F: 17.17%; M: 17.04% 35-44 y: F: 21.76%; M: 21.64% 45-54 y: F: 18.16%; M: 19.58% 55-64 y: F: 11.93%; M: 13.01% ≥65 y: F: 19.10%; M: 15.15% Mean (SD):NR	Overweight: F: 29.3; M: 43.9 Obese: F: 17.7; M: 17.9
Samouda et al (2018)	Luxembourg	Cross-sectional	Non-institutionalised resident population of Luxembourg; adults aged 25–64 years	1,484	2015	51.48	Women: 26.1(5.4) Men: 27.4 (4.4)	Overweight: F: 28.28; M: 46.77 Obese: F: 19.30; M: 21.05
Roskam et al (2010)	Netherlands	Cross-sectional	General social survey Statistics Netherlands; adults aged 25–44 years	5,607	2003, 2004	NR	NR	Obese: 10.1
Faeh et al (2011)	Switzerland	Cross-sectional	Swiss Health Surveys; adults aged ≥25 years	53,588	1992, 1997, 2002, 2007	55.00	Range: 25–74 y Mean (SD):NR	Normal weight: F: 65.23; M: 51.55 Overweight: F: 21.45; M: 39.23 Obese: F: 7.43; M: 8.53
Marques-Vidal et al (2010)	Switzerland	Cross-sectional	Swiss Health Surveys; adults aged ≥18 years	63,782	1993, 1997, 2002, 2007	55.00	1993: F: 46.1 (17.5); M: 44.3 (16.7) 1997: F: 47.8 (18.1); M: 45.2 (17.0) 2002: F: 50.4 (17.3); M: 48.6 (16.9) 2007: F: 51.3 (17.9); M: 49.6 (17.2) Mean (SD):NR	Obese 1992/3: F: 4.9; M: 6.3 1997: F: 7.2; M: 6.8 2002: F: 8.0; M: 8.9 2007: F: 8.5; M: 9.4
Marques-Vidal et al (2008)	Switzerland	Cross-sectional	Random sample of Lausanne citizens; aged 35–75 years; Caucasians	6,186	2003	52.50	53.1 (10.8)	Overweight: F: 28.3; M: 45.5 Obese: F: 14.3; M: 16.9 Abdominal obesity: F: 30.6; M: 23.9
Stringhini et al (2012)	Switzerland	Cross-sectional	Random sample of Lausanne citizens; aged 35–75 years; Caucasians	6,303	2006	53.00	F: 52.9 (10.7); M: 52.2 (10.8)	Overweight: F: 41.8; M: 62.0 Obese: F: 13.8; M:17.1 Abdominal obesity: F: 31.7; M: 26.6

Reference	Country	Study design	Inclusion criteria of population	Sample size (n)	Year of data collection / final follow-up year	Baseline gender (% women)	Baseline age in years (mean (SD) unless otherwise reported)	Proportion of people normal weight, overweight, obese (%)
Ogna et al (2014)	Switzerland	Cross-sectional	The Swiss Survey on Salt; adults aged ≥16 years	1,505	2012	51.83	47(18)	Obese: 14.2 Abdominal obesity: 33.6
Vinci et al (2019)	Switzerland	Cross-sectional	National Nutrition Survey; nationally representative; adults aged 18–75 years	2,057	2015	50.20	18–29: 18.8% 30–44: 29.9% 45–59: 29.8% 60–75: 21.6% Mean (SD):NR	Overweight: 30.7 Obese: 12.6
Southern Europe								
Tzotzas et al (2010)	Greece	Cross-sectional	Household family members of Greek adolescents attending public school; adults aged 20–70 years	16,073	2003	52.30	43.4 (19.1)	Normal weight: 42.5 Overweight: 35.2 Obese: 22.3
Devaux & Sassi (2013)	Italy	Cross-sectional	Nationally representative; adults aged 16–65 years	215,664	1995, 2000, 2003, 2005	NR	NR	Obese: F: 6.9; M: 8.9
Roskam et al (2010)	Italy	Cross-sectional	Health and health care utilization National Institute of Statistics; adults aged 25–44 years	41,613	1999, 2000	NR	NR	Obese: 7.0
Padez (2006)	Portugal	Cross-sectional	National representative; men aged 18 years	850,081	Annually 1986–2000	0.00	18	Obese: 4.2
Marques-Vidal et al (2011)	Portugal	Cross-sectional	Portuguese National Health Survey; non-institutionalised adults; aged ≥18 years; representative of continental Portugal	102,540	1996, 1999, 2006	54.33	18–34 y: 1995-6: 26.9%; 1998-9: 26.9%; 2005-6: 15.8% 35–54 y: 1995-6: 32.8%; 1998-9: 32.9%; 2005-6: 32.3% ≥55 y: 1995-6: 40.3%; 1998-9: 40.2%; 2005-6: 42% Mean (SD):NR	Obese: 1995-6: 11.5 1998-9: 12.8 2005-6: 15.1
Moreira & Padrao (2006)	Portugal	Cross-sectional	Portuguese third National Health Survey; adults aged >18 years	39,640	1998	52.92	F: 50.3 (18.88); M: 47.7 (18.51)	Underweight/normal: F: 54.3; M: 46.6 Overweight: F: 31.8; M: 42.1 Obese: F: 13.9; M: 11.3
Roskam et al (2010)	Portugal	Cross-sectional	National Health Survey Instituto Nacional de Saude; adults aged 25–44 years	12,297	1998, 1999	NR	NR	Obese: 8.1
Camoes et al (2010)	Portugal	Prospective	Representative sample of Porto, Portugal; adults aged ≥18 years	1,621	2003; follow-up 2008	61.80	52.5 (SD: NR)	Baseline obese: 21.5

Reference	Country	Study design	Inclusion criteria of population	Sample size (n)	Year of data collection / final follow-up year	Baseline gender (% women)	Baseline age in years (mean (SD) unless otherwise reported)	Proportion of people normal weight, overweight, obese (%)
Sardinha et al (2012)	Portugal	Cross-sectional	Representative sample of Alentejo, Algarve, Centro, Lisboa, and Norte; adults aged ≥18 years	6,908	2009	46.00	39.2 (12.8)	Overweight: F: 38.1; M: 46.7 Obesity: F: 19.8 M: 19.9 Abdominal obesity: F: 37.9; M: 19.3
Gaio et al (2018)	Portugal	Cross-sectional	National Health Examination Survey; Non-institutionalised individuals; adults aged 25–74 years	4,819	2015	47.80	25–34 y: 18.3% 35–44 y: 23.6% 45–54 y: 22.3% 55–64 y: 19.9% 65–74 y: 15.8% Mean (SD):NR	Normal weight: 31.5 Overweight: 39.1 Obesity: 28.6
Santos et al (2003)	Portugal	Cross-sectional	A random sample of Porto, Portugal; adults aged 18–90 years	1,436	NR	60.79	NR	Obese: 21.3
Martinez-Ros et al (2001)	Spain	Cross-sectional	Representative of the Mucria Region; adults aged 18–65 years	3,091	1993	51.00%	18–29 y: 25.0% 30–39 y: 26.4% 40–49 y: 24.6% 50–65 y: 24.0%	Obese: 20.5
Aranceta et al (2001)	Spain	Cross-sectional	National random sample; adults aged 25–60 years	5,388	1994	NR	NR	Obese: F: 15.2; M: 11.5
Gutierrez-Fisac et al (2002)	Spain	Cross-sectional	Nationally representative; adults aged 25-44 years	8,661	1987	47.70%	NR	Obese: F: 4.5; M: 5.9
	Spain	Cross-sectional	Nationally representative; adults aged 44-64 years	6,015	1987	45.30%	NR	Obese: F: 15.2; M: 10.2
	Spain	Cross-sectional	Nationally representative; adults aged 25-44 years	4,124	1995, 1997	48.50%	NR	Obese: F: 7.0; M: 9.3
	Spain	Cross-sectional	Nationally representative; adults aged 44-64 years	2,880	1995, 1997	47.20%	NR	Obese: F: 19.8; M: 16.4
Devaux & Sassi (2013)	Spain	Cross-sectional	Nationally representative; adults aged 16–65 years	39,826	1995, 1997, 2001, 2003	NR	NR	Obese: F: 10.5; M: 11.5
Mataix et al (2005)	Spain	Cross-sectional	Representative sample of adults in Andalusia; aged 25–60 years; pregnant and breastfeeding women excluded	3,421	2000	48.90	F: 41.0 (11.0) M: 40.3 (11.2)	Overweight: F: 30.7; M: 43.6 Obese: F: 20.9; M: 16.9
Sotillo et al (2007)	Spain	Cross-sectional	Representative sample of adults in Andalusia; aged 25–60 years; pregnant and breastfeeding women excluded	394	2000	57.10	F: 41.50 (13.21) M: 43.62 (15.14)	Overweight: F: 29.01; M: 42.70 Obese: F: 21.10; M: 17.13 Abdominal obesity: F: 32.00; M: 21.80

Reference	Country	Study design	Inclusion criteria of population	Sample size (n)	Year of data collection / final follow-up year	Baseline gender (% women)	Baseline age in years (mean (SD) unless otherwise reported)	Proportion of people normal weight, overweight, obese (%)
Roskam et al (2010)	Spain	Cross-sectional	National Health Survey; adults aged 25–44 years	7,741	2001	NR	NR	Obese: 10.4
Perez-Hernandez et al (2017)	Spain	Cross-sectional	Nationally representative of non-institutionalised adults aged ≥60 years	2,699	2010	53.00	68.7 (0.2)	Obese: 34.4 Abdominal obesity: 59.7
Lopez-Sobaler et al (2016)	Spain	Cross-sectional	ANIBES study; non-institutionalised adult population of Spain; adults aged 18–64 years	1,655	2013	51.80	39.97 (12.20)	Overweight: 35.8 Obese: 19.9 Abdominal obesity: 58.4
Soriguer et al (2004)	Spain	Cross-sectional	Representative sample of non-institutionalised adults in Pizarra; aged 18–65 years	1,226	NR	60.03	18–25 y: 19.09% 26–35 y: 26.18% 36–45 y: 21.70% 46–55 y: 15.82% 56–65 y: 17.21% Mean (SD):NR	Obese: F: 30.7; M: 25.5
Palomo et al (2014)	Spain	Cross-sectional	Representative sample of non-institutionalised adults in Don Benito-Villanueva de la Serena; aged 25–79 years	2,833	NR	53.50	F: 51.1 (14.9) M: 51.3 (14.6)	Obese: F: 32.6; M: 37.7
Eastern Asia								
Asahara et al (2020)	Japan	Cross-sectional	Random selection of citizens of Kobe aged 20–64 years	5,425	2018	58.00	Obese: 45.0 (11.8) Normal weight: 42.5 (12.5)	Obese: F :10.6; F: 27.2
Yoon et al (2006)	South-Korea	Cross-sectional	Korean National Health and Nutrition Examination Survey; representative of non-institutionalised South-Korea; aged ≥20 years	7,962	1998	54.80	≤6 y of schooling: F: 59.9 (12.0); M: 59.6 (11.9) 7–12 y of schooling: F: 38.0 (10.5); M: 42.5 (12.6) ≥13 y of schooling: F: 30.7 (8.6); M: 35.3 (11.1)	Obese: F: 28.1; M: 25.1 Abdominal obesity: F: 41.8; M: 20.0
Devaux & Sassi (2013)	South-Korea	Cross-sectional	Nationally representative; adults aged 16–65 years	19,113	1998, 2001, 2005	NR	NR	Obese: F: 3.5; M: 3.5
Ko et al (2015)	South-Korea	Cross-sectional	Korean National Health and Nutrition Examination Survey; representative of non-institutionalised South-Korea; aged ≥20 years	6,178	2010	56.75	20-29 y: F: 0.1%; M: 0% 30-39 y: F: 0.5%; M: 0% 40-49 y: F: 3.0%; M: 2.9% 50-59 y: F: 21.2%; M: 18.6% 60-69 y: F: 35.6%; M: 34.7% ≥70 y: F: 39.6%; M: 43.8% Mean (SD):NR	Abdominal obesity: F: 24.73; M: 25.07

Reference	Country	Study design	Inclusion criteria of population	Sample size (n)	Year of data collection / final follow-up year	Baseline gender (% women)	Baseline age in years (mean (SD) unless otherwise reported)	Proportion of people normal weight, overweight, obese (%)
So & Seo (2013)	South-Korea	Cross-sectional	Adults aged >20 years who visited a public health centre for medical check-ups in Seoul. Not representative	1,566	2011	67.80	51.06 (11.07)	Obese: F: 22.7; M: 43.0
Chung et al (2017)	South-Korea	Cross-sectional	Korean National Health and Nutrition Examination Survey; representative of South-Korea; aged ≥20 years	17,245	2012	57.45	F: 50.48 (16.6) M: 50.79 (16.4)	Obese: F: 29.7; M: 35.0
Chung & Kim (2020)	South Korea	Prospective	Korean Longitudinal Study of Ageing; nationally representative	9,991	Baseline:2006 Follow-up: 2016	NR	F: 61.7 (11.4) M: 61.0 (10.5)	Obese: F: 23.9 M: 22.9
Western Asia								
Martorell et al (2000)	Turkey	Cross-sectional	National representative; aged 15–49 years; only women (non-pregnant)	2,401	1993	NR	NR	Obese: 18.6
Erem et al (2004)	Turkey	Cross-sectional	Population from Surmene, Hayrat, Vakfıkebir, Mac¸ka and Tonya region; adults aged ≥20 years	5,016	2002	54.39	20–29: 23.42% 30–39: 25.94% 40–49: 25.59% 50–59: 14.09% 60–69: 8.12% 70+: 2.84% Mean (SD):NR	Overweight: 36.8 Obese: 23.49
Dursun et al (2018)	Turkey	Cross-sectional	Nationally representative; adults aged 18–34 years	13,546	Biannually 2008–2016	56.40	26.7 (3.5)	Obese: F: 8.3; M: 7.4
Bayram et al (2019)	Turkey	Cross-sectional	Women aged 40–64 years, living in Ankara	833	2015	100.00	40–50: 42.14% 51–64: 57.86% Mean (SD):NR	NR
Kilicarslan et al (2006)	Turkey	Cross-sectional	Outpatients of General Internal Medicine Department of Hacettepe University Hospital; women aged 18–65 years	1,500	NR	100.00	Normal weight: 41.4 (7.2) Overweight: 40.6 (7.9) Obese: 42.0 (8.4)	Normal weight: 33.33 Overweight: 33.33 Obese: 33.33
Northern America								
Huot et al (2004)	Canada	Cross-sectional	Quebec Heart Health Demonstration Project; adults aged 18–64 years living in Quebec	10,014	1993, 1997	56.68	39.9 (5.7)	NR

Reference	Country	Study design	Inclusion criteria of population	Sample size (n)	Year of data collection / final follow-up year	Baseline gender (% women)	Baseline age in years (mean (SD) unless otherwise reported)	Proportion of people normal weight, overweight, obese (%)
Kaplan et al (2003)	Canada	Cross-sectional	Canadian National Population Health Survey; people aged ≥65 years	5,980	1997	NR	NR	Obese: 12.8
Devaux & Sassi (2013)	Canada	Cross-sectional	Nationally representative; adults aged 16–65 years	266,782	1995, 2001, 2003, 2005	NR	NR	Obese: F: 15.8; M: 17.2
Ng et al (2011)	Canada	Cross-sectional	Aboriginals; Nationally representative; adults aged 25–64 years	334	2004	65.70%	F: 40 (SD: NR); M: 42.8 (SD: NR)	F: 44.5; M: 35.3
	Canada	Cross-sectional	Non-aboriginals; Nationally representative; adults aged 25–64 years	6,259	2004	54.50%	F: 44.3 (SD: NR); M: 43.8 (SD: NR)	F: 24.9; M: 26.4
Yu (2016)	USA	Cross-sectional	Non-Hispanic Whites and Blacks from NHANES aged 25–74 years	46,919	1974, 1980, 1994, biannually 1999–2012	53.50%	NR	NR
Kim (2016)	USA	Prospective	Randomly selected men and women who graduated from Wisconsin high schools in 1957 + siblings; not nationally representative	5,722	1957; follow-up 1993	NR	52.06 (4.60)	Obese: 23
Martorell et al (2000)	USA	Cross-sectional	National representative; adults aged 15–49 years; only women (non-pregnant)	5,219	1988–1994, NR how many surveys included	NR	NR	Obese: 20.7
Zhang & Wang (2004)	USA	Cross-sectional	NHANES; nationally representative; adults aged 20–60 years	6,622	1974	NR	35.3 (SE: 0.28)	NR
	USA	Cross-sectional	NHANES; nationally representative; adults aged 20–60 years	7,731	1980	NR	37.7 (SE: 0.19)	NR
	USA	Cross-sectional	NHANES; nationally representative; adults aged 20–60 years	11,533	1994	NR	37.5 (SE: 0.21)	NR
	USA	Cross-sectional	NHANES; nationally representative; adults aged 20–60 years	2,657	2000	NR	38.7 (SE: 0.38)	NR
Devaux & Sassi (2013)	USA	Cross-sectional	Nationally representative; adults aged 16–65 years	24,243	Biannually 2000–2008	NR	NR	Obese: F: 34.2; M: 29.9

Reference	Country	Study design	Inclusion criteria of population	Sample size (n)	Year of data collection / final follow-up year	Baseline gender (% women)	Baseline age in years (mean (SD) unless otherwise reported)	Proportion of people normal weight, overweight, obese (%)
Taira et al (2004)	USA	Cross-sectional	Participants who are part of an insurance company responding to a survey; not-representative; adults aged ≥18 years	43,408	2002	63.0	18–24 y: 2% 25–34 y: 6.4% 35–44 y: 12.1% 45–54 y: 19.5% 55–64 y: 20.3% 65+ y: 39.6%	Obese: 15.9
Salsberry et al (2009)	USA	Prospective	Nationally representative of women aged 14–21 years in 1979	NR	1979; follow-up 2002	100	NR	Obese: M-A: 34; W: 23; A-A: 42
Borders et al (2006)	USA	Cross-sectional	Behavioural Risk Factor Surveillance System; Texas; non-institutionalised adults aged >18 years	5,078	2003	48.97	18–24: 14.77% 25–34: 20.12% 35–44: 21.35% 45–54: 18.08% 55–64: 12.01% ≥65: 13.67% Mean (SD):NR	Normal weight: 36.48 Overweight: 36.36 Obese: 25.03
Wen et al (2018)	USA	Cross-sectional	Nationally representative; adults aged 20–64 years	10 302	2003–2008	49.65	41.28 (SD: NR)	Overweight: 33.36 Obese: 34.36
Cohen et al (2013)	USA	Prospective	National Longitudinal Survey of Youth; randomly sampled households	Baseline: 9,964 Follow-up: 4,527	1979; follow-up 2008	49.70	40 (SD:NR)	At baseline: NR Obese at 40y: 31.1
Coogan et al (2012)	USA	Prospective	African-American women aged 21–50 years from across the US	Baseline: 23,601 Follow-up: 21,457	1995; follow-up 2009	100.00	≤High school: 32.4(5.3) Some college: 32.0(5.3) College graduate: 31.3(5.4)	NR
von Hippel & Lynch (2014)	USA	Prospective	National Longitudinal Survey of Youth; randomly sampled households	8,665	1997; follow-up 2010	48.84	Baseline age: 17 y Follow-up age: 29 y	Baseline: Overweight: F: 23; M: 30; Obese: F: 8; M: 9 Follow-up: Overweight: F: 58; M: 69; Obese: F: 30; M: 30
Beltran-Sanchez et al (2016)	USA	Cross-sectional	Nationally representative; adults aged ≥20 years; Mexican Foreign-born	1,530	1999–2000, 2009–2010	50.20	20–29 y: 24.3% 30–49: 41.0% 50+: 34.6%	Obese: 32.6
	USA	Cross-sectional	Nationally representative; adults aged ≥20 years; US-born Mexican American	1,043	2000, 2010	55.00	20–29 y: 20.6% 30–49: 29.7% 50+: 49.7%	Obese: 40.3
	USA	Cross-sectional	Nationally representative; adults aged ≥20 years; Non-Hispanic White	5,791	2000, 2010	50.80	20–29 y: 14.4% 30–49: 30.8% 50+: 54.8%	Obese: 31.2

Reference	Country	Study design	Inclusion criteria of population	Sample size (n)	Year of data collection / final follow-up year	Baseline gender (% women)	Baseline age in years (mean (SD) unless otherwise reported)	Proportion of people normal weight, overweight, obese (%)
Drewnowski et al (2014)	USA	Cross-sectional	Seattle Obesity Study; representative of Seattle; adults aged ≥18 years	1,340	2009	62.00	18–44: 26% 45–64: 52% ≥65: 22% Mean (SD):NR	Non-obese: 79 Obese: 21
Hales et al (2018)	USA	Cross-sectional	NHANES; nationally representative; adults aged ≥20 years	10,792	2014, 2016	51.00	48 (SD:NR)	Obese Women: 40.8 Men: 36.5
Qobadi & Payton (2017)	USA	Cross-sectional	Mississippi Behavioural Risk Factor Surveillance System data; representative non-institutionalised adults aged ≥18 years	3,794	2014	51.30	18–24: 12.2% 25–44: 33.1% 45–64: 34.3% ≥65: 20.3% Mean (SD):NR	Normal: White: 30.0; Black: 22.9 Overweight: White: 37.0; Black: 33.0 Obese: White: 33.0; Black: 44.1
An (2015)	USA	Cross-sectional	Behavioural Risk Factor Surveillance System surveys; nationally representative; aged >18 years	11,797	1984	51.20	18–39 y: 50.81% 40–59 y: 28.00% 60–79 y: 19.14% >80 y: 2.05% Mean (SD):NR	NR
	USA	Cross-sectional	Behavioural Risk Factor Surveillance System surveys; nationally representative; aged >18 years	464,158	2013	49.81	18–39 y: 37.27% 40–59 y: 35.74% 60–79 y: 22.57% >80 y: 4.43% Mean (SD):NR	NR
Bodea et al (2009)	USA	Cross-sectional	Atlanta; participants aged >20 years	11,260	NR	50.70	47.41 (SD: NR)	NR
Central America								
Martorell et al (2000)	Mexico	Cross-sectional	National representative; aged 15–49 years; only women (non-pregnant)	3,681	1987	NR	NR	Obese: 10.4
Buttenheim et al (2010)	Mexico	Cross-sectional	National representative; adults aged 20–79 years	38,901	2000	53.00	20–29y: 37% 30–39y: 27% 40–49y: 18% 50–69y: 18%	Obese: 24
Beltran-Sanchez et al (2011)	Mexico	Cross-sectional	National representative; adults aged ≥20 years	14,280	2002	56.90%	20–39 y: 53.1% 40–59 y: 32.2% 60+ y: 14.7%	Obese: 26.9
Beltran-Sanchez et al (2016)	USA	Cross-sectional	Nationally representative; adults aged ≥20 years	7,593	2006	62.40%	20–29 y: 20.9% 30–49: 47.4% 50+: 31.7%	Obese: 31.3

Reference	Country	Study design	Inclusion criteria of population	Sample size (n)	Year of data collection / final follow-up year	Baseline gender (% women)	Baseline age in years (mean (SD) unless otherwise reported)	Proportion of people normal weight, overweight, obese (%)
Perez Ferrer et al (2014)	Mexico	Cross-sectional	Women, non-pregnant; aged 20–49 years	Urban: 8,887 Rural: 1,315	1988	100.00	Urban: 32.4 (0.1) Rural: 32.2 (0.3)	Obese: Urban: 9.5; Rural: 8.1
	Mexico	Cross-sectional	Women, non-pregnant; aged 20–49 years	Urban: 8,205 Rural: 4,308	1999	100.00	Urban: 33.8 (0.1) Rural: 33.8 (0.1)	Obese: Urban: 26.3; Rural: 21.3
	Mexico	Cross-sectional	Women, non-pregnant; aged 20–49 years	Urban: 9,906 Rural: 4,068	2006	100.00	Urban: 34.0 (0.1) Rural: 33.7 (0.2)	Obese: Urban: 30.9; Rural: 27.9
	Mexico	Cross-sectional	Women, non-pregnant; aged 20–49 years	Urban: 9,588 Rural: 4,943	2012	100.00	Urban: 33.8 (0.1) Rural: 33.4 (0.2)	Obese: Urban: 34.5; Rural: 30.7
Andrade & Lopez-Ortega (2017)	Mexico	Cross-sectional	Mexican National Health and Nutrition Survey; national representative; adults 50–94 years	11,411	2012	53.30	63.01 (10.14)	Obese: 33.8 Abdominal obesity: 83.1
Oceania								
Lawlor et al (2005)	Australia	Cross-sectional	Women aged 18–23 years; nationally representative	14,779	1996	100.00	20.7 (1.5)	Obese: 6.4
	Australia	Cross-sectional	Women aged 45–50 years; nationally representative	14,099	1996	100.00	47.7 (1.5)	Obese: 18.3
	Australia	Cross-sectional	Women aged 70–75 years; nationally representative	12,940	1996	100.00	72.6 (1.5)	Obesity: 13.9
Cameron et al (2003)	Australia	Cross-sectional	42 randomly selected Census Collector Districts across Australia; adults aged ≥25 years	11,247	2000	55.11	NR	Overweight: F: 29.9; M: 48.2 Obese: F: 22.2; M: 19.3 Abdominal obesity: F: 34.1; M: 26.8
Brown & Siahpush (2007)	Australia	Cross-sectional	National Health Survey; adults aged >18 years	26,863	2001	53.20	18–29: 18.2% 30–44: 33.4% 45–59: 24.5% ≥60: 23.9% Mean (SD):NR	Underweight/healthy weight: F: 57.75; M: 42.12 Overweight: F: 25.60; M: 42.09 Obese: F: 16.65; M: 15.79
Devaux & Sassi (2013)	Australia	Cross-sectional	Nationally representative; adults aged 16–65 years	80,215	1995, 2001, 2005	NR	NR	Obese: F: 16; M: 18

F, female; M, male; NHANES, National Health and Nutrition Examination Survey; NR, not reported; SD, standard deviation; USA, United States of America; y, years; M-A, Mexican-American; W, White; A-A, African-American.

Table S3: Results of the association between education and obesity defined by body mass index ≥30kg/m^2 (compared to normal weight if reported)

Reference	Definition of education and distribution (%)	Analysis outcome	Covariates	Association with obesity		
				Women Effect size (95% CI unless otherwise stated)	Men Effect size (95% CI unless otherwise stated)	Total Effect size (95% CI unless otherwise stated)
Eastern Europe						
Roskam et al (2010) (Czech Republic)	Tertiary: NR Upper/post-secondary: NR Lower secondary: NR Primary/no education: 7.4	RII: PR of being obese at the lowest vs the highest educational category	Age	5.30 (1.54, 18.22)	3.64 (1.09, 12.16)	NR
Devaux & Sassi (2013) (Hungary)	NR	RII: OR of being obese at the lowest vs the highest educational category	Age, year of the survey, marital status, ethnicity, smoking, occupation status	2.9 (95% CI: NR)	1.8 (95% CI: NR)	NR
Roskam et al (2010) (Hungary)	Tertiary: NR Upper/post-secondary: NR Lower secondary: NR Primary/no education: 16.0	RII: PR of being obese at the lowest vs the highest educational category	Age	2.28 (1.57, 3.31)	1.44 (0.97, 2.15)	NR
Nedo & Paulik (2012) (Hungary)	Low (no/primary school): 32.0 Medium (vocational/secondary school): 50.0 High (college/university): 17.9	OR of obesity (vs non-obese) for low and medium vs high education	Age, gender, self-perceived financial conditions, smoking, diet, physical activity	NR	NR	Low: 1.66 (0.97, 2.84) Medium: 2.16 (1.33, 3.50) vs high
Rurik et al (2014) (Hungary)	Under (not competed primary school): NR Primary (elementary school): NR secondary (graduated of secondary school/skilled worker qualification): NR Higher (College or University degree): NR	OR of obesity (vs: NR) for under primary, secondary and higher vs primary education	NR	Under: 1.11 (0.98, 1.26) Secondary: 0.63 (0.59, 0.67) Higher: 0.41 (0.37, 0.45) vs primary	Under: 0.74 (0.61, 0.91) Secondary: 0.94 (0.87, 1.02) Higher: 0.66 (0.59, 0.74) vs primary	NR
Zatonska et al (2011) (Poland)	Lower level (primary and vocational): NR Higher level (secondary and higher): NR	OR of obesity (vs NR) for lower level education vs higher level education	Reporting not clear	Lower: 0.48 (0.40, 0.59) vs higher level	Lower: 0.67 (0.52, 0.86) vs higher level	NR
Roskam et al (2010) (Slovak Republic)	Tertiary: NR Upper/post-secondary: NR Lower secondary: NR Primary/no education: 12.7	RII: PR of being obese at the lowest vs the highest educational category	Age	5.85 (1.41, 24.24)	1.58 (0.53, 4.76)	NR

Reference	Definition of education and distribution (%)	Analysis outcome	Covariates	Association with obesity		
				Women Effect size (95% CI unless otherwise stated)	Men Effect size (95% CI unless otherwise stated)	Total Effect size (95% CI unless otherwise stated)
Northern Europe						
Sarlio-Lahteenkorva et al (2006) (Denmark)	Higher (≥13 y): F: 29; M: 28 Secondary (10–12 y): F: 49; M: 54 Basic (≤9 y): F: 22; M: 18	OR of obesity (vs NR) for basic and secondary vs higher education	Age	Basic: 2.83 (1.53, 5.23) Secondary: 1.99 (1.1, 3.60) vs Higher	Basic: 2.29 (1.33, 3.94) Secondary: 1.84 (1.14, 2.95) vs Higher	NR
Roskam et al (2010) (Denmark)	Tertiary: NR Upper/post-secondary: NR Lower secondary: NR Primary/no education: 1.2	RII: PR of being obese at the lowest vs the highest educational category	Age	2.70 (1.70, 4.29)	3.11 (1.87, 5.17)	NR
Groth et al (2009) (Denmark)	Long higher education (≥17 y): F: 6; M: 10 Medium higher education (15–16 y): F: 15; M: 12 Short higher education (13–14 y) F: 8; M: 7 Vocational (13 y): F: 42; M: 46 Basic (5–12 y): F: 28; M: 26	OR of obesity (vs NR) for basic, vocational, short and medium education vs long higher education	Men: age Women: occupation	5–12 y: 6.51 (2.26, 18.73) 13 y: 3.68 (1.31, 10.38) 13–14 y: 2.95 (0.90, 9.69) 15–16 y: 1.32 (0.41, 4.24) vs ≥17 y	5–12 y: 2.90 (1.41, 5.94) 13 y: 2.19 (1.1, 4.2) 13–14 y: 1.18 (0.45, 3.1) 15–16 y: 0.96 (0.41, 2.2) vs ≥17 y	NR
Nielsen et al (2006) (Denmark)	<12 y: 53.77 ≥12 y: 43.93	OR of obesity for <12 vs ≥12 y of education	Age	NR	<12 y: 1.9 (1.1, 3.3) vs ≥12 y	NR
Devaux & Sassi (2013) (England)	NR	RII: OR of being obese at the lowest vs the highest educational category	Age, year of the survey, marital status, ethnicity, smoking, occupation status	1.9 (95% CI: NR)	1.4 (95% CI: NR)	NR
Wardle, Waller & Jarvis (2002) (England)	Age at leaving education, y: ≤14: F: 16.83; M: 15.15 15: F: 20.28; M: 20.37 16: F: 26.77; M: 27.68 17: F: 8.93; M: 6.79 18: F: 8.33; M: 6.74 ≥19: F:13.75; M: 17.86	OR of obesity (vs NR) for leaving school at ≤14, 15, 16, 17, 18 years compared to ≥19	Age, marital status, occupation, and ethnicity	≤14 y: 1.81 (1.36, 2.41) 15 y: 1.44 (1.12, 1.85) 16 y: 1.52 (1.20, 1.91) 17 y: 1.55 (1.17, 2.05) 18 y: 1.29 (0.96, 1.74) vs leaving school at ≥19 y	≤14 y: 1.77 (1.30, 2.40) 15 y: 1.63 (1.27, 2.09) 16 y: 1.43 (1.14, 1.81) 17 y: 1.66 (1.23, 2.26) 18 y: 1.32 (0.96, 1.82) vs leaving school at ≥19 y	NR
Roskam et al (2010) (England)	England Tertiary: NR Upper/post-secondary: NR Lower secondary: NR Primary/no education: 5.9	RII: PR of being obese at the lowest vs the highest educational category	Age	2.19 (1.66, 2.87)	1.70 (1.26, 2.29)	NR

Reference	Definition of education and distribution (%)	Analysis outcome	Covariates	Association with obesity		
				Women Effect size (95% CI unless otherwise stated)	Men Effect size (95% CI unless otherwise stated)	Total Effect size (95% CI unless otherwise stated)
Klumbiene et al (2004) (Estonia)	Low (0–9 y): 21 Medium (10–12 y): 49 High (>12 y): 30	OR of obesity (vs NR) for high and medium education vs low education	Survey year, age, place of residence	High: 0.44 (0.31, 0.64) Medium: 0.75 (0.55, 1.03) vs low education	High: 1.12 (0.69, 1.82) Medium: 1.09 (0.70, 1.68) vs low education	NR
Roskam et al (2010) (Estonia)	Tertiary: NR Upper/post-secondary: NR Lower secondary: NR Primary/no education: 4.2	RII: PR of being obese at the lowest vs the highest educational category	Age and country	3.33 (1.67, 6.66)	1.69 (0.84, 3.38)	NR
Sulander & Uutela (2007) (Finland)	Lower (0–8 y): F: 74.5; M: 70.8 Higher (≥9 y): F: 25.5; M: 29.2	OR of obesity (vs NR) for lower education vs higher education	Age, survey year, smoking and physical activity	Lower: 1.53 (1.30, 1.81) vs higher education	Lower: 1.44 (1.17, 1.77) vs higher education	NR
Sarlio-Lahteenkorva et al (2006) (Finland)	Higher (≥13 y): F: 20; M: 24 Secondary (10–12 y): F: 47; M: 42 Basic (≤9 y): F: 32; M: 34	OR of obesity (vs NR) for basic and secondary vs higher education	Age	Basic: 2.65 (1.82, 3.88) Secondary: 2.16 (1.48, 3.15) vs Higher	Basic: 1.72 (1.28, 2.31) Secondary: 1.48 (1.10, 2.00) vs Higher	NR
Klumbiene et al (2004) (Finland)	Low (0–9 y): 27 Medium (10–12 y): 32 High (>12 y): 41	OR of obesity (vs NR) for high and medium education vs low education.	Survey year, age, place of residence	High: 0.56 (0.44, 0.73) Medium: 0.84 (0.67, 1.07) vs low education	High: 0.59 (0.46, 0.76) Medium: 0.80 (0.63, 1.02) vs low education	NR
Roskam et al (2010) (Finland)	Tertiary: NR Upper/post-secondary: NR Lower secondary: NR Primary/no education: 16.8	RII: PR of being obese at the lowest vs the highest educational category	Age	1.59 (1.06, 2.37)	1.52 (1.01, 2.29)	NR
Laaksonen et al (2004) (Finland)	Higher (University): F: 24.1; M: 31.9 Intermediate (secondary): F: 31.5; M: 27.0 Basic (compulsory): F: 43.3; M: 40.6	OR of obesity (vs NR) for basic and intermediate education vs higher education	Age, childhood SES, adult SES, material resources, economic satisfaction	Basic: 1.08 (0.74, 1.57) Intermediate: 1.21 (0.89, 1.66) vs higher education	Basic: 1.21 (0.63 to 2.31) Intermediate: 1.25 (0.73 to 2.12) vs higher education	NR
Seppanen-Nuijten et al (2009) (Finland)	Low: F: 29.3; M: 30.5 Middle: F: 31.2; M: 42.1 High: F: 39.4; M: 27.4	OR of obesity (vs NR) for high and middle vs low education	Age	High: 0.59 (0.45, 0.77) Middle: 0.82 (0.63, 1.07) vs low education	High: 0.57 (0.43, 0.76) Middle: 0.77 (0.60, 0.99) vs low education	NR
Salonen et al (2009) (Finland)	Basic: F: 28.0; M: 27.8 Secondary: F: 32.5; M: 28.5 Higher: F: 37.7; M: 42.2	OR of obesity (vs NR) for low and middle education vs high education	Age, SES in childhood, SES in adulthood, income	Basic: 1.4 (0.9, 2.1) Secondary: 1.3 (0.9, 1.9) vs higher education	Basic: 1.3 (0.7, 2.0) Secondary: 0.8 (0.5, 1.2) vs higher education	NR

Reference	Definition of education and distribution (%)	Analysis outcome	Covariates	Association with obesity		
				Women Effect size (95% CI unless otherwise stated)	Men Effect size (95% CI unless otherwise stated)	Total Effect size (95% CI unless otherwise stated)
Roskam et al (2010) (Latvia)	Tertiary: NR Upper/post-secondary: NR Lower secondary: NR Primary/no education: 13.8	RII: PR of being obese at the lowest vs the highest educational category	Age	1.50 (0.92, 2.45)	0.86 (0.45, 1.62)	NR
Klumbiene et al (2004) (Lithuania)	Low (0–9 y): 20 Medium (10–12 y): 40 High (>12 y): 40	OR of obesity (vs NR) for high and medium education vs low education	Survey year, age, place of residence	High: 0.70 (0.54, 0.92) Medium: 1.06 (0.82, 1.39) vs low education	High: 0.84 (0.58, 1.21) Medium: 1.01 (0.70, 1.46) vs low education	NR
Roskam et al (2010) (Lithuania)	Tertiary: NR Upper/post-secondary: NR Lower secondary: NR Primary/no education: 3.4	RII: PR of being obese at the lowest vs the highest educational category	Age	2.68 (1.84, 3.90)	0.96 (0.59, 1.56)	NR
Hughes et al (2017) (Northern Ireland)	1997 Tertiary: 21.4 Secondary: 41.7 Primary: 36.7	RII: the difference in predicted values of obesity between the lowest and highest education level	Age	1.5 (95%CI: NR)	0.8 (95%CI: NR)	NR
	2005/6 Tertiary: 27.6 Secondary: 43.4 Primary: 29.1	RII: the difference in predicted values of obesity between the lowest and highest education level	Age	1.6 (95%CI: NR)	1.4 (95%CI: NR)	NR
	2010/11 Tertiary: 32.5 Secondary: 42.5 Primary: 24.7	RII: the difference in predicted values of obesity between the lowest and highest education level	Age	2.1 (95%CI: NR)	1.1 (95%CI: NR)	NR
Roskam et al (2010) (Norway)	Tertiary: NR Upper/post-secondary: NR Lower secondary: NR Primary/no education: 0.2	RII: PR of being obese at the lowest vs the highest educational category	Age	1.75 (0.76, 4.01)	3.42 (1.70, 6.92)	NR
Roskam et al (2010) (Republic of Ireland)	Tertiary: NR Upper/post-secondary: NR Lower secondary: NR Primary/no education: 9.7	RII: PR of being obese at the lowest vs the highest educational category	Age	1.98 (0.94, 4.19)	1.34 (0.67, 2.65)	NR
Hughes et al (2017) (Republic of Ireland)	1998 Tertiary: 32.6 Secondary: 51.6 Primary: 15.8	RII: the difference in predicted values of obesity between the lowest and highest education level	Age	4.2 (95%CI: NR)	1.7 (95%CI: NR)	NR

Reference	Definition of education and distribution (%)	Analysis outcome	Covariates	Association with obesity		
				Women Effect size (95% CI unless otherwise stated)	Men Effect size (95% CI unless otherwise stated)	Total Effect size (95% CI unless otherwise stated)
Hughes et al (2017) (Republic of Ireland)	2002 Tertiary: 38.5 Secondary: 49.4 Primary: 12.1	RII: the difference in predicted values of obesity between the lowest and highest education level	Age	8.2 (95%CI: NR)	3.2 (95%CI: NR)	NR
	2007 Tertiary: 41.5 Secondary: 45.6 Primary: 13.0	RII: the difference in predicted values of obesity between the lowest and highest education level	Age	1.7 (95%CI: NR)	1.5 (95%CI: NR)	NR
Lindstrom et al (2003) (Sweden)	1986 >12 y: F: 17.6; M: 16.3 10–12 y: F: 13.0; M: 16.6 ≤9 y: F: 64.7; M: 60.9 Other: F: 4.7; M: 6.1	OR of obesity (vs NR) for ≤9 y, 10–12 y and other education vs >12 y of education	Age and country of origin	≤9 y: 6.75 (2.07, 22.01) 10–12 y: 3.14 (0.78, 12.74) Other: 8.97 (2.30, 34.98) vs >12 y	≤9 y: 1.24 (0.61, 2.54) 10–12 y: 0.42 (0.13, 1.38) Other: 1.25 (0.41, 3.80) vs >12 y	NR
	1994 >12 y: F: 25.5; M: 25.6 10–12 y: F: 20.1; M: 20.4 ≤9 y: F: 47.7; M: 45.7 Other: F: 6.7; M: 8.3	OR of obesity (vs NR) for ≤9 y, 10–12 y and other education vs >12 y of education	Age and country of origin	≤9 y: 2.31 (1.40, 3.79) 10–12 y: 1.03 (0.54, 1.98) Other: 2.16 (1.07, 4.35) vs >12 years	≤9 y: 2.29 (1.50, 3.51) 10–12 y: 1.04 (0.59, 1.85) Other: 1.85 (1.01, 3.39) vs >12 years	NR
Molarius (2003) (Sweden)	low (elementary school): F: 29.5; M: 38.1 medium (upper secondary school): F: 61.2; M: 56.7 high (at least 3 y of University or college): F: 9.3; M: 6.9	OR of obesity (vs NR) for low and medium education vs high education for men aged 25–74 years; for women aged 25–64 years	Age, physical activity and alcohol use	Low: 2.3 (1.3, 4.2) Medium: 2.2 (1.3, 3.7) vs high	Low: 2.5 (1.3, 4.8) Medium: 2.0 (1.1, 3.7) vs high	NR
Devaux & Sassi (2013) (Sweden)	NR	RII: OR of being obese at the lowest vs the highest educational category	Age, year of the survey, marital status, ethnicity, smoking, occupation status	3.3 (95% CI: NR)	2.8 (95% CI: NR)	NR
Roskam et al (2010) (Sweden)	Tertiary: NR Upper/post-secondary: NR Lower secondary: NR Primary/no education: 2.5	RII: PR of being obese at the lowest vs the highest educational category	Age	3.87 (2.12, 7.04)	4.33 (2.39, 7.83)	NR
Western Europe						
Devaux & Sassi (2013) (Austria)	NR	RII: OR of being obese at the lowest vs the highest educational category	Age, year of the survey, marital status, ethnicity, smoking, occupation	2 (95% CI: NR)	2.3 (95% CI: NR)	NR

Reference	Definition of education and distribution (%)	Analysis outcome	Covariates	Association with obesity		
				Women Effect size (95% CI)	Men Effect size (95% CI)	Total Effect size (95% CI)
Roskam et al (2010) (Belgium)	Tertiary: NR Upper/post-secondary: NR Lower secondary: NR Primary/no education: 8.6	RII: PR of being obese at the lowest vs the highest educational category	Age and country	6.25 (4.05, 9.65)	2.17 (1.48, 3.19)	NR
Charafeddine et al (2009) (Belgium)	1997 Primary education: F: 22.39; M: 18.72 Lower secondary: F: 21.45; M: 20.93 Higher secondary: F: 28.30; M: 30.73 Higher education: F: 27.86; M: 29.62	Relative risk of developing obesity, lowest vs. highest educational level	Age	Lowest: 3.63 (2.35, 5.61) vs highest	Lowest: 1.83 (1.20, 2.79) vs highest	NR
	2001 Primary education: F: 22.84; M: 18.60 Lower secondary: F: 21.50; M: 21.20 Higher secondary: F: 27.48; M: 30.87 Higher education: F: 28.18; M: 29.33	Relative risk of developing obesity, lowest vs. highest educational level	Age	Lowest: 3.57 (2.48, 5.15) vs highest	Lowest: 2.12 (1.50, 3.00) vs highest	NR
	2004 Primary education: F: 23.53; M: 18.03 Lower secondary: F: 21.09; M: 18.97 Higher secondary: F: 26.32; M: 31.42 Higher education: F: 29.06; M: 31.58	Relative risk of developing obesity, lowest vs. highest educational level	Age	Lowest: 3.29 (2.35, 4.62) vs highest	Lowest: 2.62 (1.88, 3.67) vs highest	NR
Czernichow et al (2004) (France)	Primary: F: 22.8; M: 20.9 Secondary: F: 42.3; M: 33.4 University: F: 34.9; M: 37.0	OR of obesity (vs NR) for University and secondary school vs primary school	Age	University: 0.55 (0.39, 0.76) Secondary: 0.65 (0.48, 0.88) vs primary education	University: 0.64 (0.48, 0.87) Secondary: 0.76 (0.57, 1.02) vs primary education	NR
Singh-Manoux et al (2009) (France)	1970 Low: NR Intermediate: NR High: NR	RII: OR of being obese comparing lowest with highest education	Age	6.04 (3.65, 9.99)	1.73 (1.10, 2.72)	NR
	1980 Low: NR Intermediate: NR High: NR	RII: OR of being obese comparing lowest with highest education	Age	6.18 (3.50, 10.91)	2.12 (1.36, 3.30)	NR
	1991 Low: NR Intermediate: NR High: NR	RII: OR of being obese comparing lowest with highest education	Age	4.93 (3.01, 8.07)	2.60 (1.57, 4.30)	NR
	2003 Low: NR Intermediate: NR High: NR	RII: OR of being obese comparing lowest with highest education	Age	4.78 (3.59, 6.38)	2.51 (1.90, 3.31)	NR
Devaux & Sassi (2013) (France)	NR	RII: OR of being obese at the lowest vs the highest educational category	Age, survey, marital status, ethnicity, smoking, occupation	4.8 (95% CI: NR)	3.2 (95% CI: NR)	NR

Reference	Definition of education and distribution (%)	Analysis outcome	Covariates	Association with obesity		
				Women Effect size (95% CI unless otherwise stated)	Men Effect size (95% CI unless otherwise stated)	Total Effect size (95% CI unless otherwise stated)
Roskam et al (2010) (France)	Tertiary: NR Upper/post-secondary: NR Lower secondary: NR Primary/no education: 2.6	RII: PR of being obese at the lowest vs the highest educational category	Age and country	4.21 (2.46, 7.21)	3.28 (1.74, 6.19)	NR
Drewnowski et al (2014) (France)	≤High school: 36 Some college: 30 ≥College: 38	RR of obesity (vs non-obese) for ≥college and some college vs ≤high school	Age, gender, living alone or not, residential area, income, and neighbourhood property values	NR	NR	≥College: 0.51 (0.42, 0.62) Some college: 0.71 (0.60, 0.85) vs ≤high school
Icks et al (2007) (Germany)	1990-92 Low: F: 25; M: 8 Middle: F: 60; M: 67 High: F: 15; M: 24 1998 Low: F: 17; M: 6 Middle: F: 63; M: 66 High: F: 20; M: 29	OR of obesity (vs NR) for low and middle education vs high education	Age	Low: 4.79 (3.30, 6.94) Middle: 2.60 (1.82, 3.71) vs high education	Low: 2.62 (1.80, 3.81) Middle: 2.32 (1.78, 3.00) vs high education	NR
Nocon et al (2007) (Germany)	Low: NR Medium: NR High: NR	OR of obesity (vs normal weight) of low and medium vs high education	Age, gender, income, occupation	NR	NR	Low: 2.58 (1.99, 3.34) Medium: 1.80 (1.41, 2.31) vs high
Roskam et al (2010) (Germany)	Tertiary: NR Upper/post-secondary: NR Lower secondary: NR Primary/no education: 10.3	RII: PR of being obese at the lowest vs the highest educational category	Age and country	5.07 (2.95, 8.71)	1.66 (1.06, 2.61)	NR
Kuntz & Lampert (2010) (Germany)	Low (no school-leaving certificate): F: 31.4; M: 24.3 Intermediate (high school): F: 17.3; M: 16.7 High (college and University entrance qualification): F:10.1; M: 11.9	OR of obesity (vs NR) for low and intermediate vs high education	Age, occupation, income	Low: 1.67 (1.26, 2.20) Intermediate: 1.37 (1.05, 1.79) vs high	Low: 1.54 (1.19, 1.98) Intermediate: 1.22 (0.95, 1.56) vs high	NR
Maier et al (2014) (Germany)	High level (12-13 y): 42.0 Medium level (10 y): 30.5 Low level (<9 y): 27.5	OR of obesity (vs NR) for low and medium level compared to high level of education	Gender, age, deprivation, lifestyle and marital status	NR	NR	Low: 2.33 (2.16, 2.53) Medium: 1.53 (1.41, 1.66) vs high level

Reference	Definition of education and distribution (%)	Analysis outcome	Covariates	Association with obesity		
				Women Effect size (95% CI unless otherwise stated)	Men Effect size (95% CI unless otherwise stated)	Total Effect size (95% CI unless otherwise stated)
Tchicaya & Lorentz (2012) (Luxembourg)	1995 Primary: F: 56.46; M: 35.87 Secondary: F: 32.79; M: 42.86 Tertiary: F: 10.75; M: 21.27	OR of obesity (vs NR) for primary and secondary vs tertiary education	Age, nationality, marital status, profession, residence, exercise, diet	Primary: 5.03 (2.29, 1.07) Secondary: 2.36 (1.07, 5.20) vs tertiary education	Primary: 1.45 (0.99, 2.13) Secondary: 1.02 (0.71, 1.47) vs tertiary education	NR
	2007 Primary: F: 31.47; M: 23.78 Secondary: F: 48.45; M: 53.25 Tertiary: F: 20.08; M: 22.97	OR of obesity (vs NR) for Primary and Secondary vs Tertiary education	Age, nationality, marital status, profession, residence, exercise, diet	Primary: 2.06 (1.43, 2.98) Secondary: 2.08 (1.48, 2.92) vs tertiary education	Primary: 0.76 (0.54, 1.06) Secondary: 0.86 (0.65, 1.14) vs tertiary education	NR
Samouda et al (2018) (Luxembourg)	Primary/lower secondary: F: 25.13; M: 24.44 Upperpost-secondary/no tertiary: F: 40.45; M: 36.67 Tertiary education: F: 34.03; M: 38.61	OR of obesity (vs NR) for secondary and tertiary education vs primary.	Age, country of birth, exercise, diet, alcohol, self-perceived health, pain, sleep, depression	Tertiary: 0.33 (0.16, 0.68) Secondary: 0.60 (0.34, 1.04) vs Primary	Tertiary: 0.85 (0.41, 1.80) Secondary: 1.82 (0.92, 3.62) vs Primary	NR
Roskam et al (2010) (Netherlands)	Tertiary: NR Upper/post-secondary: NR Lower secondary: NR Primary/no education: 4.5	RII: PR of being obese at the lowest vs the highest educational category	Age and country	2.87 (1.89, 4.34)	3.61 (2.28, 5.73)	NR
Faeh et al (2011) (Switzerland)	low: ≤compulsory schooling: NR middle: vocational training or high school: NR high: technical college, upper vocational or university education: NR	OR of obesity (vs normal weight) for low vs middle education and low vs high education	Age, survey year, income and occupation	Low vs middle: 1.80 (1.55, 2.09) Low vs high: 2.99 (2.32, 3.86)	Low vs middle: 1.41 (1.16, 1.71) Low vs high: 1.94 (1.53, 2.45	NR
Marques-Vidal et al (2010) (Switzerland)	Low: 1992/3: 21.2; 1997: 22.0; 2002: 19.2; 2007: 13.8 Middle: 1992/3: 57.2; 1997: 60.7; 2002: 63.9; 2007: 58.9 High: 1992/3: 21.6; 1997: 17.2; 2002: 16.9; 2007: 27.3	OR of obesity (vs NR) for high and middle vs low education	Age, survey year, nationality, smoking	High: 0.35 (0.30, 0.41) Middle: 0.59 (0.53, 0.64) vs lower education	High: 0.43 (0.37, 0.49) Middle: 0.72 (0.64, 0.81) vs lower education	NR
Marques-Vidal et al (2008) (Switzerland)	Basic: NR Apprenticeship (A): NR High school (HS): NR University (U): NR	OR of obesity for A, HS, U vs basic education	Age, smoking, physical activity	U: 0.27 (0.18, 0.40) HS: 0.41 (0.30, 0.55) A: 0.64 (0.50, 0.81) vs basic education	U: 0.30 (0.21, 0.43) HS: 0.55 (0.40, 0.74) A: 0.75 (0.58, 0.96) vs basic education	NR

Reference	Definition of education and distribution (%)	Analysis outcome	Covariates	Association with obesity		
				Women Effect size (95% CI unless otherwise stated)	Men Effect size (95% CI unless otherwise stated)	Total Effect size (95% CI unless otherwise stated)
Stringhini et al (2012) (Switzerland)	Tertiary: F: 16.5; M: 24.0 Post-secondary/secondary: F: 25.7; M: 23.2 <secondary: F: 57.8; M: 52.8	RII: PR of being obese at the lowest vs the highest educational category	Age, place of birth	4.77 (3.15, 7.22)	2.95 (2.09, 4.16)	NR
Ogna et al (2014) (Switzerland)	Primary: 15.6 Secondary: 44.1 Tertiary: 40.3	OR of obesity (vs NR) for tertiary and secondary vs primary education	Age, gender, language, country of birth, smoking, physical activity	NR	NR	Tertiary: 0.60 (0.38, 0.94) Secondary: 0.88 (0.57, 1.36) vs primary education
Vinci et al (2019) (Switzerland)	Tertiary: 52.6 Secondary: 42.6 Primary: 4.7	OR of obesity (vs normal weight) for primary and secondary education vs tertiary education	Age, gender, marital status, nationality, and household status	Primary: 1.91 (1.65, 2.20) Secondary: 1.7 (1.18, 2.67) vs tertiary	Primary: 0.76 (0.73, 0.79) Secondary: 1.73 (1.48, 2.03) vs tertiary	NR
Southern Europe						
Tzotzas et al (2010) (Greece)	Illiterate: 4.3 Primary school: 26.1 High school: 45.6 University: 24.0	OR of obesity (vs healthy weight) of primary school, high school and University education vs no education	Age	University: 0.64 (0.49, 0.81) High school: 0.58 (0.46, 0.74) Primary: 0.76 (0.60, 0.96) vs no education	University: 0.79 (0.60, 1.05) High school: 0.83 (0.63, 1.09) Primary: 0.91 (0.69, 1.20) vs no education	University: 0.72 (0.59, 0.87) High school: 0.76 (0.63, 0.91) Primary: 0.83 (0.69, 1.00) vs no education
Devaux & Sassi (2013) (Italy)	NR	RII: OR of being obese at the lowest vs the highest educational category	Age, year of the survey, marital status, ethnicity, smoking, occupation status	6.8 (95% CI: NR)	2.2 (95% CI: NR)	NR
Roskam et al (2010) (Italy)	Tertiary: NR Upper/post-secondary: NR Lower secondary: NR Primary/no education: 6.1	RII: PR of being obese at the lowest vs the highest educational category	Age	6.03 (4.71, 7.71)	2.31 (1.90, 2.79)	NR
Padez (2006) (Portugal)	4 y: 15.7 6 y: 30.4 9 y: 32.8 11 y: 9.4 12+ y: 14.1	OR of obesity (vs: NR) for 12+, 11, 9 and 6 years vs 4 years of education.	Year of examination	NR	12+ y: 2.66 (2.65, 2.67) 11 y: 1.83 (1.82, 1.84) 9 y: 1.79 (1.78, 1.8) 6 y: 1.27 (1.26, 1.27) vs 4 y	NR

Reference	Definition of education and distribution (%)	Analysis outcome	Covariates	Association with obesity		
				Women Effect size (95% CI unless otherwise stated)	Men Effect size (95% CI unless otherwise stated)	Total Effect size (95% CI unless otherwise stated)
Marques-Vidal et al (2011) (Portugal)	Primary: 1995-6: 74.2; 1998-9: 69.0; 2005-6: 59.4 Secondary: 1995-6: 18.9; 1998-9: 22.7; 2005-6: 29.5 University: 1995-6: 6.9; 1998-9: 8.3; 2005-6: 11.1	OR of obesity (vs NR) for primary and secondary education vs University	Age and survey year	Primary: 3.80 (3.25, 4.43) Secondary: 1.76 (1.49, 2.09) vs University	Primary: 1.79 (1.57, 2.05) Secondary: 1.30 (1.13, 1.50) vs University	NR
Moreira & Padrao (2006) (Portugal)	≤4 y: F: 54.0; M: 49.7 5–9 y: F: 22.8; M: 28.7 10–12 y: F: 12.6; M: 13.2 >12 y: F: 10.6; M: 8.4	OR of obesity (vs NR) for >12, 10–12 and 5–9 years vs ≤4 years of education	Age, smoking habits and physical activity	>12 y: 0.19 (0.14, 0.27) 10–12 y: 0.25 (0.19, 0.33) 5–9 y: 0.56 (0.49, 0.66) vs ≤4 years of education	>12 y: 0.40 (0.30, 0.54) 10–12 y: 0.58 (0.46, 0.72) 5–9 y: 0.78 (0.68, 0.90) vs ≤4 years of education	NR
Roskam et al (2010) (Portugal)	Tertiary: NR Upper/post-secondary: NR Lower secondary: NR Primary/no education: 61.0	RII: PR of being obese at the lowest vs the highest educational category	Age	6.78 (4.55, 10.10)	2.02 (1.42, 2.87)	NR
Camoes et al (2010) (Portugal)	<5 y: n:NR 5–11 y: n:NR >11 y: n:NR	RR of developing obesity for 5–11 years of education and >11 y of education vs <5 y of education	Age, education, energy intake and physical activity	>11 y: 0.43 (0.22, 0.84) 5–11 y: 0.53 (0.29, 0.96) vs <5 y	>11 y: 0.61 (0.22, 1.66) 5–11 y: 0.93 (0.39, 2.19) vs <5 y	NR
Sardinha et al (2012) (Portugal)	≤4 y: F: 14.2; M: 10.8 5–9 y: F: 19.2; M: 24.8 10–12 y: F: 27.5; M: 30.6 College: F: 39.0; M: 33.8	OR of obesity vs normal weight for ≤4, 5–9 and 10–12 years of education vs college	Age for female/male sample; age and gender (for all sample)	≤4 y: 3.62 (2.65, 4.94) 5–9 y: 2.68 (2.00, 3.58) 10–12 y: 1.94 (1.45, 2.59) vs college	≤4 y: 1.97 (1.41, 2.74) 5–9 y: 1.96 (1.49, 2.58) 10–12 y: 1.22 (0.92, 1.63) vs college	≤4 y: 2.76 (2.20, 3.45) 5–9 y: 2.33 (1.91, 2.85) 10–12 y: 1.56 (1.27, 1.91) vs college
Gaio et al (2018) (Portugal)	No schooling/1st cycle of basic education: 27.6 2nd/ 3rd cycle of basic education: 31.6 Secondary school: 21.4 Higher education: 19.3	PR of obesity (vs healthy weight) for 2nd/3rd, secondary and higher vs no schooling	Age, marital status, occupation, living area and smoking status	Higher:0.36 (0.26, 0.49) Sec.: 0.60 (0.48, 0.76) 2nd/3rd: 0.81 (0.70, 0.93) vs no schooling/1st cycle	Higher: 0.54 (0.40, 0.73) Sec.: 0.90 (0.70, 1.16) 2nd/3rd: 0.91 (0.74, 1.11) vs no schooling/1st cycle	NR
Santos et al (2003) (Portugal)	≤4 y: NR 5–11 y: NR ≥12 y: NR	OR of obesity (vs non-obesity) for ≥12 and 5–11 y of education vs ≤4 y	Age, occupation, marital status, smoking, exercise, energy intake	≥12 y: 0.19 (0.10, 0.35) 5–11 y: 0.36 (0.23, 0.56) vs ≤4 y	≥12 y: 0.62 (0.29, 1.31) 5–11 y: 0.81 (0.44, 1.47) vs ≤4 y	NR
Aranceta et al (2001) (Spain)	Low: NR Medium: NR High: NR	OR of obesity (vs: non-obesity) for low and medium education vs High education	Age	Low: 1.80 (1.78, 1.81) Medium: 1.55 (1.54, 1.56) vs high	Low: 2.36 (2.29, 2.42) Medium: 1.02 (1.01, 1.04) vs high	NR

Reference	Definition of education and distribution (%)	Analysis outcome	Covariates	Association with obesity		
				Women Effect size (95% CI unless otherwise stated)	Men Effect size (95% CI unless otherwise stated)	Total Effect size (95% CI unless otherwise stated)
Martinez-Ros et al (2001) (Spain)	<Primary: NR Primary: NR Secondary: NR University: NR	OR of obesity (vs: NR) of University, secondary and primary vs <primary education	Age, employment situation and type of residence	University: 0.29 (0.12, 0.71) Secondary: 0.54 (0.29, 1.01) Primary: 0.88 (0.64, 1.21) <primary	University: 0.82 (0.49, 1.39) Secondary: 0.50 (0.29, 0.87) Primary: 1.07 (0.76, 1.52) vs <primary	NR
Gutierrez-Fisac et al (2002) (Spain)	1987 25–44 y Elementary: F: 56.6; M: 48.7 Secondary: F: 27.4; M: 31.1 Third level: F: 16.0; M: 20.3	PR of obesity (vs NR) of elementary and secondary vs third level	Age	Elementary: 4.53 (2.06, 9.95) Secondary: 2.52 (1.08, 5.89) vs third level	Elementary: 2.15 (1.47, 3.15) Secondary: 1.12 (0.72, 1.75) vs third level	NR
	1987 44–64 y Elementary: F: 87.9; M: 78.0 Secondary: F: 7.6; M: 11.2 Third level: F: 4.5; M: 10.8	PR of obesity (vs NR) of elementary and secondary vs third level	Age	Elementary: 2.42 (1.20, 4.86) Secondary: 1.12 (0.47, 2.63) vs third level	Elementary: 1.85 (1.18, 2.89) Secondary: 1.35 (0.77, 2.37) vs third level	NR
	1995/97 25–44 y Elementary: F: 49.1; M: 44.4 Secondary: F: 31.7; M: 36.3 Third level: F: 19.2; M: 19.2	PR of obesity (vs NR) of elementary and secondary vs third level	Age	Elementary: 5.73 (2.53, 12.99) Secondary: 2.82 (1.18, 6.75) vs third level	Elementary: 1.94 (1.23, 3.06) Secondary: 1.72 (1.07, 2.75) vs third level	NR
	1995/97 44–64 y Elementary: F: 56.6; M: 71.9 Secondary: F: 27.4; M: 17.5 Third level: F: 16.0; M: 10.7	PR of obesity (vs NR) of elementary and secondary vs third level	Age	Elementary: 3.47 (1.48, 8.17) Secondary: 0.95 (0.33, 2.73) vs third level	Elementary: 1.47 (0.95, 2.30) Secondary: 0.85 (0.49, 1.49) vs third level	NR
Devaux & Sassi (2013) (Spain)	NR	RII: OR of being obese at the lowest vs the highest educational category	Age, year of the survey, marital status, ethnicity, smoking, occupation	18 (95% CI: NR)	2.2 (95% CI: NR)	NR
Mataix et al (2005) (Spain)	University: F: 15.8; M: 21.7 Secondary: F: 21.7; M: 25.7 Primary/no schooling: F: 62.5; M: 52.6	OR of obesity (vs NR) for primary/no schooling and secondary school vs University	Gender, age, exercise, alcohol and smoking	NR	NR	Primary/no schooling: 2.45 (1.78, 3.39) Secondary: 1.77 (1.23, 2.55) vs University

Reference	Definition of education and distribution (%)	Analysis outcome	Covariates	Association with obesity		
				Women Effect size (95% CI unless otherwise stated)	Men Effect size (95% CI unless otherwise stated)	Total Effect size (95% CI unless otherwise stated)
Sotillo et al (2007) (Spain)	University: F: 10.8; M: 16.0 Secondary: F: 16.9; M: 18.9 Primary/ no schooling: F: 66.6; M: 65.1	OR of obesity (vs NR) for primary/no education and secondary education vs University	Gender, age, exercise, alcohol and smoking	NR	NR	Primary/ no schooling: 5.02 (1.05, 24.04) Secondary: 1.43 (0.24, 8.55) vs University
Roskam et al (2010) (Spain)	Tertiary: NR Upper/post-secondary: NR Lower secondary: NR Primary/no education: 11.6	RII: PR of being obese at the lowest vs the highest educational category	Age	5.09 (3.08, 8.44)	2.72 (1.88, 3.93)	NR
Soriguer et al (2004) (Spain)	No studies: NR Primary: NR Secondary: NR University: NR	OR of obesity (vs non-obese) for no studies, primary and secondary vs University	Age, gender, alcohol intake, smoking and physical activity	NR	NR	No studies: 3.8 (0.31, 2.35) Primary: 3.0 (0.13, 2.05) Secondary: 2.3 (0.23, 1.93) vs University
Perez-Hernandez et al (2017) (Spain)	Primary or less: 58 Secondary: 23.3 University: 18.8	OR of obesity (vs NR) for University and secondary education vs primary education or less	Age (for total sample also for gender)	University: 0.28 (0.18, 0.45) Secondary: 0.40 (0.27, 0.59) vs ≤primary education	University: 0.60 (0.43, 0.83) Secondary: 0.84 (0.60, 1.18) vs ≤primary education	University: 0.44 (0.33, 0.57) Secondary: 0.58 (0.45, 0.75) vs ≤primary education
Lopez-Sobaler et al (2016) (Spain)	Primary or less: 26.8 Secondary: 48.9 University: 24.3	OR of obesity (vs healthy weight) for University and secondary education vs primary or less	Gender, age, region, income, employment, smoking, exercise, television watching, sleep	NR	NR	University: 0.41 (0.25, 0.65) Secondary: 0.56 (0.38, 0.81) vs ≤primary
Palomo et al (2014) (Spain)	University: F: 13.8; M: 10.7 Secondary: F: 19.7; M: 22.0 Primary: F: 51.9; M: 56.8 Illiterate: F: 14.6; 10.5	OR of obesity (vs NR) for non-University vs University graduates	Age and employment status	Non-university : 2.5 (1.5, 4.2) vs University	Non-University 1.5 (1.0 to 2.3) vs University	NR
Eastern Asia						
Asahara et al (2020) (Japan)	High: NR Low: NR	OR of obesity (vs normal weight) for low vs high education	Age	Low: 1.69 (1.29, 2.22) vs high	Low: 1.16 (0.96, 1.40) vs high	NR

Reference	Definition of education and distribution (%)	Analysis outcome	Covariates	Association with obesity		
				Women Effect size (95% CI unless otherwise stated)	Men Effect size (95% CI unless otherwise stated)	Total Effect size (95% CI unless otherwise stated)
Eastern Asia						
Yoon et al (2006) (South Korea)	Elementary (≤6 y): F: 38.00; M: 21.41 Middle/high (7–12 y): F: 45.61; M: 51.54 College or higher (≥13 y): F: 16.38; M: 27.05	OR of obesity (vs NR) for ≥13 y and 7–12 y of schooling vs ≤6 y of schooling	Age, residential area, marital status, smoking, alcohol intake, exercise, diet and income	≥13 y: 0.38 (0.27, 0.54) 7–12 y: 0.73 (0.58, 0.91) vs ≤6 y of schooling	≥13 y: 1.25 (0.89, 1.77) 7–12 y: 1.27 (0.95, 1.68) vs ≤6 y of schooling	NR
Devaux & Sassi (2013) (South Korea)	NR	RII: OR of being obese at the lowest vs the highest educational category	Age, year of the survey, marital status, ethnicity, smoking, occupation status	17 (95% CI: NR)	0.8 (95% CI: NR)	NR
So & Seo (2013) (South Korea)	≤Elementary school: F: 7.4; M: 7.0 Middle school: F: 9.6; M: 7.7 High school: F: 27.1; M: 25.5 ≥College: F: 55.8; M: 59.8	OR of obesity (vs health weight) for ≥college, high school and middle school vs ≤elementary school	Gender, age, lifestyle factors, economic status	NR	NR	≥College: 0.57 (0.33, 0.98) High school: 0.58 (0.36, 0.94) Middle school: 0.68 (0.39, 1.19) vs ≤elementary school
Chung et al (2017) (South Korea)	≤Elementary school: F: 32.0; M: 17.6 Junior high school: F: 10.3; M: 11.8 Senior high school: F: 31.7; M: 35.7 ≥College: F: 26.0; M: 34.9	OR of obesity (vs non-obese) for ≥college, junior and senior high school vs ≤elementary school	Age, marital status, residential area, occupation, health insurance, smoking, alcohol, exercise, sleep, diet, perceived health	≥College: 0.59 (0.46, 0.75) Senior high school: 0.89 (0.72, 1.09) Junior high school: 1.19 (0.98, 1.44) vs ≤elementary school	≥College: 1.41 (1.12, 1.77) Senior high school: 1.27 (1.03, 1.58) Junior high school: 1.41 (1.10, 1.82) vs ≤elementary school	NR
Chung & Kim (2020) (South Korea)	≤Elementary school: F: 57.5% M: 31.2% Middle/high school: F: 37.5% M: 51.1% ≥College: F: 5.0% M: 17.7%	OR of obesity (vs NR) for ≥college, middle/high school vs ≤elementary school	Age, marital status, rural/urban area, religion, occupation, income, smoking, exercise	≥College: 0.33 (0.19, 0.56) Middle/high school: 0.63 (0.51, 0.78) vs ≤elementary school	≥College: 1.33 (0.96, 1.85) Middle/high school: 1.14 (0.90, 1.45) vs ≤elementary school	NR
Western Asia						
Martorell et al (2000) (Turkey)	Low: NR High: NR	OR of obesity (vs: NR) for low and medium education vs high education	Age	High: 0.46 (95% CI NR), P<0.001 vs. low	NR	NR
Erem et al (2004) (Turkey)	Illiterate: 12.26 Primary: 45.41 Secondary: 9.48 High school: 23.62 University: 9.23	OR of obesity (vs NR) for university, high school, secondary school and primary school vs illiterate.	Age, gender, history of obesity, exercise, alcohol, smoking, marital status, income and occupation	NR	NR	University: 0.33 (0.20, 0.54) High school: 0.40 (0.28, 0.57) Secondary: 0.64 (0.44, 0.92) Primary: 0.70 (0.54, 0.91) vs illiterate

Reference	Definition of education and distribution (%)	Analysis outcome	Covariates	Association with obesity		
				Women Effect size (95% CI unless otherwise stated)	Men Effect size (95% CI unless otherwise stated)	Total Effect size (95% CI unless otherwise stated)
Dursun et al (2018) (Turkey)	NR	Ordinary least squares estimates (SE): the propensity to be obese for having a middle school diploma (vs primary education or no education)	Year of birth, survey year, residence	-0.051 (0.008), p<0.001	0.014 (0.010), not significant	NR
Bayram et al (2019) (Turkey)	<High school: 55.10 ≥High school: 44.90	OR of obesity (vs NR) for <high school vs ≥high-school	Age, income, marital status, occupation and living arrangement	<High school: 9.67 (5.63, 16.61) vs ≥High school	NR	NR
Kilicarslan et al (2006) (Turkey)	University: 44.6 High school: 26.2 Primary school: 29.2	OR of obesity (vs normal weight) for primary and high school vs University	Reporting not clear	Primary: 1.41 (1.41, 9.11) High school: 1.17 (0.50, 2.73) vs University	NR	NR
Northern America						
Huot et al (2004) (Canada)	Elementary school: NR High school: NR College: NR University: NR	OR of obesity (vs NR) for University, college and high school vs elementary school	Income, diet, age, language spoken, smoking, physical activity, residential area	University: 0.39 (0.25, 0.61) College: 0.81 (0.62, 1.05) High school: 0.85 (0.67, 1.07) vs. elementary school	University: 0.63 (0.43, 0.92) College: 0.83 (0.63, 1.10) High school: 0.89 (0.70, 1.15) vs. elementary school	NR
Kaplan et al (2003)	NR	OR of obesity (vs: NR) for ≤secondary vs >secondary	Age, marital status, place of birth, smoking, alcohol, physical activity	≤secondary: 1.48 (1.24, 1.76) vs >secondary	≤secondary: 2.17 (1.80, 2.63) vs >secondary	≤secondary: 1.73 (1.53, 1.96) vs >secondary
Devaux & Sassi (2013) (Canada)	NR	RII: OR of being obese at the lowest vs the highest educational category	Age, year of the survey, marital status, ethnicity, smoking, occupation status	2.2 (95% CI: NR)	1.6 (95% CI: NR)	NR
Ng et al (2011) (Canada)	Aboriginals: ≥High School Graduation (%): F: 61.8; M: 49.0	Multivariable logistic regression: estimates predicting obesity for high school graduate or not	Age, lifestyle, SES	0.495 (SE: 0.18), p=0.005	-0.738 (SE: 0.31), p=0.019	NR
Ng et al (2011) (Canada)	Non-aboriginals: ≥High School Graduation (%): F: 66.4; M: 68.5	Multivariable logistic regression: estimates predicting obesity for high school graduate or not	Age, lifestyle, SES	-0.316 (SE:0.14), p=0.024	-0.532 (SE: 0.17), p=0.001	NR

Reference	Definition of education and distribution (%)	Analysis outcome	Covariates	Association with obesity		
				Women Effect size (95% CI unless otherwise stated)	**Men** Effect size (95% CI unless otherwise stated)	**Total** Effect size (95% CI unless otherwise stated)
Yu (2016) (USA)	<high school: NR High school: NR Some college: NR At least 4-year college: NR	Linear probability models: probability of obesity for <high school, high school and some college versus ≤4 year college	Age, gender, race, survey year	NR	NR	<high school: 0.0826 (SE: 0.0110), p<0.05 High school: 0.0540 (SE: 0.0108), p<0.05 Some college: 0.0130 (SE: 0.0135) vs ≤4 year college
Kim (2016) (USA)	High school: 51 Some college: 17 ≥ college: 31	The probability of being obese of some college and college or higher compared to high school	Age, age squared, gender, birth order, IQ scores and parental income	NR	NR	≥ college: -0.060 (0.015), p<0.05 Some college: -0.011 (0.011), not sig vs high school
Martorell et al (2000) (USA)	Low: NR High: NR	OR of obesity (vs: NR) for low and medium education vs high education	Age	High: 1.15 (95% CI NR), P=not significant vs. low	NR	NR
Zhang & Wang (2004) (USA)	1971–1974 Low (<high school): 17.4 Medium (high school): 49.7 High (≥college): 33.0	OR of obesity (vs NR) of low and high education vs medium	Age	Low: White: 1.40 (1.03, 1.91); Black: 1.96 (1.06, 3.61) vs medium High: White: 0.45 (0.31, 0.65); Black: 0.89 (0.43, 1.84) vs medium	Low: White: 0.66 (0.39, 1.12); Black: 0.38 (0.13, 1.07) vs medium High: White: 0.53 (0.36, 0.78); Black: 0.24 (0.05, 1.26) vs medium	NR
	1976–1980 Low (<high school): 11.6 Medium (high school): 50.6 High (≥college): 37.9	OR of obesity (vs NR) of low and high education vs medium	Age	Low: White: 1.67 (1.28, 2.18); Black: 1.34 (0.70, 2.55) vs medium High: White: 0.51 (0.38, 0.69); Black: 0.64 (0.39, 1.07) vs medium	Low: White: 0.83 (0.51, 1.32); Black: 0.56 (0.29, 1.60) vs medium High: White: 0.62 (0.48, 0.82); Black: 0.61 (0.25, 1.46) vs medium	NR
	1988–1994 Low (<high school): 11.8 Medium (high school): 43.3 High (≥college): 44.9	OR of obesity (vs NR) of low and high education vs medium	Age	Low: White: 0.93 (0.60, 1.46); Black: 0.98 (0.71, 1.34) vs medium High: White: 0.58 (0.43, 1.78); Black: 0.69 (0.53, 0.91) vs medium	Low: White: 1.50 (0.93, 2.41); Black: 0.99 (0.66, 1.49) vs medium High: White: 0.78 (0.56, 1.09); Black: 1.15 (0.88, 1.50) vs medium	NR

Reference	Definition of education and distribution (%)	Analysis outcome	Covariates	Association with obesity		
				Women Effect size (95% CI unless otherwise stated)	Men Effect size (95% CI unless otherwise stated)	Total Effect size (95% CI unless otherwise stated)
Zhang & Wang (2004) (USA)	1999–2000 Low (<high school): 21.5 Medium (high school): 25.7 High (≥college): 52.9	OR of obesity (vs NR) of low and high education vs medium	Age	Low: White: 1.15 (0.68, 1.94); Black: 0.64 (0.27, 1.51) vs medium High: White: 0.78 (0.51, 1.19); Black: 0.92 (0.54, 1.56) vs medium	Low: White: 0.91 (0.50, 1.65); Black: 1.65 (0.70, 3.91) vs medium High: White: 0.78 (0.49, 1.24); Black: 1.12 (0.42, 3.01)vs medium	NR
Devaux & Sassi (2013) (USA)	NR	RII: OR of being obese at the lowest vs the highest educational category	Age, year of the survey, marital status, ethnicity, smoking, occupation	1.6 (95% CI: NR)	1.0 (95% CI: NR)	NR
Taira et al (2004) (USA)	<8th grade: 5.8 Some high school: 5.5 High school: 26.3 Some college: 28.4 College: 19.5 Post graduate: 14.5	OR of obesity (vs non-obese) of postgraduate, college, some college, high school and some high school vs <8th grade	Age, gender, ethnicity, type of insurance	NR	NR	Postgraduate: 0.82 (0.71, 0.94) College: 0.86 (0.75, 0.99) Some college: 1.2 (1.1, 1.4) High school: 1.3 (1.1, 1.4) Some high school: 1.1 (0.95, 1.3) vs <8th grade
Salsberry et al (2009) (USA)	<12 y: M-A: 19; W: 6; A-A: 10 12 y: M-A: 38; W: 41; A-A: 42 >12 y: M-A: 43; W: 53; A-A: 48	OR of obesity (vs: NR) for <12 y and 12 y vs >12 y of education	Age	<12 y: M-A: 0.36 (0.18,0.70); W: 1.43 (0.91,2.24); A-A: 1.42 (0.93,2.21) 12 y: M-A: 0.84 (0.51,1.39); W: 1.04 (0.83,1.32); A-A: 0.92 (0.70,1.19) vs >12 y	NR	NR
Borders et al (2006) (USA)	<High school: 15.18 High school: 27.27 Some college: 27.35 College graduate: 30.20	OR of obesity (vs healthy weight) for college graduates, some college, and high school vs <high school	Demographic, social, behavioural, and psychological covariates	College graduate: 0.69 (0.45, 1.04) Some college: 1.24 (0.84, 1.82) High school: 1.24 (0.85, 1.79) vs <high school	College graduate: 0.57 (0.32, 1.00) Some college: 1.18 (0.66, 2.08) High school: 1.28 (0.74, 2.21) vs <high school	NR

Reference	Definition of education and distribution (%)	Analysis outcome	Covariates	Association with obesity		
				Women Effect size (95% CI unless otherwise stated)	Men Effect size (95% CI unless otherwise stated)	Total Effect size (95% CI unless otherwise stated)
Wen et al (2018) (USA)	<High school: 16.63 High school: 25.02 Some college: 32.27 ≥Bachelor degree: 26.03	OR of obesity (vs non-obese) of ≥Bachelor degree, some college and high school vs less than high school	Age, gender, ethnicity, income, neighbourhood	NR	NR	≥Bachelor degree: 0.84 (95% CI: NR), P< .01 Some college: 1.15 (95% CI: NR), P< .05 High school: 1.13 (95% CI: NR), P< .05 vs <high school
Cohen et al (2013) (USA)	<High school (<HS) at 25 y: 9.5 High school graduates (HS) at 25 y: 66.4 College graduates (CG) at 25 y: 24.1	Generalized linear modelling with the log linear link function: RR of obesity at 40 or 41 for different educations among Blacks, Hispanics and Whites	Gender, ethnicity, maternal and paternal education, urban/rural residence as child and adult, speaking a foreign language as a child, income, family size	NR	NR	Black CG vs HS: 1.09 (0.87, 1.36) CG vs <HS: 1.31 (0.96, 1.77) HS vs <HS: 1.20 (0.96, 1.50) Hispanic CG vs HS: 0.70 (0.42, 1.17) CG vs <HS: 0.74 (0.42, 1.30) HS vs <HS: 1.07 (0.82, 1.40) White CG vs HS: 0.69 (0.57, 0.83) CG vs <HS: 0.85 (0.63, 1.14) HS vs <HS: 1.22 (0.97, 1.55)
Coogan et al (2012) (USA)	≤High school: 44.9 Some college: 26.9 College graduate: 28.3	RR of obesity in 2009 for ≤HS and SC versus CG	Age, childhood factors and adult factors; lifestyle factors	≤HS: 1.67 (1.50, 1.87) SC: 1.49 (1.39, 1.59) vs CG	NR	NR
von Hippel & Lynch (2014) (USA)	<High school: F: 8; M: 11 High school diploma: F: 56; M: 63 Associate's degree: F: 6; M: 4 Bachelor's degree: F: 22; M: 17 Graduate degree: F: 8; M: 5	OR (SD) of obesity (vs NR) at age 29 for graduate, bachelor degree and high school vs <high school	Age (and pregnancy for females)	Graduate: 0.82 (0.11) Bachelor: 0.73 (0.16) Associate: 0.44 (0.06) High school: 0.35 (0.08) vs <High school	Graduate: 0.94 (0.12) Bachelor: 0.96 (0.20) Associate: 0.60 (0.09) High school: 0.53 (0.12) vs <High school	NR
Beltran-Sanchez et al (2016) (USA)	Mexican Foreign-born Low: 51.4 Medium: 35.5 High: 13.1	Coefficient estimates from logistic models	Age, gender	NR	NR	High: -0.10, not sign Medium: -0.13, not sign vs low education
Beltran-Sanchez et al (2016) (USA)	US-born Mexican American Low: 35.7 Medium: 22.7 High: 41.6	Coefficient estimates from logistic models	Age, gender	NR	NR	High: -0.07, not sign Medium: -0.19, not sign vs low education

Reference	Definition of education and distribution (%)	Analysis outcome	Covariates	Association with obesity		
				Women Effect size (95% CI unless otherwise stated)	Men Effect size (95% CI unless otherwise stated)	Total Effect size (95% CI unless otherwise stated)
Beltran-Sanchez et al (2016) (USA)	Non-Hispanic White Low: 16.9 Medium: 27.6 High: 55.5	Coefficient estimates from logistic models	Age, gender	NR	NR	High: -0.24, p<0.01 Medium: -0.10, not sign vs low education
Drewnowski et al (2014) (USA)	≤High school: 18 Some college: 25 ≥College: 57	Poisson regression: RR of obesity (vs non-obese) for ≥college and some college vs ≤high school	Age, gender, residential area, education, income, and neighbourhood residential property values	NR	NR	≥College: 0.73 (0.56, 0.95) Some college: 0.77 (0.58, 1.02) vs ≤high school
Hales et al (2018) (USA)	≤High school (≤HS): F: 42.40; M: 47.02 Some college (SC): F: 32.87; M: 27.39 College graduates (CG): F: 24.68; M: 25.51	PR of obesity for <HS, SC vs CG	Age, race, smoking, urbanization	≤HS: 1.47 (1.32, 1.64) SC: 1.42 (1.29, 1.57) vs CG	≤HS: 1.11 (0.95, 1.30) SC: 1.36 (1.17, 1.57) vs CG	NR
Qobadi & Payton (2017) (USA)	<High school (<HS): White: 15.1; Black: 24.4 High school (HS): White: 27.5; Black: 34.0 Some college (SC): White: 35.5; Black: 29.3 College graduate (CG): White: 21.8; Black: 12.3	OR of obesity (vs NR) for <HS, HS and SC vs CG	Gender, age, income, employment, physical activity	NR	NR	Black: <HS: 0.78 (0.46, 1.3) HS: 0.93 (0.59, 1.5) SC: 0.97 (0.62, 1.5) vs college White: <HS: 1.4 (0.8, 2.4) HS: 1.6 (1.1, 2.3) SC: 1.5 (1.2, 2.3) vs college
An (2015) (USA)	1984: Primary school and below: 6.96 Some high school: 10.93 High school graduate: 34.19 Some college: 25.90 College graduate and above: 22.02	RII: the difference in predicted values of obesity between the lowest and highest education level	Gender, age group, and race and/or ethnicity	NR	NR	-1.0544 (-1.339,-0.7698)
	2013: Primary school and below: 4.67 Some high school: 9.94 High school graduate: 28.60 Some college: 31.02 College graduate and above: 25.77	RII: the difference in predicted values of obesity between the lowest and highest education level	Gender, age group, and race and/or ethnicity	NR	NR	-0.5055 (-0.5386,-0.4725)
Bodea et al (2009) (USA)	<high school (<HS): 5.20 high school graduates (HS): 19.69 vocational/technical (V/T): 3.05 some college (SC): 18.21 University degree: 53.85	OR of obesity for <HS, HS, V/T, SC vs University degree	Gender, age, ethnicity, income, residential density	NR	NR	<HS: 1.64, p<0.001 (95% CI:NR) HS: 1.54, p<0.001 (95% CI:NR) V/T: 1.45, p<0.001 95% CI:NR) SC: 1.25, p<0.001 (95% CI:NR) vs University degree

Reference	Definition of education and distribution (%)	Analysis outcome	Covariates	Association with obesity		
				Women Effect size (95% CI unless otherwise stated)	Men Effect size (95% CI unless otherwise stated)	Total Effect size (95% CI unless otherwise stated)
Central America						
Martorell et al (2000) (Mexico)	Low: NR High: NR	OR of obesity (vs: NR) for low and medium education vs High education	Age	High: 0.59 (95% CI NR), P<0.001 vs. low	NR	NR
Buttenheim, 2010 (Mexico)	Illiterate: 7 1–5y: 22 6–8y: 25 9–11y: 24 12+y: 22	OR of obesity (vs NR) for 12+, 9–11y, 6–8y and 1–5y vs illiterate	Age, household asset ownership	12+: U: 0.54 (0.41, 0.69); R: 0.72 (0.53, 0.96) 9–11y: U: 0.64 (0.51, 0.82); R: 0.99 (0.75, 1.31) 6–8y: U: 0.87 (0.70, 1.09); R: 1.30 (1.05, 1.61) 1–5y: U: 1.00 (0.78, 1.27); R: 1.38 (1.15, 1.66) vs illiterate	12+: U: 0.83 (0.49, 1.42); R: 1.26 (0.79, 2.02) 9–11y: U: 0.78 (0.46–1.32); R: 0.96 (0.59, 1.57) 6–8y: U: 0.94 (0.56, 1.60); R: 1.03 (0.68, 1.55) 1–5y: U: 0.84 (0.48, 1.45); R: 1.12 (0.78, 1.60) vs illiterate	NR
Beltran-Sanchez et al (2011) (Mexico)	0 y: 12.6 1–6 y: 42.2 7–9 y: 24.1 10–12 y: 10.3 13+ y: 10.5	OR of obesity (vs NR) for 0, 1–6, 10–12 and 13+ years vs 7–9 years of education	Age and early life experiences (toilet at 12, born in city, stunted)	0 y: 1.09 (95% CI: NR) 1–6 y: 1.34 (95% CI: NR), p<0.01 10–12 y: 0.61 (95% CI: NR), p<0.01 13+ y: 0.49 (95% CI: NR), p<0.001 vs 7–9 y	0 y: 0.54 (95% CI: NR), p<0.001 1–6 y: 0.75 (95% CI: NR), p<0.05 10–12 y: 0.97 (95% CI: NR) 13+ y: 0.72 (95% CI: NR) vs 7–9 y	NR
Beltran-Sanchez et al (2016) (Mexico)	Low: 61.1 Medium: 24.8 High: 14.1	Coefficient estimates from logistic models	Age, gender	NR	NR	High: -0.18, p<0.05 Medium: –0.01, not sig vs low education
Perez Ferrer et al (2014) (Mexico)	1988 Higher education: Urban (U): 10.2 (0.6); Rural (R): 2.2 (0.6) High school: U: 17.4 (0.7); R: 8.4 (1.6) Secondary: U: 17.0 (0.6); R: 9.4 (1.4) Primary or less: U: 55.4 (1.3); R: 79.9 (3.2)	RII: the prevalence ratio between the two ends of the educational hierarchy (the lowest vs the highest) – obesity prevalence at the bottom divided by obesity prevalence at the top	Age	U: 2.87 (1.94, 4.25) R: 1.16 (0.34, 3.98)	NR	NR
	1999 Higher education: U: 14.6 (0.6); R: 1.8 (0.3) High school: U: 20.5 (0.6); R: 5.8 (0.6) Secondary: U: 24.3 (0.6); R: 13.7 (0.8) Primary or less: U: 40.6 (0.8); R: 78.8 (1.2)	RII: the prevalence ratio between the two ends of the educational hierarchy (the lowest vs the highest) – obesity prevalence at the bottom divided by obesity prevalence at the top	Age	U: 2.22 (1.86, 2.66) R: 0.93 (0.66, 1.32)	NR	NR

Reference	Definition of education and distribution (%)	Analysis outcome	Covariates	Association with obesity		
				Women Effect size (95% CI unless otherwise stated)	Men Effect size (95% CI unless otherwise stated)	Total Effect size (95% CI unless otherwise stated)
Perez Ferrer et al (2014) (Mexico)	2006 Higher education: U: 16.2 (0.8); R: 2.4 (0.4) High school: U: 20.8 (0.7); R: 5.6 (0.7) Secondary: U: 28.8 (0.8); R: 24.6 (1.2) Primary or less: U:34.4 (0.9); R: 67.5 (1.3)	RII: the prevalence ratio between the two ends of the educational hierarchy (the lowest vs the highest) – obesity prevalence at the bottom divided by obesity prevalence at the top	Age	U: 1.71 (1.45, 2.00) R: 0.90 (0.65, 1.24)	NR	NR
	2012 Higher education: U: 22.6 (0.8); R: 6.5 (0.7) High school: U: 22.7 (0.7); R: 13.0 (0.8) Secondary: U: 31.2 (0.8); R: 33.9 (1.3) Primary or less: U: 23.4 (0.8); R: 46.6 (1.4)	RII: the prevalence ratio between the two ends of the educational hierarchy – obesity prevalence at the bottom divided by obesity prevalence at the top	Age	U: 1.55 (1.33, 1.80) R: 1.13 (0.89, 1.44)	NR	NR
Andrade & Lopez-Ortega (2017) (Mexico)	No education: 18.1 Primary incomplete: 29.9 Primary + secondary: 40.8 College or more: 11.2	Multivariable poisson regression: RR of obesity (vs :NR) for no, primary and secondary education vs college or more	Gender, age, residence, insurance	NR	NR	No education: 0.90 (0.76, 1.06) Primary incomplete: 1.09 (0.94, 1.26) Primary + secondary: 1.00 (0.87, 1.15) vs college or more
Oceania						
Lawlor et al (2005) (Australia)	18–23 y: No formal qualification: 3.0 School-certificate only: 67.8 Post-school certificate/diploma: 18.2 University degree: 11.0	RII: OR of being obese comparing most with least advantaged	Age	0.58 (0.42, 0.80)	NR	NR
	45–50 y: No formal qualification: 18.3 School-certificate only: 48.6 Post-school certificate/diploma: 19.1 University degree: 14.0	RII: OR of being obese comparing most with least advantaged	Age	0.34 (0.30, 0.43)	NR	NR
	70–75 y: No formal qualification: 34.8 School-certificate only: 50.6 Post-school certificate/diploma: 11.0 University degree: 3.6	RII: OR of being obese comparing most with least advantaged	Age	0.50 (0.40, 0.61)	NR	NR

Reference	Definition of education and distribution (%)	Analysis outcome	Covariates	Association with obesity		
				Women Effect size (95% CI unless otherwise stated)	Men Effect size (95% CI unless otherwise stated)	Total Effect size (95% CI unless otherwise stated)
Cameron et al (2003) (Australia)	University/further education: F: 32.70; M: 41.81 High school (HS): F: 19.52; M: 18.03 Some high school (SHS): F: 40.87; M: 33.89 ≤Primary school (PS): F: 6.90; M: 6.18	OR of obesity (vs NR) for PS, SHS and HS vs University/further education	Age, smoking, physical activity, television viewing, country of birth, income, occupation	PS: 2.12 (1.18, 3.80) SHS: 1.48 (1.19, 1.83) HS: 1.04 (0.77, 1.40) vs University/further education	PS: 2.40 (1.59, 3.61) SHS: 2.19 (1.6, 3.01) HS: 1.14 (0.92, 1.42) vs University/further education	NR
Brown & Siahpush (2007) (Australia)	Tertiary (T): F: 26.0; M: 26.8 Vocational (V): F: 19.2; M: 30.6 Post-school qual. (P): F: 3.4; M: 1.8 Secondary (S): F: 11.6; M: 11.5 <Secondary (<S): F: 39.7; M: 29.4	RR of the likelihood of being obese (vs healthy weight) for <secondary, secondary and vocational vs tertiary education	Age, country of birth, marital status, residential area, exercise, smoking, occupation, income, and index of SES disadvantage	<S: 1.40 (1.18, 1.67) S: 1.10 (0.87, 1.40) P: 1.24 (0.88, 1.75) V: 1.26 (1.04, 1.52) vs tertiary	<S: 2.12 (1.71, 2.64) S: 1.48 (1.13, 1.94) P: 2.44 (1.43, 4.15) V: 1.92 (1.56, 2.37) vs tertiary	NR
Devaux & Sassi (2013)	NR	RII: OR of being obese at the lowest vs the highest educational category	Age, year of the survey, marital status, ethnicity, smoking, occupation	1.9 (95% CI: NR)	1.6 (95% CI: NR)	NR

CI, confidence interval; F, female; M, male; NR, not reported; OR, odds ratio; PR, prevalence ratio; RII, relative index of inequality; RR, risk ratio; SD, standard deviation; vs, versus; y, years.

Table S4: Results of the association between education and central obesity defined by WC>102 cm for men and WC>88cm for women WC (compared to normal weight if reported)

Reference	Education measurement	Analysis outcome	Covariates	Association with obesity		
				Women **Effect size (95% CI unless otherwise stated)**	**Men** **Effect size (95% CI unless otherwise stated)**	**Total** **Effect size (95% CI unless otherwise stated)**
Eastern Europe						
Rurik et al (2014) (Hungary)	Under (not competed primary school): NR Primary (completed elementary school): NR secondary (graduated of secondary school/skilled worker qualification): NR Higher (College or University degree): NR	Univariable logistic regression: OR of abdominal obesity (vs NR) for under primary, secondary and higher education vs primary education	NR	Under: 1.02 (0.89, 1.16) Secondary: 0.57 (0.53, 0.61) Higher: 0.38 (0.35, 0.42) vs primary	Under: 0.94 (0.78, 1.14) Secondary: 0.99 (0.91, 1.07) Higher: 0.81 (0.72, 0.89) vs primary	NR
Northern Europe						
Nielsen et al (2006) (Denmark)	<12 years: 53.77 ≥12 years: 43.93	Multiple logistic regression: OR of abdominal obesity (vs NR) defined by WC for <12 vs ≥12 years of education	Occupation, partner status; smoking; musculoskeletal complaints; fatherhood; chronic disease; unemployment; alcohol intake; age; asthma	NR	<12 y: 1.0 (0.6, 1.8) vs ≥12 y	NR
Western Europe						
Czernichow et al (2004) (France)	Primary: F: 22.8; M: 20.9 Secondary: F: 42.3; M: 33.4 University: F: 34.9; M: 37.0	Multivariable logistic regression analysis: OR of abdominal obesity (vs NR) for University and secondary school vs primary school	Age	University: 1.15 (0.77, 1.72) Secondary: 0.94 (0.65, 1.37) vs primary education	University: 0.81 (0.56, 1.16) Secondary: 1.07 (0.75, 1.53) vs primary education	NR
Marques-Vidal et al (2008) (Switzerland)	Basic: NR Apprenticeship (A): NR High school (HS): NR University (U): NR	Multivariable analysis: OR of abdominal obesity for apprenticeship, high school, University vs basic education	Age, smoking, physical activity	U: 0.38 (0.29, 0.50) HS: 0.48 (0.38, 0.60) A: 0.69 (0.57, 0.84) vs basic education	U: 0.70 (0.51, 0.96) HS: 1.07 (0.81, 1.42) A: 1.18 (0.92, 1.52) vs basic education	NR
Stringhini et al (2012) (Switzerland)	Tertiary: F: 16.5; M: 24.0 Post-secondary/secondary: F: 25.7; M: 23.2 <secondary: F: 57.8; M: 52.8	Log binomial regression: RII: prevalence ratio of abdominal obesity between the lowest vs the highest ends of the educational hierarchy	Age, place of birth	2.60 (2.06, 3.27)	1.48 (1.17, 1.87)	NR

Reference	Education measurement	Analysis outcome	Covariates	Association with obesity		
				Women Effect size (95% CI unless otherwise stated)	Men Effect size (95% CI unless otherwise stated)	Total Effect size (95% CI unless otherwise stated)
Ogna et al (2014) (Switzerland)	Primary: 15.6 Secondary: 44.1 Tertiary: 40.3	Multivariable logistic regression of abdominal obesity (vs NR) for tertiary and secondary education vs primary education	Age, gender, language, country of birth, smoking, exercise	NR	NR	Tertiary: 0.76 (0.53, 1.09) Secondary:1.04 (0.73, 1.48) vs primary education
Southern Europe						
Tzotzas et al (2010) (Greece)	Illiterate: 4.3 Primary school: 26.1 High school: 45.6 University: 24.0	Multinomial regression: OR of abdominal obesity vs healthy weight of primary school, high school and University education vs no education	Age	University: 0.92 (0.72,1.18) High school: 0.79 (0.63, 1.00) Primary: 0.92 (0.72,1.17) vs no education	University: 0.97 (0.74, 1.27) High school: 0.98 (0.75, 1.28) Primary: 0.98 (0.74, 1.28) vs no education	University: 0.99 (0.82, 1.19) High school: 0.98 (0.81, 1.17) Primary: 0.97 (0.81, 1.17) vs no education
Camoes et al (2010) (Portugal)	<5 y: n:NR 5–11 y: n:NR >11 y: n:NR	RR of developing abdominal obesity for 5–11 years of education and >11 y of education vs <5 y of education	Age, education, energy intake and physical activity	>11 y: 0.45 (0.29, 0.69) 5–11 y: 0.79 (0.54, 1.14) vs <5 y	>11 y: 1.31 (0.22, 1.66) 5–11 y: 1.18 (0.39, 2.19) vs <5 y	NR
Sardinha et al (2012) (Portugal)	≤4 y: F: 14.2; M: 10.8 5–9 y: F: 19.2; M: 24.8 10–12 y: F: 27.5; M: 30.6 College: F: 39.0; M: 33.8	Binary logistic regression: OR of abdominal obesity vs normal weight for ≤4, 5–9 and 10–12 years of education vs college	Age (and gender for total sample)	≤4 y: 3.31 (2.59, 4.23) 5–9 y: 2.24 (1.81, 2.78) 10–12 y: 1.67 (1.36, 2.05) vs college	≤4 y: 1.59 (1.14, 2.22) 5–9 y: 1.60 (1.22, 2.11) 10–12 y: 1.02 (0.76, 1.36) vs college	≤4 y: 5.48 (4.60, 6.52) 5–9 y: 2.40 (2.05, 3.82) 10–12 y: 1.33 (1.13, 1.56) vs college
Mataix et al (2005) (Spain)	University: F: 15.8; M: 21.7 Secondary: F: 21.7; M: 25.7 Primary/no schooling: F: 62.5; M: 52.7	Multiple logistic regression analysis: OR of abdominal obesity (vs NR) for primary/no schooling and secondary school vs University	Gender, age, physical exercise, alcohol and smoking	NR	NR	Primary/no schooling: 1.67 (1.27, 2.19) Secondary: 1.09 (0.79, 1.51) vs University
Sotillo et al (2007) (Spain)	University: F: 10.8; M: 16.0 Secondary: F: 16.9; M: 18.9 Primary/ no schooling: F: 66.6; M: 65.1	Multiple logistic regression analysis: OR of abdominal obesity (vs NR) for primary/no education and secondary education vs University	Gender, age, physical exercise, alcohol and smoking	NR	NR	Primary/ no schooling: 3.88 (0.83, 18.24) Secondary: 2.26 (0.40, 12.72) vs University
Perez-Hernandez et al (2017) (Spain)	Primary or less: 58 Secondary: 23.3 University: 18.8	Logistic regression: OR of abdominal obesity (Vs?) for University and secondary education vs primary education or less	Age (for total sample also for gender)	University: 0.39 (0.27,0.55) Secondary: 0.38 (0.27, 0.54) vs primary education or less	University: 0.70 (0.51, 0.96) Secondary: 0.85 (0.62, 1.18) vs primary education or less	University: 0.53 (0.42, 0.68) Secondary: 0.57 (0.45, 0.73) vs primary education or less

Reference	Education measurement	Analysis outcome	Covariates	Association with obesity		
				Women Effect size (95% CI unless otherwise stated)	Men Effect size (95% CI unless otherwise stated)	Total Effect size (95% CI unless otherwise stated)
Eastern Asia						
Yoon et al (2006) (South-Korea)	Elementary (≤6 y): F: 38.0; M: 21.4 Middle/high (7–12 y): F: 45.6; M: 51.5 College or higher (≥13 y): F: 16.4; M: 27.1	Multivariable analysis: OR of abdominal obesity (vs NR) for ≥13 y and 7–12 y of schooling vs ≤6 y of schooling	Age, residential area, marital status, smoking, alcohol intake, exercise, diet and income	≥13 y: 0.35 (0.26, 0.49) 7–12 y: 0.65 (0.53, 0.81) vs ≤6 y of schooling	≥13 y: 1.32 (0.91, 1.90) 7–12 y: 1.39 (1.04, 1.85) vs ≤6 y of schooling	NR
Ko et al (2015) (South-Korea)	<7 y: F: 30.35; M: 15.31 7–9 y: F: 10.64; M: 12.09 10–12 y: F: 26.75; M: 29.42 >12 y: F: 32.26; M: 43.19	Generalized linear models: PR of abdominal obesity (vs NR) for >12 y, 10–12 y and 7–9 y vs <7 y of education	Age, residential area, marital status, occupation and income	>12 y: 0.40 (0.29, 0.56) 10–12 y: 0.60 (0.47, 0.76) 7–9 y: 0.91 (0.74, 1.11) vs <7 y of schooling	>12 y: 1.34 (0.98, 1.82) 10–12 y: 1.33 (1.00, 1.76) 7–9 y: 1.14 (0.84, 1.56) vs <7 y of schooling	NR
Central America						
Andrade & Lopez-Ortega (2017) (Mexico)	No education: 18.1% Primary incomplete: 29.9% Primary + secondary: 40.8% College or more: 11.2%	Multivariable poisson regression: RR of abdominal obesity (vs: NR) for no, primary and secondary education vs college or more	Gender, age, residence, insurance	NR	NR	No education: 0.91 (0.87, 0.95) Primary incomplete: 0.95 (0.91, 0.99) Primary + secondary: 0.97 (0.93, 1.01) vs college or more
Oceania						
Cameron et al (2003) (Australia)	University/further education: F: 32.67; M: 41.85 High school (HS): F: 19.50; M: 18.06 Some high school (SHS): F: 40.94; M: 33.79 ≤Primary school (PS): F: 6.86; M: 6.22	Logistic regression: OR of abdominal obesity for PS, SHS and HS vs University/further education	Age, smoking, physical activity, television viewing, country of birth, income, occupation	PS: 2.68 (1.64, 4.36) SHS: 1.47 (1.19, 1.82) HS: 1.31 (1.01, 1.70) vs University/further education	PS: 2.31 (1.69, 3.15) SHS: 1.65 (1.17, 2.33) HS: 0.93 (0.69, 1.27) vs University/further education	NR

CI, confidence interval; F, female; M, male; NR, not reported; OR, odds ratio; PR, prevalence ratio; RII, relative index of inequality; RR, risk ratio; SD, standard deviation; vs, versus; y, years.

Table S5: Meta-regression of a subset of studies reporting on RII and OR for regional differences of the association between education and obesity

Meta-regression	Studies that report RII	Studies that report category comparison
	OR (95% CI) (number of studies, data points*)	OR (95% CI) (number of studies, data points*)
Northern vs Eastern Europe in women	0.81 (0.45, 1.44) I^2=32.36% (1 study, 12 data points)	0.75 (0.42, 1.31) I^2= 56.48% (11 studies, 11 data points)
Western vs Eastern Europe in women	1.65 (0.91, 3.00) I^2=31.18% (3 studies, 9 data points)	1.05 (0.48, 2.29) I^2=82.85% (10 studies, 10 data points)
Southern vs Eastern Europe in women	Insufficient observations	1.30 (0.43, 3.92) I^2=95.99% (9 studies, 9 data points)
Northern vs Western Europe in women	0.50 (0.36, 0.68) I^2=31.42% (3 studies, 15 data points)	0.72 (0.52, 1.00) I^2=74.75% (19 studies, 19 data points)
Northern vs Southern Europe in women	0.37 (0.27, 0.51) I^2=20.31% (1 study, 12 data points)	0.59 (0.40, 0.88) I^2=91.81% (18 studies, 18 data points)
Southern vs Western Europe in women	1.33 (0.95, 1.86) I^2=11.82% (3 studies, 9 data points)	1.22 (0.78, 1.89) I^2=93.22% (17 studies, 17 data points)
Northern vs Eastern Europe in men	1.00 (0.41, 2.42) I^2=67.83% (1 study, 12 data points)	1.06 (0.64, 1.75) I^2=45.21% (11 studies, 11 data points)
Western vs Eastern Europe in men	1.59 (0.89, 2.81) I^2=27.88% (3 studies, 9 data points)	1.05 (0.31, 3.55) I^2=98.01% (10 studies, 10 data points)
Eastern vs Southern Europe in men	Insufficient observations	1.20 (0.68, 2.13) I^2=84.49% (9 studies, 9 data points)
Northern vs Western Europe in men	0.70 (0.42, 1.16) I^2=64.57% (3 studies, 15 data points)	1.00 (0.65, 1.55) I^2=95.93% (19 studies, 19 data points)
Northern vs Southern Europe in men	0.77 (0.40, 1.51) I^2=67.05% (1 study, 12 data points)	0.88 (0.66, 1.16) I^2=74.00% (18 studies, 18 data points)
Southern vs Western Europe in men	0.91 (0.67, 1.22) I^2= 21.96% (3 studies, 9 data points)	1.12 (0.71, 1.76) I^2=96.64% (17 studies, 17 data points)

RII, relative index of inequality; OR, odds ratio; CI, confidence interval; I^2, measure of heterogeneity. *Some studies report on multiple countries or ethnicities, and therefore have multiple data points.

Table S6: Quality assessment – QUIPS tool

Reference	QUIPS Quality Assessment (high/moderate/low risk of bias)						Height/weight/WC measured by trained personnel (M) or self-reported (SR)
	Study population	Attrition / response rate	Prognostic factor measurement	Outcome measurement	Confounding	Statistical analysis	
An (2015)	Low	Moderate	Low	Moderate	Low	Low	SR
Andrade & Lopez-Ortega (2017)	Low	Moderate	Low	Low	Low	Moderate	M
Asahara et al (2020)	Low	Low	Low	Moderate	Moderate	Low	SR
Bayram et al (2019)	Moderate	High	Moderate	Low	Low	Moderate	M
Beltran-Sanchez et al (2011)	Low	Low	Low	Low	Low	Moderate	M
Bodea et al (2009)	Moderate	High	Low	Moderate	Low	Low	SR
Borders et al (2006)	Low	Moderate	Low	Moderate	Low	Low	SR
Brown & Siahpush (2007)	Low	Low	Low	Low	Low	Low	M
Buttenheim et al (2010)	Low	Low	Low	Low	Low	Moderate	M
Cameron et al (2003)	Low	Low	Low	Low	Low	Moderate	M
Camoes et al (2010)	Moderate	Moderate	Moderate	Low	Low	Low	M
Charafeddine et al (2009)	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	SR
Chung et al (2017)	Low	Moderate	Low	Low	Low	Low	M
Chung & Kim (2020)	Low	Low	Low	Moderate	Low	Moderate	SR
Cohen et al (2013)	Low	Low	Low	Low	Low	Low	SR
Coogan et al (2012)	Low	Low	Low	Moderate	Low	Low	SR
Czernichow et al (2004)	Low	Moderate	Low	Low	Moderate	Moderate	M
Devaux & Sassi (2013)	Moderate	Moderate	Low	Moderate	Low	Moderate	SR
Drewnowski et al (2014)	Low	High	Low	Moderate	Moderate	Low	SR
Dursun et al (2018)	Moderate	Moderate	Moderate	Moderate	Low	Moderate	SR
Erem et al (2004)	Low	Moderate	Low	Low	Low	Moderate	M
Faeh et al (2011)	Low	Low	Low	Moderate	Low	Low	SR
Gaio et al (2018)	Low	Low	Low	Low	Low	Low	M
Groth et al (2009)	Low	Moderate	Low	Moderate	High	Moderate	SR
Gutierrez-Fisac et al (2002)	Moderate	Low	Low	Moderate	Moderate	Moderate	SR
Hales et al (2018)	Low	Moderate	Low	Low	Low	Low	M
Hughes et al (2017)	Moderate	Moderate	Low	Low	High	High	M
Huot et al (2004)	Moderate	High	Moderate	Moderate	Low	Moderate	SR
Icks et al (2007)	Moderate	Low	Low	Low	High	Moderate	M
Kaplan et al (2003)	Moderate	Low	Low	Moderate	Low	Moderate	SR
Kilicarslan et al (2006)	High	High	Low	Moderate	High	Moderate	SR
Kim (2016)	High	High	High	Moderate	Low	Moderate	SR
Klumbiene et al (2004)	Low	Low	Low	Moderate	Low	Moderate	SR
Ko et al (2015)	Low	Moderate	Low	Low	Low	Moderate	M
Kuntz & Lampert (2010)	Moderate	Moderate	Low	Moderate	Low	Moderate	SR
Laaksonen et al (2004)	Moderate	Moderate	Low	Moderate	Low	Moderate	SR
Lawlor et al (2005)	Low	Low	Low	Moderate	Moderate	Moderate	SR
Lindstrom et al (2003)	Moderate	Moderate	Low	Moderate	Moderate	Moderate	SR
Lopez-Sobaler et al (2016)	Low	Moderate	Low	Low	Low	Low	M

Maier et al (2014)	Moderate	Moderate	Low	Moderate	Low	Moderate	SR
Marques-Vidal et al (2008)	Moderate	Low	Moderate	Low	Low	High	M
Marques-Vidal et al (2010)	Low	Moderate	Low	Moderate	Low	Moderate	SR
Marques-Vidal et al (2011)	Low	Moderate	Low	Moderate	Moderate	Moderate	SR
Martinez-Ros et al (2001)	Moderate	Low	Low	Low	Low	Moderate	M
Martorell et al (2000)	High	Moderate	High	Moderate	Moderate	High	NR
Mataix et al (2005)	Low	Low	Low	Low	Low	Moderate	M
Molarius (2003)	Moderate	Low	Low	Moderate	Low	Low	SR
Moreira & Padrao (2006)	Low	Moderate	Low	Moderate	Low	Moderate	SR
Nedo & Paulik (2012)	Low	Moderate	Low	Moderate	Low	Low	SR
Ng et al (2011)	Moderate	Moderate	Moderate	Low	Low	Moderate	M
Nielsen et al (2006)	Low	Low	Moderate	Low	Low	Moderate	M
Nocon et al (2007)	Moderate	Low	Low	Low	Low	Low	M
Ogna et al (2014)	Low	Moderate	Low	Low	Low	Moderate	M
Padez (2006)	Low	Low	Low	Low	Moderate	Moderate	M
Palomo et al (2014)	Low	Low	Low	Low	Low	High	M
Perez Ferrer et al (2014)	Low	Moderate	Low	Low	Moderate	Low	M
Perez-Hernandez et al (2017)	Low	Moderate	Low	Low	Moderate	Moderate	M
Qobadi & Payton (2017)	Low	Low	Low	Moderate	Low	Moderate	SR
Roskam et al (2010)	Moderate	Moderate	Low	Moderate	Moderate	Low	SR
Rurik et al (2014)	Moderate	High	Low	Low	High	High	M
Salonen et al (2009)	Low	Low	Low	Low	Low	Moderate	M
Salsberry et al (2009)	Low	Low	Low	Moderate	Low	Moderate	SR
Samouda et al (2018)	Low	High	Low	Low	Low	Moderate	M
Santos & Barros (2003)	Moderate	Low	Low	Low	Low	Low	M
Sardinha et al (2012)	Low	Moderate	Low	Low	High	Moderate	M
Sarlio-Lahteenkorva et al (2006)	Moderate	Moderate	Low	Moderate	High	Moderate	SR
Seppanen-Nuijten et al (2009)	Moderate	Moderate	Low	Low	Moderate	Moderate	M
Singh-Manoux et al (2009)	Moderate	Low	Low	Moderate	Low	Moderate	SR
So & Seo (2013)	Low	Moderate	Low	Low	Low	Low	M
Soriguer et al (2004)	Moderate	Low	Moderate	Low	Low	Moderate	M
Sotillo et al (2007)	Moderate	Low	Low	Low	Low	Moderate	M
Stringhini et al (2012)	Low	Moderate	Low	Low	Low	Low	M
Sulander & Uutela (2007)	High	Moderate	Moderate	Moderate	Low	Moderate	SR
Taira et al (2004)	Moderate	Moderate	Low	Low	Low	Low	M
Tchicaya & Lorentz (2012)	Low	Moderate	Low	Moderate	Low	Moderate	SR
Tzotzas et al (2010)	Low	Low	Low	Moderate	Moderate	Low	M
Vinci et al (2019)	Low	Low	Low	Low	Moderate	Low	M
von Hippel & Lynch (2014)	Low	High	Low	Moderate	Low	Moderate	SR
Wardle, Waller & Jarvis (2002)	Moderate	Moderate	Moderate	Low	Low	Moderate	M
Wen et al (2018)	Low	Moderate	Low	Low	Low	High	M
Yoon et al (2006)	Low	Moderate	Low	Low	Low	Moderate	M
Yu (2016)	Moderate	Low	Low	Low	Low	Moderate	M

Zatonska et al (2011)	Low	Moderate	Moderate	Low	High	Moderate	M
Zhang & Wang (2004)	Moderate	High	Low	Low	Moderate	Moderate	M

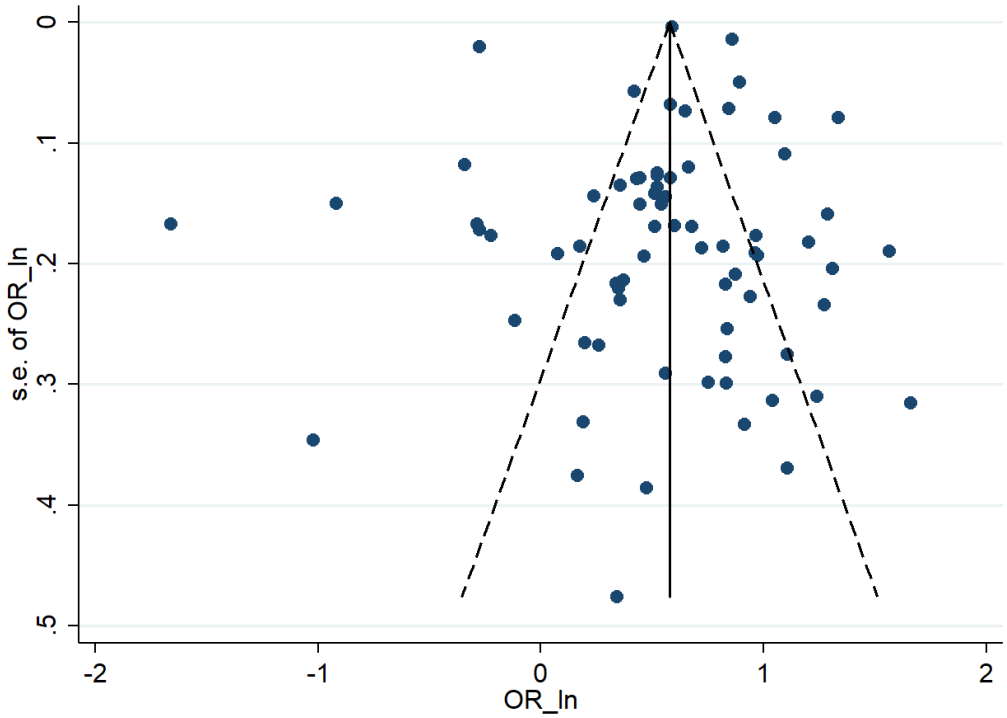

Figure S1: Funnel plot for the meta-analysis of the association between educational attainment using three or four categories and obesity defined by BMI (Egger's p-value = 0.686)

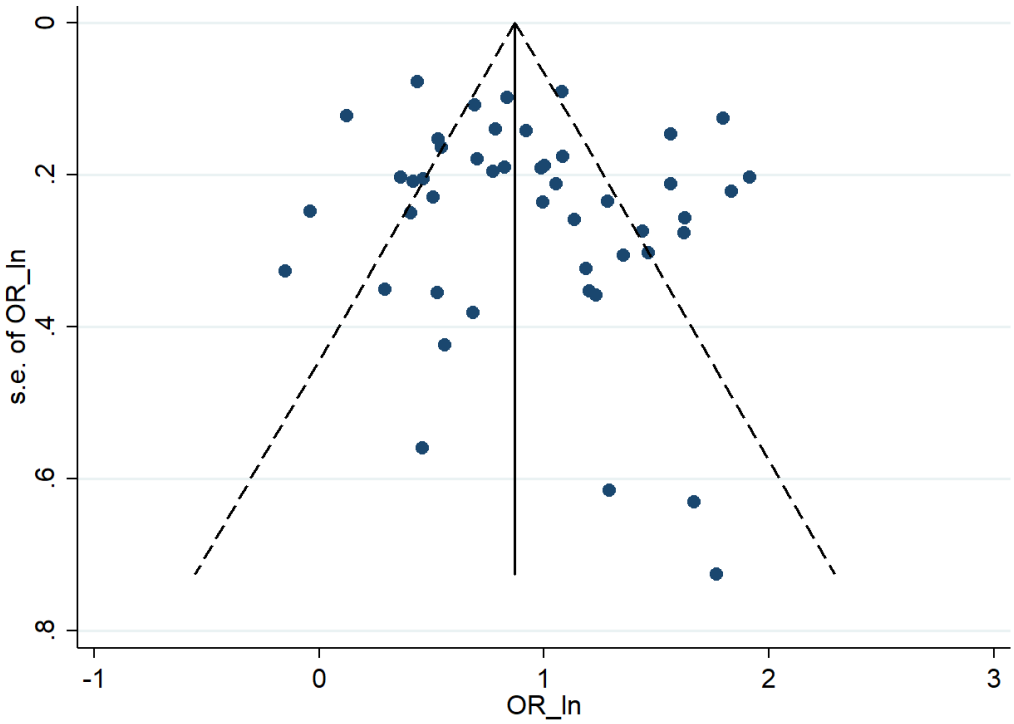

Figure S2: Funnel plot for the meta-analysis of the association between educational attainment and obesity defined by BMI using the RII estimate (Egger's p-value = 0.217)

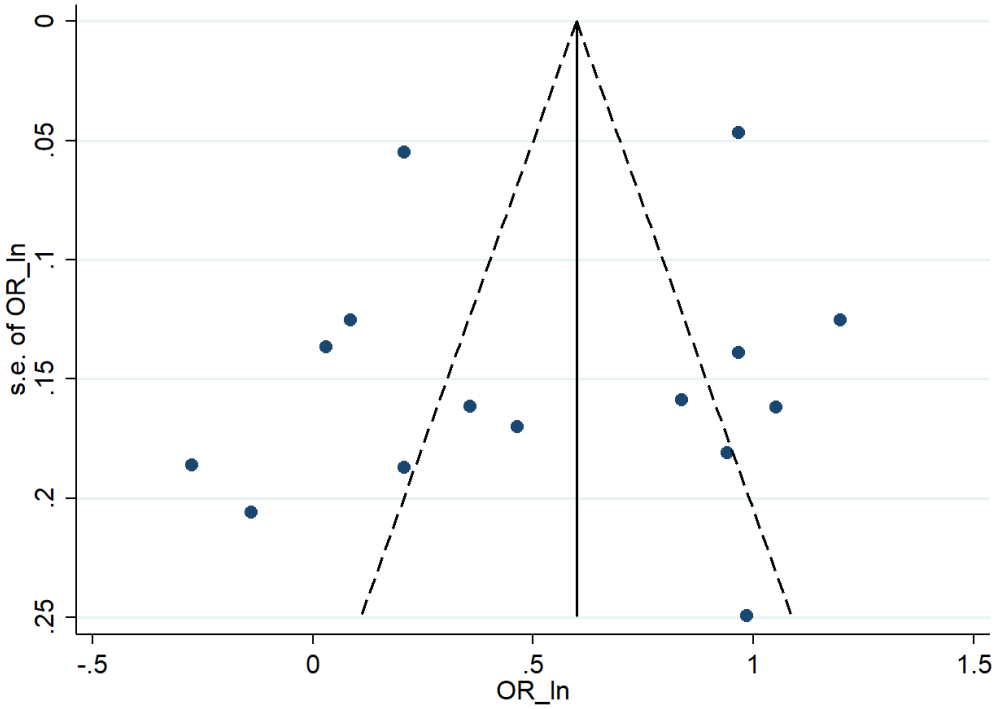

Figure S3: Funnel plot for the meta-analysis of the association between educational attainment using three or four categories and central obesity defined by WC (Egger's p-value = 0.652)

Chapter 4

4. The relationship between socioeconomic position, obesity and incident arthritis

The aim of this Chapter was to understand the relationships between SEP, obesity and incident arthritis using data from ELSA. As described in more detail in Section 7.2.4, there were concerns about the potential misclassification of self-reported RA diagnoses in ELSA. Therefore, it was decided to focus on the OA analyses in the publication. However, the misclassification of RA diagnoses was thought to be non-differential and would likely underestimate the true effect. It was, therefore, decided to still present the results of the RA analyses in this PhD as an Appendix (Appendix F), as they may still contribute to the knowledge gap of the pathways between SEP, obesity and incident RA. The results for RA will be discussed in the Discussion chapter.

Publications

Witkam, R., Gwinnutt, J. M., Selby, D.A, Cooper, R., Humphreys, J.,& Verstappen, S. M. (2022). Does body mass index mediate the relationship between socioeconomic position and incident osteoarthritis?. Seminars in arthritis and rheumatism, 56, 152063.
*Dr Jennifer Humphreys and Professor Suzanne Verstappen contributed equally to this paper.

4.1 Abstract

Objectives: To investigate associations of socioeconomic position (SEP) and obesity with incident osteoarthritis (OA), and to examine whether body mass index (BMI) mediates the association between SEP and incident OA.

Methods: Data came from the English Longitudinal Study of Ageing, a population-based cohort study of adults aged ≥50 years. The sample population included 9,281 people. Cox regression analyses were performed to investigate the associations between SEP (measured by education, occupation, income, wealth and deprivation) and obesity (BMI ≥30 kg/m^2) at baseline and self-reported incident OA. The mediating effect of BMI on the relationship between SEP and incident OA were estimated using Structural Equation Models.

Results: After a mean follow-up time of 7.8 years, 2,369 participants developed OA. Number of person-years included in the analysis was 65,456. Lower SEP was associated with higher rates of OA (for example, hazard ratio (HR) lowest vs highest education category 1.52 (95% confidence interval (CI) 1.30, 1.79)). Obesity compared with non-obesity was associated with increased rates of incident OA (HR 1.37 (95% CI 1.23, 1.52)). BMI mediated the relationship between a lower SEP and OA (β=0.005, p<0.001) and the direct effect was not significant (β=0.004, p=0.212).

Conclusions: Strategies to reduce social inequalities and obesity prevalence may help to reduce OA risk.

Keywords: Socioeconomic position; obesity; osteoarthritis; prospective study; mediation

4.2 Introduction

Osteoarthritis (OA) is a common form of arthritis globally and it is a leading cause of years lived with disability(1). Although both genetic and lifestyle factors play a role in the development of OA (2), obesity is considered as one of the main risk factors for the disease(3). Underlying mechanisms for the relationship between obesity and the development of OA have been attributed to mechanical stress on load bearing joints and adipose tissue releasing pro-inflammatory cytokines leading to joint inflammation(4).

Socioeconomic position (SEP) is a multifactorial concept referring to an individual's economic and social position within a society, and can be measured using multiple indicators, including education, occupation, income and deprivation(5). Whilst all these indicators are interlinked (e.g. education is linked to occupation, which in turn is related to income level(6)), they each have unique properties and are not interchangeable(6). A lower SEP has been associated with increased risk of OA(7-10) in cross-sectional and retrospective studies. However, due to significant limitations of these study designs(11, 12), prospective longitudinal studies investigating the temporal association between SEP and incident OA are needed.

SEP is considered a distal factor (indirectly affecting health) and the association between a lower SEP and OA likely occurs via more proximal factors (directly affecting health), such as lifestyle and environmental factors(13). Identifying mediators through which a lower SEP is associated with incident OA may help to improve targeted prevention strategies. As lower SEP has also been consistently associated with obesity in the general population in high-income countries(14-16), obesity (both total and central(17)) may therefore be a mediator of the relationships between SEP and incident OA. However, this may be different for men and women as previous research suggest that the association between SEP and obesity differs by gender(17).

A recent Mendelian Randomisation study from UK-Biobank reported that body mass index (BMI) mediated the relationship between education and OA (proportion mediated: 23%)(18). However, UK Biobank is a non-representative sample of the UK population(19), a single indicator as a proxy for SEP (education) was used and the study design was not a prospective longitudinal study. Therefore, the current study aims to 1) assess associations of SEP and obesity (both total and central) with incident OA, 2) whether these associations differ in sub groups (by gender and SEP), and 3) whether BMI mediates any associations observed between SEP and incident OA.

4.3 Methods

4.3.1 Participants and study design

Data came from the English Longitudinal Study of Aging (ELSA), a large longitudinal panel study documenting the health, social and economic circumstances of adults aged ≥50 years and their partners, living in private households in England(20). The original sample in 2002 and refreshment samples in 2006, 2008, 2012 and 2014 (to keep the sample representative of the general population) was drawn from the

Health Survey of England (HSE). This is a yearly cross-sectional survey aiming to monitor the health of the general population in England, with a multi-stage stratified probability sampling design. The first stage includes a random selection of primary sampling units based on postcodes. In the second stage, a random sample of postal addresses were drawn from the primary sample units. Participants of HSE who were 50 years or older and who agreed to take part in future studies were invited to participate in ELSA.

Participants of ELSA were surveyed every two years from 2002–2019 and, with consent, an additional nurse visit was offered where a series of measurements took place(21). Waves refer to different cycles of data collection, which includes the follow-up of data collection as well as data collection of newly recruited participants in that particular cycle. Nine waves have been published so far.

Participants were eligible for inclusion in the presented analyses if they had at least one nurse visit with anthropometric measurements. Baseline assessment was defined at the time of first anthropometric measurements. Participants who gave a self-reported diagnosis of OA (i.e. prevalent cases) at baseline assessment were excluded.

Written informed consent was obtained from all participants and ethical approval was acquired from the NHS Research Ethics Committees under the National Research and Ethics Service. The UK Data Service provided anonymized data for this study(22).

4.3.2 Measurements/instruments

4.3.2.1 Exposure variables: obesity and SEP at baseline (waves 2, 4 or 6)

Height (m), weight (kg) and waist circumference (WC, cm) were measured by nurses following standardised protocols in waves 2, 4 and 6(21). The first measurement of total and central obesity for each participant was taken as their baseline measure. Total obesity was defined by baseline BMI ≥30 kg/m^2 and central obesity defined by baseline WC ≥102 cm for men or ≥88 cm for women.

The following variables were used as indicators of SEP: education (no qualifications, other, National Vocational Qualification (NVQ) 1/Certificate of Secondary Education (CSE) or other grade equivalent, NVQ2/General Certificate of Education (GCE) O level equivalent (qualification normally obtained at age 16 in England), NVQ3/GCE A level equivalent (qualification normally obtained at age 18 in England), higher education/below degree, NVQ4/NVQ5/degree or equivalent), occupation (current or most recent) classified using the UK National Statistics Socioeconomic Classification-5 (NS-SEC5) (semi-routine occupations, lower supervisory and technical occupations, small employers and own account workers, intermediate occupations, managerial and professional occupations), income quintiles, wealth quintiles (includes non-housing and primary housing wealth minus debts) and the Index of Multiple Deprivation (IMD) quintiles (based on area-level instead of personal data)(23). The IMD is a measure of relative deprivation of small areas in England based on 39 indicators across seven domains of deprivation (income; employment; education, skills and training; health deprivation and disability; crime; barriers to housing and

services; and living environment)(23). IMD 2004, 2007 and 2010 were used for waves 2, 4 and 6, respectively.

4.3.2.2 Outcome variable: incident OA at follow-up waves (waves 3–9)

The outcome of interest was incident OA. In each wave, participants were asked 'Has a doctor ever told you that you have (or had) any of the following conditions on this card?'. If 'Arthritis' was chosen, they were then asked 'Which type or types of arthritis do you have?', with as answer options 'osteoarthritis', 'rheumatoid arthritis' or 'some other kind of arthritis'. Participants who indicated a diagnosis of OA were asked for updates on their condition in subsequent waves, but could not report the same diagnosis again; however, they were able to report diagnoses of other types of arthritis. Participants who did not indicate an arthritis diagnosis in previous waves or newly recruited participants were asked the original question.

4.3.2.3 Covariates / additional variables

Covariates were identified using directed acyclic graphs. Data on covariates were collected at baseline (waves 2, 4 or 6, depending on when participants entered the study) and were self-reported, including: gender (male, female), age (in years, continuous variable), ethnicity (white, non-white), alcohol consumption (less than monthly, 1x/month–4x/week, (almost) every day), smoking status (never smoked, ex-smoker, current smoker), and physical activity (sedentary, low, moderate, high based on the classification used in the Allied Dunbar Survey of Fitness(24)).

4.3.4 Statistical analysis

Descriptive statistics were used to describe the baseline sample. Cox proportional hazards regression analyses estimated associations between each socioeconomic indicator and incident OA (adjusting for age and gender) as well as for obesity and incident OA (adjusting for age, gender, smoking status, alcohol consumption, physical activity and SEP indicators). Person year follow up was calculated from baseline to either a) date of interview of self-reported OA diagnosis, b) loss to follow-up (including non-response and death), c) end of follow-up (Wave 9). BMI and WC were entered into the models as continuous variables, per 1kg/m^2 increment for BMI and 5-cm increment for WC. To investigate whether associations differed by gender (or by SEP for the obesity analyses), interaction terms between obesity/SEP and gender and obesity and SEP were included in the model. The proportional hazard assumption was tested using the Schoenfeld residuals test(25), where a p-value of <0.05 indicates the proportional hazards assumption holds (Supplementary Table S1).

Exposure variables and covariates had missing data (all <5%, except for alcohol which had 11%). To account for missing data, multiple imputation using chained equations was performed with 10 cycles(26). Moreover, longitudinal survey weights were used to correct for historical non-response, improving the representativeness of the sample(27). These analyses were performed in Stata v14.

To estimate the mediating effect of BMI on the relationship between SEP and incident OA, mediation analyses were performed. A mediator (i.e. BMI) is an intermediate variable between an exposure (i.e. SEP) and an outcome (i.e. incident OA)(28). The total effect of SEP on incident OA can be divided into the indirect effect (i.e. effect mediated by BMI) and direct effect (i.e. effect not explained by BMI). Different statistical methods of analysing mediating effects exist, including structural equation modelling (SEM) and causal mediation analysis. SEM includes path analysis with latent variables(29), where direct and indirect effects are measured simultaneously. The advantage of using SEM is that 'latent variables' can be constructed and these allow multiple observed indicators to be captured within one unobserved construct. This is specifically useful for the operationalisation of SEP, since no single observed variable can capture SEP in its totality. However, using mediation analyses in a SEM approach has been criticised as associations between variables represent descriptive rather than causal relationships(30). Causal mediation analysis, using counterfactuals, is an alternative approach. The outcome is modelled assigning all participants as first exposed and then unexposed, and the causal/total effect is defined as the difference between those two predicted outcomes(31, 32). Here, we estimated the mediating effect of BMI on the relationship between SEP and incident OA using SEM as the main analysis and causal mediation analysis as a sensitivity analysis.

SEM was performed using the Lavaan package(33) in R v4.1.1(34). Using confirmatory factor analysis, SEP was defined as a latent variable with education, occupation, wealth and income as indicators. Initially, IMD was also added as an observed indicator for SEP; however, as the factor loading was non-significant ($p<0.05$), it was therefore not included in the final model. The following fit indices assessed model fit: comparative fit index (CFI) (≥0.95 indicates good fit), root mean square error of approximation (RMSEA) (≤0.08 indicates good fit) and standardised root mean square residual (SRMSR) (≤0.08 indicates good fit)(35). As the indicators for SEP were non-normally distributed ordinal variables, the diagonally weighted least squares estimator was used (WLSMV in Lavaan)(36). Bootstrapping was used to calculate confidence intervals around the indirect effects, as recommended by Pesigan et al (37). As previous research indicated that the association between SEP and obesity differs by gender(17), stratified analyses were performed. Causal mediation analysis was performed using the R package for Causal Mediation Analysis(38) for each SEP indicator individually.

4.4 Results

4.4.1 Description of the cohort

Of the people who had at least one nurse visit at waves 2, 4 or 6 (n=11,848), 2,567 people were excluded due to having prevalent OA at baseline, resulting in a final sample of 9,281 participants. Number of person-years included in the analysis was 65,456. After a mean follow-up of 7.8 years, 2,369 participants (25.5% of the sample) developed OA. Table 1 presents the characteristics at baseline for those who developed OA and those who did not. Those who developed OA were more often women, older, had a lower education and higher total and central obesity rates at baseline compared with those who did not develop OA.

Table 1: Baseline characteristics of the sample, stratified by those who developed OA and those who did not

	Total cohort (N=9,281)	
	Non-OA cases (N=6,912) N (%)	OA cases* (N=2,369) N (%)
Gender (female, %)	3,295 (47.7%)	1,468 (62.0%)
Age (mean (SD))	63.4 (9.8)	64.0 (9.3)
Ethnic group		
White	6,692 (96.9%)	2,308 (97.5%)
Non-white	218 (3.2%)	59 (2.5%)
Missing	2 (0.0%)	0 (0.0%)
Education		
Degree/NVQ4/5	1,146 (16.6%)	320 (13.5%)
Higher education/below degree	914 (13.2%)	296 (12.5%)
A level/NVQ3	566 (8.2%)	154 (6.5%)
O level/NVQ2/GCE	1,284 (18.6%)	454 (19.2%)
CSE/NVQ1	323 (4.7%)	88 (3.7%)
Other	531 (7.7%)	222 (9.4%)
No qualification	2,139 (31.0%)	832 (35.1%)
Missing	9 (0.0%)	3 (0.1%)
Occupation (NS-SEC5) (current or most recent occupation if retired)		
Managerial/professional	2,376 (35.3%)	735 (31.0%)
Intermediate	869 (12.9%)	338 (14.3%)
Small employers	794 (11.8%)	246 (10.4%)
Lower supervisory/technical	677 (10.1%)	236 (10.0%)
Semi-routine	2,020 (30.0%)	756 (31.9%)
Missing	176 (2.5%)	58 (2.4%)
Smoking status		
Never smoked	2,695 (39.1%)	913 (38.5%)
Ex-smoker	3,087 (44.8%)	1,093 (46.1%)
Current smoker	1,116 (16.2%)	357 (15.1%)
Missing	14 (2.0%)	6 (0.3%)
Alcohol consumption		
Less than monthly	1,457 (24.0%)	566 (23.9%)
1x/month–4x/week	3,172 (52.2%)	1,118 (47.2%)
(Almost) every day	1,452 (23.9%)	455 (19.2%)
Missing	831 (12.0%)	230 (9.7%)
BMI (mean (SD)) [kg/m^2]	27.5 (4.7)	28.7 (5.2)
Missing	270 (3.9%)	111 (4.7%)
WHO BMI categories†		
Underweight	78 (1.1%)	15 (0.6%)
Normal weight	2,003 (29.0%)	496 (20.9%)
Overweight	2,869 (41.5%)	959 (40.5%)
Obesity	1,692 (25.5%)	788 (33.3%)
WC (mean (SD)) [cm]	95.17 (13.3)	96.6 (13.4)
Missing	160 (2.3%)	55 (2.3%)
Central obesity‡	3,117 (46.2%)	1,333 (56.3%)

BMI, body mass index; cm, centimetres; NS-SEC, National Statistics Socio-economic classification; NVQ, National Vocational Qualification; OA, osteoarthritis; SD, standard deviation; WC, waist circumference. *Characteristics defined at baseline, when participants are recruited (not at OA onset) †WHO categories defined as: underweight (BMI <18.5 kg/m2), normal weight (BMI 18.5–24.9 kg/m2), overweight (BMI 25.0–29.9 kg/m2), obese (BMI >30.0 kg/m2). ‡Central obesity defined as: WC ≥102 cm for men or ≥88 cm for women.

4.4.2 Associations between socioeconomic position and incident osteoarthritis

Participants with lower SEP were more likely to develop OA than those with higher SEP (Table 2). For example, the HR of the lowest vs highest education category was 1.52 (95% CI 1.30, 1.79)). Formal tests of interaction between SEP indicators and gender/obesity were not statistically significant ($0.08 \leq p \leq 0.89$) except for between gender and deprivation ($p=0.014$). Stratified analyses (Supplementary Table S2) showed that the relationship between higher deprivation and incident OA was stronger for men (most vs least deprived HR 1.89 (95% CI 1.46, 2.46)) than women (HR 1.33 (95% CI 1.07, 1.64)).

Table 2: Weighted* Cox proportional hazards regression for the associations between different SEP indicators and OA incidence

Predictors	Unadjusted HR (95% CI)	Age and gender adjusted HR (95% CI)
Education		
No qualification	1.86 (1.59, 2.16)	1.52 (1.30, 1.79)
Other	1.63 (1.33, 2.00)	1.35 (1.10, 1.66)
NVQ1/CSE	1.28 (0.97, 1.68)	1.23 (0.93, 1.61)
O level/NVQ2/GCE	1.44 (1.22, 1.70)	1.30 (1.10, 1.54)
A level/NVQ3	1.08 (0.87, 1.36)	1.05 (0.84, 1.31)
Higher education/below degree	1.26 (1.05, 1.52)	1.20 (1.00, 1.45)
Degree/NVQ4/5	ref	ref
Occupation (NS-SEC5)		
Semi-routine	1.47 (1.30, 1.66)	1.28 (1.13, 1.45)
Lower supervisory/technical	1.28 (1.07, 1.53)	1.28 (1.07, 1.53)
Small employers	1.08 (0.91, 1.29)	1.07 (0.90, 1.28)
Intermediate	1.34 (1.15, 1.55)	1.09 (0.93, 1.27)
Managerial/ professional	ref	ref
Wealth (1=lowest wealth, 5=highest wealth)		
Quintile 1	1.81 (1.54, 2.11)	1.65 (1.41, 1.94)
Quintile 2	1.50 (1.29, 1.74)	1.44 (1.24, 1.68)
Quintile 3	1.37 (1.19, 1.59)	1.31 (1.13, 1.52)
Quintile 4	1.20 (1.04, 1.38)	1.17 (1.01, 1.35)
Quintile 5	ref	ref
Income (1=lowest income, 5=highest income)		
Quintile 1	1.47 (1.26, 1.71)	1.26 (1.07, 1.47)
Quintile 2	1.56 (1.35, 1.82)	1.36 (1.16, 1.59)
Quintile 3	1.42 (1.22, 1.64)	1.29 (1.11, 1.50)
Quintile 4	1.15 (1.00, 1.33)	1.11 (0.96, 1.28)
Quintile 5	ref	ref
Index of Multiple Deprivation (1= most deprived, 5= least deprived)		
Quintile 1	1.56 (1.33, 1.84)	1.53 (1.30, 1.80)
Quintile 2	1.18 (1.01, 1.38)	1.14 (0.98, 1.33)
Quintile 3	1.16 (1.01, 1.34)	1.13 (0.98, 1.30)
Quintile 4	1.03 (0.90, 1.18)	0.99 (0.87, 1.14)
Quintile 5	ref	ref

CI, confidence interval; HR, hazard ratio; NS-SEC, national statistic socio-economic classification; NVQ, National Vocational Qualification; OA, osteoarthritis; ref, reference category. *Longitudinal survey weights were used to correct for historical non-response. Formal tests of interaction between SEP and gender/obesity were run but in all cases $0.08<p<0.89$ except for gender*IMD ($p=0.014$). Stratified analyses for this can be found in Supplementary Table S2.

4.4.3 Associations between obesity and incident osteoarthritis

Total and central obesity were both associated with incident OA and these associations were maintained after adjustment for covariates, including SEP indicators (Table 3). Risk of OA incidence increased by 1% for each 1 kg/m^2 increase in BMI and increased by 3% for each 5 cm increase in WC. There was no evidence of gender or SEP differences in the associations between total obesity and OA (p-values from tests of interaction 0.25<p<0.93).

Table 3: Weighted* Cox proportional hazards regression for the associations between different definitions of obesity and OA

Predictors	Unadjusted HR (95% CI)	Fully adjusted HR (95% CI)
Total obesity (BMI≥30kg/m^2)		
Obesity	1.54 (1.39, 1.71)	1.37 (1.23, 1.52)
No obesity	ref	ref
Central obesity (WC≥102 cm for men and ≥88 cm for women)		
Central obesity	1.46 (1.33, 1.62)	1.29 (1.17, 1.43)
No central obesity	ref	ref
Continuous		
BMI per 1 kg/m^2 increment	1.01 (1.00, 1.02)	1.01 (1.00, 1.02)
WC per 5 cm increment	1.01 (1.00, 1.03)	1.03 (1.01, 1.05)

CI, confidence interval; HR, hazard ratio; NS-SEC, national statistic socio-economic classification; ref, reference category; WC, waist circumference. Fully adjusted model for obesity/central obesity: adjusted for gender, age, alcohol, smoking, physical activity, education, occupation, wealth, income and IMD. *Longitudinal survey weights were used to correct for historical non-response. Formal tests of interaction between obesity and gender/SEP were run but in all cases 0.08<p<0.97.

4.4.4 The mediating effect of body mass index on the relationship between socioeconomic position and incident osteoarthritis

The confirmatory factor analysis indicated a good fit for the definition of the latent variable SEP, using four indicators: education, NS-SEC5, wealth quintiles and income quintiles (CFI 0.998, RMSEA 0.038, SRMR 0.007). The fit indices of the different SEMs are shown in Supplementary Table S3.

The total, direct and indirect effects via BMI of a lower SEP on OA incidence in the total population and stratified for women and men are shown in Table 4 and Figure 1 (results for WC are shown in Supplementary Table S4). The indirect pathway (i.e. SEP->BMI->OA) was statistically significant (0.005 (95% CI 0.004, 0.006), but not the direct effect (0.004 (95% CI -0.002, 0.011)). This indicates that BMI mediates the relationship between a lower SEP and incident OA. Causal mediation analyses showed similar results for the separate indicators for SEP (Supplementary Table S5).

Table 4: The total, direct and indirect effect via BMI of SEP on incident OA adjusted for age and gender

	Total		Direct		Indirect	
	Regression estimate (95% CI)	p-value	Regression estimate (95% CI)	p-value	Regression estimate (95% CI)	p-value
Combined	0.009 (0.002, 0.016)	p=0.009	0.004 (-0.002, 0.011)	p=0.212	0.005 (0.004, 0.006)	p<0.001
Women	0.012 (0.002, 0.023)	p=0.021	0.004 (-0.007, 0.015)	p=0.463	0.008 (0.006, 0.011)	p<0.001
Men	0.006 (-0.004, 0.015)	p=0.162	0.005 (-0.005, 0.013)	p=0.310	0.002 (0.001, 0.003)	p=0.002

CI, confidence interval; OA, osteoarthritis. Proportion mediated (indirect effect/total effect*100%) not calculated as complete mediation was observed (only the indirect effect of BMI was statistically significant).

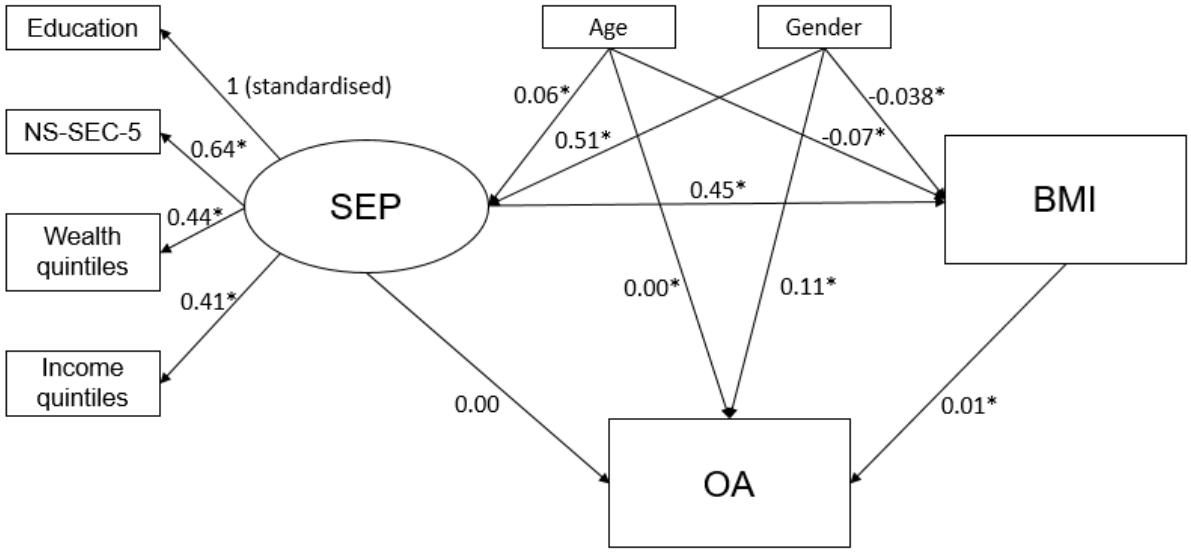

Figure 1: The structural equation model for the relationships between SEP, BMI and incident OA adjusted for age and gender

*statistically significant (p<0.05). BMI, body mass index; NS-SEC, national statistics socioeconomic classification; OA, osteoarthritis; SEP, socioeconomic position.

4.5 Discussion

In this English study including adults aged >50 years, both total and central obesity, as well as a lower SEP at baseline were associated with increased rates of OA over an average follow-up of 7.8 years. BMI/WC mediated the relationship between a lower SEP and incident OA. There were no notable differences between measurements of obesity, i.e. BMI or WC.

The relationships of both total and central obesity with OA have been demonstrated previously(3); however, for central obesity, most studies to date were cross-sectional in design and did not adjust for SEP(39, 40). This study indicates that there is a longitudinal association for both types of obesity independent from SEP, strengthening the view that in addition to mechanical stress on joints, inflammation induced by central adiposity may also be an important factor in the disease process of developing OA(4).

Moreover, cross-sectional and retrospective studies have linked a lower SEP with OA(7-10); however, prospective cohort studies were lacking. A recent study, only using education as SEP indicator, also found a mediating effect of BMI for the association between lower education and OA incidence(18). To our knowledge, ours is the first study investigating the mediating effect of BMI on the causal pathway between multiple indicators of SEP and the development of OA. We did not find gender differences in the associations of individual SEP indicators included in the SEM (education/occupation/wealth/income) and obesity with incident OA; however, stratified analysis in the SEM indicated that the mediated effect (i.e. the indirect effect) was higher in women than men. This might be driven by the relationships between SEP and obesity, as previous research suggest that the SEP-obesity relationship is stronger among women compared with men(17).

Notably, we found that the relationship between higher area-level deprivation and incident OA was stronger for men than women. This may be due to higher rates of manual occupations among men living in deprived areas, which is associated with the development of OA in part through increased loading on joints and increased risk for joint trauma(41). However, we did not see gender differences for the relationship between individual SEP indicators, including occupation, and incident OA in our study. This discrepancy may be explained by the fact that the IMD is an area-level variable and does not fully capture an individual's experience of deprivation(42). Further research should investigate what specific neighbourhood factors are important for the development of OA.

Our study has limitations. Firstly, the OA diagnosis was self-reported, which may lead to recall bias or misclassification. A previous systematic review and meta-analysis by Peeters et al (2015) studied the sensitivity and specificity of self-reported OA in population-based studies compared to medical records or American College of Rheumatology (ACR) criteria. This study showed a high sensitivity and specificity for self-reported OA (0.75 and 0.89, respectively)(43). We expect the remaining misclassification to be non-differential (i.e. it is equally distributed among obese vs non-obese; high vs low SEP); in this case, the true effect will be underestimated. Secondly, we only included BMI and WC at baseline (i.e. the first point of

measurement at either wave 2, 4 or 6) and we did not take into account change of BMI/WC over time or life course effects of high BMI/WC as no early life data on BMI/WC were available in this study. However, additional analysis suggested that BMI/WC in this study population remained constant over different waves (Supplementary Table S6) and adjusting for BMI/WC changes over different waves suggested little change to the estimates for the relationships of obesity with incident OA (Supplementary Table S7). Lastly, this study is only generalisable to the older population (aged ≥50 years) of England; the associations between SEP, obesity and incident OA may be different for a younger population. Risk factors may differ between early and later onset OA, for example, the main risk factor for early OA is joint injuries(44) whereas for later onset OA this is obesity(3). In addition, recent improvements of educational and occupational opportunities, especially for women, may not reflect the social environment of the ELSA population.

A strength of this study is that we were able to use nurse-measured heights, weights and waist circumferences, reducing social desirability bias(45). Moreover, using a latent variable for SEP in the SEMs, we were able to capture SEP indicators reflecting early life (i.e. education), later life (i.e. occupation and income) and current life (i.e. accumulated wealth) in one measure. However, we cannot be certain that our latent variable represents SEP in its entirety and we may have missed other important factors not captured in ELSA. For instance, when we included IMD, the confirmatory factor analysis for the latent variable 'SEP' indicated poor fit, indicating that our latent variable is a better measure for individual rather than neighbourhood SEP. Including a sensitivity analysis using a causal mediation analysis approach increased the robustness of our findings. Lastly, the longitudinal data and large sample size allowed the study of incidence and more precise estimates.

OA is not only a debilitating disease for the individual(1), but also comes at substantial societal cost, both in terms of loss of productivity and healthcare costs(46). Our research shows that preventing obesity may contribute to reducing incident OA and the aforementioned individual and societal impacts of OA. Further research should focus on effective treatment and prevention interventions with the aim to reduce obesity. However, social inequalities in health will not be solved by focussing on intermediate factors, such as obesity, alone. Public health approaches should also focus on improving upstream structural factors (e.g. education, occupation, income), which will increase the opportunities and reduce the barriers for people to lead healthy lives(47).

In conclusion, our results indicate that both SEP and obesity are associated with the development of OA in both men and women. BMI mediated the relationship between a lower SEP and incident OA. Efforts to reduce obesity, specifically in low SEP groups, may help to decrease the risk for OA.

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4.7 Supplementary material

Table S1: Results of the Schoenfeld test to test proportional hazard assumption

Exposure variables	**Schoenfeld test (p-value)**
Obesity	0.46
BMI	0.79
Central obesity	0.45
WC	0.80
Education	0.79
Occupation	0.63
Wealth	0.43
Income	0.79
IMD	0.05

*A p-value >0.05 indicates that the proportional hazard assumption is met. BMI, body mass index; IMD, index of multiple deprivation; WC, waist circumference.

Table S2: The relationship between deprivation and incident OA, stratified by gender

Interaction terms	**HR (95% CI)**	**HR (95% CI)**
*Gender*IMD†*	*Women*	*Men*
Quintile 1 (=most deprived)	1.33 (1.07, 1.64)	1.89 (1.46, 2.46)
Quintile 2	0.99 (0.81, 1.20)	1.43 (1.12, 1.83)
Quintile 3	0.96 (0.80, 1.16)	1.43 (1.14, 1.80)
Quintile 4	0.91 (0.77, 1.08)	1.13 (0.91, 1.41)
Quintile 5 (=least deprived)	ref	ref

†P-value gender*IMD was 0.014. CI, confidence interval; HR, hazard ratio; IMD, index of multiple deprivation.

Table S3: Fit indices of the structural equation models

	CFI	**RMSEA**	**SRMR**
Combined	0.943	0.070	0.033
Women	0.999	0.028	0.005
Men	0.998	0.043	0.008

CFI, comparative fit index; RMSEA, root mean square error of approximation; SRMSR, standardised root mean square residual.

Table S4: The total, direct and indirect effect via WC of SEP on incident OA

	Fit indices	**Total** Regression estimate (95% CI)	**Direct** Regression estimate (95% CI)	**Indirect** Regression estimate (95% CI)
Combined	CFI 0.949 RMSEA 0.068 SRMR 0.032	0.009 (0.002, 0.017) p=0.010	0.005 (-0.003, 0.005) p=0.167	0.004 (0.003, 0.005) p<0.001
Women	CFI 0.945 RMSEA 0.079 SRMR 0.036	0.013 (0.003, 0.025) p=0.017	0.005 (-0.005, 0.017) p=0.347	0.008 (0.006, 0.010) p<0.000
Men	CFI 0.929 RMSEA 0.086 SRMR 0.040	0.006 (-0.003, 0.015) p=0.202	0.004 (-0.005, 0.013) p=0.369	0.002 (0.001, 0.003) p=0.001

CFI, comparative fit index; OA, osteoarthritis; RMSEA, root mean square error of approximation; SE, standard error; SRMSR, standardised root mean square residual.

Table S5: Causal mediation analysis for the total, direct and indirect effect via BMI of different SEP indicators on OA incidence adjusted for age and gender, as a sensitivity analysis

	Total		Direct		Indirect	
	Regression estimate (95% CI)	**p-value**	**Regression estimate (95% CI)**	**p-value**	**Regression estimate (95% CI)**	**p-value**
Education	0.005 (0.001, 0.010)	0.014	0.003 (-0.001, 0.010)	0.190	0.002 (0.002, 0.004)	<0.001
Occupation	0.004 (-0.001, 0.010)	0.092	0.002 (-0.003, 0.010)	0.472	0.002 (0.002, 0.004)	<0.001
Wealth	0.007 (0.001, 0.010)	0.012	0.003 (-0.003, 0.010)	0.364	0.004 (0.003, 0.010)	<0.001
Income	0.003 (-0.004, 0.010)	0.390	0.373 (-6.026, 5.870)	0.730	0.002 (0.001, 0.003)	<0.001

Table S6: Change of BMI/WC over different waves

	Median (IQR)	**Mean (SD)**
BMI		
W2	27.2 (24.6, 30.4)	27.8 (4.7)
W4	27.4 (24.7, 30.8)	28.1 (5.1)
W6	27.5 (24.7, 30.9)	28.2 (5.1)
Change W2 to W4	0.27 (-0.69, 1.21)	0.29 (2.2)
Change W4 to W6	0.07 (-0.93, 0.98)	-0.03 (2.0)
Change W2 to W6	0.32 (-0.92, 1.55)	0.3 (2.4)
WC		
W2	95.2 (86.3, 103.7)	95.2 (12.8)
W4	96.3 (87.3, 105.1)	96.6 (13.4)
W6	96.0 (86.3, 105.0)	96.1 (13.7)
Change W2 to W4	1.7 (-1.8, 5.1)	1.7 (5.9)
Change W4 to W6	-0.3 (-3.9, 3.2)	-0.4 (6.2)
Change W2 to W6	1.4 (-2.8, 5.7)	1.4 (6.9)

BMI, body mass index; IQR, interquartile range; SD, standard deviation; W, wave; WC, waist circumference.

Table S7: Weighted* Cox proportional hazards regression for the associations between different definitions of obesity and incident OA adjusting for individual changes of BMI/WC over waves 2, 4 and 6

Predictors	**Adjusted model 1 HR (95% CI)**	**Adjusted model 2 HR (95% CI)**
Total obesity (BMI≥30kg/m²)		
Obesity	1.37 (1.23, 1.52)	1.39 (1.24, 1.54)
No obesity	ref	ref
Central obesity (WC≥102 cm for men and ≥88 cm for women)		
Central obesity	1.29 (1.17, 1.43)	1.31 (1.18, 1.45)
No central obesity	ref	ref
Continuous		
BMI per 1 kg/m² increment	1.01 (1.00, 1.02)	1.01 (1.00, 1.02)
WC per 5 cm increment	1.03 (1.01, 1.05)	1.04 (1.02, 1.06)

CI, confidence interval; HR, hazard ratio; NS-SEC, national statistic socio-economic classification; ref, reference category; WC, waist circumference. Model 1 adjusted for gender, age, alcohol, smoking, physical activity, education, occupation, wealth, income and IMD. Model 2 also adjusted for changes in BMI/WC over waves 2, 4 and 6. *Longitudinal survey weights were used to correct for historical non-response.

Chapter 5

5. The relationship between socioeconomic position, obesity and the progression of osteoarthritis

Publications

Witkam, R., Gwinnutt, J. M., D.A, Cooper, R., Humphreys, J., & Verstappen, S. M. (2022). The association between lower socioeconomic position and functional limitations is partially mediated by obesity in older adults with knee osteoarthritis: findings from the English Longitudinal Study of Ageing. *Frontiers in Public Health – Section: Aging & Public Health*. In press.

5.1 Abstract

Objective: To assess the longitudinal associations of socioeconomic position (SEP) with functional limitations and knee joint replacement surgery (JRS) in people with symptomatic knee osteoarthritis (OA), and whether body mass index (BMI) mediated these relationships.

Methods: Data came from the English Longitudinal Study of Ageing, a national longitudinal panel study of adults aged ≥50 years. A total of 1,499 participants (62.3% female; mean age 66.5 (standard deviation (SD) 9.4) years; 47.4% obese) self-reporting an OA diagnosis and knee pain, with at least one BMI measurement were included. Mixed effect models estimated longitudinal associations of each SEP variable (education, occupation, income, wealth and deprivation index) and obesity (BMI ≥30.0 kg/m^2) with repeated measures of functional limitations. Cox regression analyses estimated associations between SEP indicators and obesity at baseline and risk of knee JRS at follow-up. Structural equation modelling estimated any mediating effects of BMI on these relationships.

Results: Lower SEP and obesity at baseline were associated with increased odds of functional limitations in people with knee OA (e.g. difficulty walking 100 yards: no qualification vs degree adjOR 4.33 (95% CI 2.20, 8.55) and obesity vs no obesity adjOR 3.06 (95% CI 2.14, 4.37); similar associations were found for the other SEP indicators). A small proportion of the association between lower SEP and functional limitations could be explained by BMI (6.2–12.5%). Those with lower income, lower wealth and higher deprivation were less likely to have knee JRS (e.g. adjHR most vs least deprived 0.37 (95% CI 0.19, 0.73)); however, no clear association was found for education and occupation. Obesity was associated with increased hazards of having knee JRS (adjHR 1.87 (95% CI 1.32, 2.66)). As the direction of the associations for SEP and obesity with knee JRS were in opposite directions, no mediation analyses were performed.

Conclusions: Lower SEP was associated with increased odds of functional limitations but lower hazards of knee JRS among people with knee OA, potentially indicating underutilisation of JRS in those with lower SEP. Obesity partially mediated the relationship between lower SEP and increased odds of functional limitations, suggesting adiposity as a potential interventional target.

Keywords (3 to 6 keywords): Socioeconomic position; obesity; functional limitations; joint replacement surgery; cohort study; ageing

5.2 Introduction

Globally, osteoarthritis (OA) is one of the leading causes of years lived with disability[1]. Evidence has shown that there is a "discordance" between joint damage (measured through imaging) and symptomatic progression (measured through pain and disability questionnaires) in OA[2]. Functional limitations, rather than structural changes, capture the impact of the disease on the day-to-day lives of people with OA[3]. In addition, functional disability is an important predictor for mortality in people with OA[4].

There is currently no cure for OA. Therefore, the mainstay of treatment combines management of symptoms with pain relief, physiotherapy and, in end stage disease, joint replacement surgery (JRS)[5]. Although JRS improves pain, function, and quality of life[6], joint replacements have a finite life expectancy and revision surgery may carry risks, such as infections[5]. Understanding risk factors for functional limitations and JRS in people with OA is important as it allows physicians to monitor closely patients who are at increased risk for these adverse outcomes and identify factors that may modify this risk early in the disease process.

Socioeconomic position (SEP) refers to an individual's economic and social position within a society[7]. Those with lower SEP have increased risk for OA[8] and a number of cross-sectional studies have found lower SEP to be associated with worse pain and function in people with OA[9, 10]. However, recent research indicates that OA patients with lower SEP are less likely to undergo JRS than OA patients with higher SEP, even in tax-based healthcare systems where medical care is free at the point of use for everyone[11-13]. This indicates that there may be an unmet need for JRS among those with lower SEP.

The relationship between lower SEP and worse disease progression may be mediated by obesity. Obesity is a well-known risk factor for the development of OA[14], and a recent prospective study indicated that body mass index (BMI) mediates the relationship between lower SEP and incident OA at any site[15]. Although there is conflicting evidence about the relationship between obesity and radiographic progression of knee OA[16-18], recent systematic reviews indicated a strong association between BMI and symptomatic progression measured by pain and function[18], and weight loss resulted in symptomatic improvements (i.e. pain and function) in people with knee OA[19]. Obese knee OA patients also have a higher need for knee JRS[20] and at a younger age[21] than non-obese knee OA patients. As the association between SEP and obesity is gender specific[22], the mediating effect of obesity for the relationship between SEP and OA disease progression may also differ by gender. Longitudinal studies are needed to understand how SEP and obesity interact in the progression of OA over time. This could be useful for risk stratification and to target obesity interventions to those who might benefit most.

Therefore, this study aimed to understand the relationships between SEP, obesity and symptomatic OA progression. The main research questions were 1) What are the longitudinal associations between SEP and functional limitations and knee JRS in people with symptomatic knee OA, and do they differ by gender or obesity status?; 2) What are the longitudinal associations between obesity and functional limitations and

knee JRS in people with symptomatic knee OA, and do they differ by gender?; 3) Does BMI mediate the associations between a lower SEP and progression of symptomatic knee OA, and do they differ by gender?

5.3 Methods

5.3.1 Participants and study design

This study used data from the English Longitudinal Study of Aging (ELSA), a national longitudinal panel study recording the health, social and economic circumstances of adults aged ≥50 years and their partners, living in private households in England[23]. Data collection cycles (referred to as 'waves') occur every two years with data currently available for analysis for nine waves between 2002 and 2019. With consent an additional nurse visit was offered at waves 2, 4, 6 and 8 where a series of measurements (e.g. blood pressure, blood tests, anthropometric measurements) took place[24]. Each wave aims to reassess all members of ELSA (regardless of how long they have been in the study), and collects data on newly recruited participants drawn from the Health Survey of England (HSE). The HSE is an annual cross-sectional study aiming to monitor the health of a representative sample of the English population. Written informed consent was obtained from all participants and ethical approval was acquired from the NHS Research Ethics Committees under the National Research and Ethics Service. The UK Data Service provided anonymized data for this study.

Symptomatic knee OA was defined using two questions asked at each wave. First, participants were asked 'Has a doctor ever told you that you have (or had) any of the following conditions on this card?'. If 'Arthritis' was chosen, they could indicate the type of arthritis (osteoarthritis, rheumatoid arthritis or some other kind of arthritis). A second question was used to specifically classify a patient as having knee OA: 'Do you feel knee pain?' (does not specify a timeframe). If participants answered 'yes' to this question in the same or a previous wave of the self-reported OA diagnosis, they were classified as having knee OA. Participants with at least one BMI measurement were included. Prevalent OA cases from wave 1 were excluded as we could not ascertain the self-reported date of diagnosis. Baseline assessment was defined as the first time participants reported having OA during waves 2–8. Figure S1 shows the flowchart of sample selection for this study.

5.3.2 Measurements/instruments

5.3.2.1 Exposure variables: socioeconomic position and obesity at baseline

SEP was only assessed at baseline. The following categorical variables were used as indicators of SEP: highest qualification of education obtained (no qualifications, foreign/other; National Vocational Qualification (NVQ) 1/Certificate of Secondary Education (CSE) or other grade equivalent; NVQ2/General Certificate of Education (GCE) O-level equivalent (qualification normally obtained at age 16 in the UK); NVQ3/GCE A-level equivalent (qualification normally obtained at age 18 in the UK); higher education/below degree; NVQ4/NVQ5/degree or equivalent), current or most recent occupation classified using the UK National Statistics Socioeconomic Classification (NS-SEC)5[25] (semi-routine occupations; lower supervisory

and technical occupations; small employers and own account workers; intermediate occupations; managerial and professional occupations), household equivalised income fifths, household wealth fifths (includes non-housing and primary housing wealth minus debts) and relative deprivation fifths of small areas in England (based on the Index of Multiple Deprivation (IMD))[26]. The IMD is a measurement of relative deprivation of small areas in England based on seven categories of deprivation (income; employment; education, skills and training; health deprivation and disability; crime; barriers to housing and services; and living environment). The reference category for all socioeconomic indicators was the category representing the highest SEP group (i.e. having a degree, managerial and professional occupations, highest income fifth, highest wealth fifth and lowest (least deprived) IMD fifth).

Weight and height were measured by nurses in waves 2, 4 and 6 and by trained interviewers in wave 8. The BMI measurement closest to self-reported OA diagnosis was used. Obesity was defined as a BMI of 30 kg/m^2 or higher. In the regression models, obesity (BMI ≥30.0 kg/m^2) was compared with non-obesity (BMI <30.0 kg/m^2).

5.3.2.2 Outcome variables: functional limitations and joint replacement surgery

The first outcome was functional limitations, measured through five self-reported mobility indicators and the Activities of Daily Living (ADL), a self-reported physical capability questionnaire[27], at baseline and follow-up assessments. The five self-reported mobility indicators were recorded as binary variables (ability to perform the activity, yes/no), including: 1) walking 100 yards, 2) getting up from a chair after sitting for long periods, 3) climbing several flights of stairs without resting, 4) climbing one flight of stairs without resting , and 5) stooping, kneeling or crouching. Unlike ADL, which creates a validated score[28], the mobility indicators were not summed to avoid loss of information on specific mobility indicators. ADL comprises six activities, including dressing, walking across a room, bathing/showering, eating, getting in or out of bed and using the toilet. For each ADL, participants answered the question "because of a health or memory problem, do you have difficulty doing any of the activities on this card? Exclude any difficulties that you expect to last less than three months", where participants could respond with yes or no. For this study, a continuous indicator of the number of ADLs where a participants reported 'yes' was used. This resulted in a score from 0–6, where 0 is no difficulties and 6 is all difficulties present.

The second outcome measure was the first self-reported knee JRS due to arthritis at follow-up (waves 3–9). If participants answered 'yes' to the question 'whether right/left knee joint was replaced', they were further asked what the reason for the knee replacement was (arthritis, fracture, other reason). If the answer was 'arthritis', it was recorded as knee JRS due to arthritis.

5.3.2.3 Covariates/additional variables

Data on covariates were collected at the baseline wave for each participant and were self-reported, including: gender (male, female), age (in years, continuous variable), ethnicity (white, non-white), smoking

status (never smoked, ex-smoker, current smoker), and physical activity based on the classification used in the Allied Dunbar Survey of Fitness[29] (sedentary, low, moderate, high).

An adapted version of the Rheumatic Disease Comorbidity Index (RDCI)[30] was used to account for comorbid illness. All comorbid diseases comprising the RDCI were used (i.e. lung disease, cardiovascular disease, fracture, depression and cancer (all self-reported)), except for stomach ulcers, which are not recorded in ELSA. This resulted in a score from 0–8 (where 0 is no comorbidities and 8 the highest comorbidity score). NHS diabetes guidelines indicate that blood sugar levels need to be stable prior to performing surgery as peri-operative complications are more common in people with high blood sugar levels[31]. Hence, it was decided to account for time-varying glycated haemoglobin (HbA1c) levels. HbA1c values were measured using nurse-collected blood samples in waves 2, 4, 6 and 8.

5.3.3 Statistical analysis

5.3.3.1 Descriptive and longitudinal analysis

Baseline characteristics of the study sample were reported for categorical and continuous data using frequencies (%) and means with standard deviation (SD) respectively.

Linear mixed models (LMM) for continuous outcomes and generalised LMM for binary outcomes were used to estimate longitudinal associations between each SEP variable and repeated measures of functional limitations (adjusted for age and gender) and between obesity and repeated measures of functional limitations (adjusting for age, gender, SEP and RDCI). The association between SEP and functional limitations were only adjusted for age and gender as we did not want to adjust for any potential mediators. Mixed effects models take into account the within-person correlation across each participants' repeated measures.

Cox proportional hazards regression analyses estimated associations between each SEP variable and hazards of knee JRS (adjusting for age and gender) and for obesity and hazards of knee JRS (adjusting for age, gender, SEP, RDCI and time-varying HbA1C). Participants contributed person-time from baseline to either a) date of the wave of knee JRS (the outcome), b) loss to follow-up (including non-response and death), c) end of follow-up (wave 9), whichever came first. As severe obesity (BMI >35) may be a contraindication for JRS, this association was tested for non-linearity using multivariable fractional polynomials (MFP). The proportional hazards assumption was tested using the Schoenfeld residuals test, where a p-value of <0.05 indicates violation of the assumption. The assumption was fulfilled for all analyses.

To investigate whether the aforementioned associations differed by gender (or by SEP for the obesity analyses), interaction terms between obesity/SEP and gender and obesity and SEP were included in the models. If an interaction term was statistically significant ($p \leq 0.05$), stratified analyses were performed.

Missing data were all <3.2%, except for wealth and income, which had 5.8% of missing values from the primary baseline sample of 1499 (Table 1). The missing data was assumed to be missing at random (MAR).

All independent variables with missing data were imputed using multiple imputations using chained equations (MICE) with 10 cycles. Analyses were performed in Stata v14 (StataCorp, College Station, TX).

As a sensitivity analysis, the aforementioned analyses were repeated in a larger sample that also included people with knee OA without a BMI measurement (n=305). Using MICE, BMI was imputed in this sample at the time of OA diagnosis.

5.3.3.2 Mediation analysis

Structural equation modelling (SEM) using the Lavaan package in R was used to estimate the mediating effect of BMI on the relationship between SEP and functional limitations. The total effect of SEP on functional limitations can be divided into the indirect effect (i.e. effect mediated by BMI) and direct effect (i.e. effect independent of BMI).

Using confirmatory factor analysis, SEP was defined as a latent variable with education, occupation, wealth and income as observed indicators (the factor loading of IMD was non-significant ($p<0.05$) and was therefore not included as an indicator). Mobility was defined as a latent variable with the five different indicators mentioned previously. Due to the unbalanced nature of our dataset (i.e. different number of time points for each observation), we were not able to use repeated measures in the SEM; therefore, average scores of both mobility and ADL were calculated.

Fit indices were used to assess the fit of the model, including comparative fit index (CFI) (≥0.95 indicates good fit), root mean square error of approximation (RMSEA) (≤0.08 indicates good fit) and standardised root mean square residual (SRMSR) (≤0.08 indicates good fit). The diagonally weighted least squares estimator (called 'WLSMV' in Lavaan) was used as the SEP indicators were non-normally distributed ordinal variables[32]. Confidence intervals around the indirect effects and the proportion mediated were calculated through bootstrapping. The analyses were adjusted for age, gender and number of follow-up waves. Analyses were also stratified by gender (adjusting for age and number of follow-up waves), as the association between SEP and obesity is gender specific[22].

5.4 Results

5.4.1 Description of the cohort

A total of 3,851 participants reported incident OA cases in waves 2–8 of ELSA. Of these, 1,804 (46.8%) reported knee pain on or before their OA diagnosis and were subsequently classified as having symptomatic knee OA. Of these, 1,499 (83.0%) had at least one BMI measurement; these participants comprised the primary baseline sample (Figure S1). Of the primary sample, 711 (47.4%) were obese. The participants with obesity were slightly younger and had lower SEP (in terms of education, occupation, income, wealth and deprivation) compared with the participants without obesity (Table 1).

Table 1: Baseline characteristics of the primary sample (n=1,499) stratified by obesity status

Characteristics	With obesity (n=711)		Without obesity (n=788)	
	Frequencies (%) / mean (SD)	Missing	Frequencies (%) / mean (SD)	Missing
Age, years	65.3 (8.8)	4 (0.6%)	67.7 (9.8)	8 (1.0%)
Gender, female	467 (65.7%)	0 (0.0%)	467 (59.3%)	0 (0.0%)
Ethnicity, white	682 (95.9%)	0 (0.0%)	759 (96.3%)	0 (0.0%)
Education		5 (0.7%)		4 (0.5%)
No qualification	267 (37.6%)		261 (33.1%)	
Other	75 (10.5%)		93 (11.8%)	
CSE / NVQ1	40 (5.6%)		34 (4.3%)	
O-level / NVQ2 / GCE	139 (19.5%)		126 (16.0%)	
A-level / NVQ3	53 (7.5%)		58 (7.4%)	
Higher education / <degree	72 (10.1%)		107 (13.6%)	
Degree / NVQ4/5	60 (8.4%)		105 (13.3%)	
Occupation		23 (3.2%)		21 (2.7%)
Semi-routine	303 (42.6%)		260 (33.0%)	
Lower supervisory / technical	90 (12.7%)		75 (9.5%)	
Small employers	65 (9.1%)		102 (12.9%)	
Intermediate	87 (12.2%)		100 (12.7%)	
Managerial / professional	143 (20.1%)		230 (29.2%)	
Income fifths		34 (4.8%)		53 (6.7%)
1: lowest	168 (23.6%)		159 (20.2%)	
2	155 (21.8%)		178 (22.6%)	
3	149 (21.0%)		141 (17.9%)	
4	111 (15.6%)		141 (17.9%)	
5: highest	94 (13.2%)		116 (14.7%)	
Wealth fifths		34 (4.8%)		53 (6.7%)
1: lowest	210 (29.5%)		159 (20.2%)	
2	152 (21.4%)		158 (20.1%)	
3	128 (18.0%)		137 (17.4%)	
4	117 (16.5%)		140 (17.8%)	
5: highest	70 (9.8%)		141 (17.9%)	
Area-level deprivation fifths		2 (0.3%)		3 (0.4%)
1: most deprived	145 (20.4%)		121 (15.4%)	
2	152 (21.4%)		161 (20.4%)	
3	145 (20.4%)		164 (20.8%)	
4	140 (19.7%)		183 (23.2%)	
5: least deprived	127 (17.9%)		156 (19.8%)	
Smoking status		1 (0.1%)		3 (0.4%)
Never smoked	248 (31.5%)		278 (35.3%)	
Ex-smoker	372 (47.2%)		382 (48.5%)	
Current smoker	90 (11.4%)		125 (15.9%)	
Physical activity		2 (0.3%)		0 (0.0%)
Sedentary	46 (6.5%)		46 (5.8%)	
Low	303 (42.6%)		236 (29.9%)	
Medium	281 (39.5%)		373 (47.3%)	
High	79 (11.1%)		133 (16.9%)	
RDCI comorbidities, two or more	353 (49.6%)	0 (0.0%)	350 (45.4%)	1 (0.0%)

CSE, Certificate of Secondary Education; GCE, General Certificate of Education; kg, kilograms; m, meters. NVQ, National Vocational Qualification; RDCI, rheumatic disease comorbidity index; SD, standard deviation.

5.4.2 The associations between socioeconomic indicators and functional limitations and knee joint replacement surgery in people with symptomatic knee OA

5.4.2.1 Functional limitations

A lower SEP (education, occupation, income, wealth and area-level deprivation) was associated with limitations in mobility (Table 2) and worse ADL scores (Table 3). For example, those with no qualification were more likely to have difficulties with walking 100 yards (adjOR 4.33 (95% CI 2.20, 8.55)) and had worse daily function based on ADL scores (adj regression-coefficient 0.31 (95% CI 0.11, 0.48)) compared with those with a degree.

For the mobility indicators, stratified analyses showed that the associations were generally stronger for men compared with women (Table S2) and for non-obese compared to obese people with OA (Table S3). For ADL scores, the associations between lower education, higher deprivation index and more limitations in ADL were stronger for men than women (Table S4).

Similar results were found for the sensitivity analyses with imputed data for missing BMI (Table S5 and S6).

5.4.2.2 Knee joint replacement surgery

Over a mean follow-up of 4.7 years (SD 2.8), 144 (9.6%) people with symptomatic knee OA reported having at least one knee JRS (8,427 person-years). Education and occupation were not associated with undergoing knee JRS (Table 4). However, those with the lowest income, lowest wealth and highest deprivation index were less likely to undergo knee JRS compared with the highest income, highest wealth and lowest deprivation index (adjusted hazard ratios (adjHRs) 0.64 (95% CI 0.38, 1.06), 0.55 (95% CI 0.33, 0.93), and 0.37 (95% CI 0.19, 0.73), respectively).

The interaction terms indicated that the relationships of education and occupation with knee JRS differed by gender. Stratified analyses indicated opposite effect sizes for men and women; for example, adjHRs no qualification vs degree were 2.00 (95% CI 0.65, 6.14) for men and 0.39 (95% CI 0.19, 0.79) for women (Table S7). There was no interaction between obesity and SEP indicators for knee JRS. The results were in line with those of the sensitivity analyses (Table S8).

5.4.3 The associations between obesity and functional limitations and knee joint replacement surgery in people with symptomatic knee OA

5.4.3.1 Functional limitations

Overall, those with obesity had increased risks for limitations in mobility (e.g. for walking 100 yards: adjOR 3.06 (95% CI 2.14, 4.37)) and daily function based on higher ADL scores (adj regression-coefficient 0.16 (95% CI 0.06, 0.27)) compared with those without obesity (Tables 2 and 3). There were no gender differences for this association. Similar results were found for the sensitivity analyses with (Table S5 and S6).

5.4.3.2 Knee joint replacement surgery

Obese people with symptomatic knee OA were more likely to report knee JRS than the non-obese people with OA (adjHR 1.87 (95% CI 1.32, 2.66)) (Table 4). The MFP analysis indicated a linear relationship between BMI and knee JRS fit the data best: the higher the BMI, the higher the hazards for knee JRS (adjHR 1.07 (95% CI 1.04, 1.10)). There were no gender differences for this association. The results did not differ in the sensitivity analyses (Table S8).

Table 2: Generalised linear mixed model for the relationships of socioeconomic indicators and obesity with difficulties in mobility

Predictors	OR (95% CI) of reporting difficulty with each of the specified physical tasks									
	Walking 100 yards		Getting up from chair		Climbing several stairs		Climbing one stair		Stooping, kneeling, crouching	
	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted
Education										
No qualification	6.06 (3.04, 12.07)	4.33 (2.20, 8.55)†	3.02 (2.01, 4.53)	3.07 (2.04, 4.61)†	8.37 (4.89, 14.34)	6.84 (4.01, 11.67)†‡	9.28 (5.35, 16.09)	6.69 (3.90, 11.49)‡	3.19 (2.01, 5.05)	2.91 (1.83, 4.63)†‡
Other	1.51 (0.65, 3.52)	1.29 (0.56, 2.97)†	1.93 (1.18, 3.16)	1.94 (1.19, 3.18)†	3.21 (1.68, 6.16)	2.93 (1.54, 5.57)†‡	3.10 (1.60, 5.98)	2.57 (1.35, 4.89)‡	1.97 (1.12, 3.45)	1.89 (1.08, 3.32)†‡
CSE / NVQ1	3.42 (1.19, 9.83)	2.66 (0.94, 7.52)†	2.95 (1.57, 5.56)	3.00 (1.58, 5.63)†	4.15 (1.80, 9.55)	3.55 (1.56, 8.11)†‡	3.27 (1.43, 7.50)	2.75 (1.22, 6.21)‡	2.33 (1.13, 4.82)	2.16 (1.05, 4.47)†‡
O-level / NVQ2 / GCE	1.76 (0.82, 3.77)	1.72 (0.81, 3.63)†	2.33 (1.49, 3.64)	2.33 (1.49, 3.65)†	3.03 (1.69, 5.45)	3.00 (1.69, 5.35)†‡	2.65 (1.45, 4.83)	2.51 (1.40, 4.51)‡	1.93 (1.16, 3.20)	1.91 (1.15, 3.17)†‡
A-level / NVQ3	1.25 (0.49, 3.22)	1.39 (0.55, 3.53)†	1.88 (1.08, 3.26)	1.88 (1.08, 3.25)†	2.27 (1.10, 4.68)	2.34 (1.15, 4.78)†‡	1.94 (0.93, 4.05)	2.08 (1.01, 4.26)‡	1.28 (0.69, 2.38)	1.30 (0.70, 2.41)†‡
Higher education / <degree	0.96 (0.42, 2.21)	0.92 (0.41, 2.09)†	1.73 (1.07, 2.80)	1.73 (1.07, 2.80)†	2.10 (1.12, 3.94)	2.02 (1.09, 3.76)†‡	1.37 (0.71, 2.63)	1.32 (0.69, 2.49)‡	1.52 (0.88, 2.61)	1.49 (0.87, 2.57)†‡
Degree / NVQ4/5	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Occupation										
Semi-routine	4.44 (2.66, 7.43)	4.54 (2.74, 7.51)	2.00 (1.48, 2.70)	1.95 (1.44, 2.63)	3.37 (2.22, 5.10)	3.36 (2.23, 5.04)†	5.47 (3.65, 8.19)	5.29 (3.57, 7.84)	2.23 (1.58, 3.16)	2.14 (1.51, 3.03)
Lower supervisory / technical	3.39 (1.70, 6.80)	3.13 (1.59, 6.15)	1.57 (1.04, 2.38)	1.60 (1.05, 2.42)	1.95 (1.10, 3.45)	1.89 (1.08, 3.30)†	3.27 (1.89, 5.64)	3.25 (1.92, 5.50)	2.35 (1.43, 3.84)	2.38 (1.46, 3.90)
Small employers	2.46 (1.21, 5.00)	2.11 (1.05, 4.24)	1.63 (1.07, 2.49)	1.63 (1.07, 2.49)	2.06 (1.17, 3.64)	1.97 (1.12, 3.44)†	2.40 (1.39, 4.15)	2.21 (1.30, 3.75)	1.86 (1.15, 3.03)	1.84 (1.13, 2.98)
Intermediate	1.05 (0.52, 2.13)	1.13 (0.56, 2.28)	1.07 (0.72, 1.60)	1.02 (0.68, 1.53)	2.01 (1.18, 3.43)	2.05 (1.21, 3.45)†	1.88 (1.10, 3.19)	1.77 (1.05, 2.99)	1.44 (0.91, 2.28)	1.32 (0.83, 2.11)
Managerial / professional	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Income fifths										
1: lowest	8.92 (4.44, 17.93)	7.37 (3.70, 14.68)	2.25 (1.52, 3.33)	2.26 (1.53, 3.34)†	3.94 (2.32, 6.67))	3.45 (2.04, 5.81)†‡	7.88 (4.61, 13.47)	6.39 (3.79, 10.78)	1.87 (1.19, 2.94)	1.71 (1.08, 2.69)‡
2	9.23 (4.61, 18.50)	6.34 (3.20, 12.57)	2.01 (1.37, 2.96)	2.02 (1.37, 3.00)†	5.09 (2.98, 8.69)	3.99 (2.35, 6.80)†‡	8.65 (5.10, 14.65)	6.40 (3.83, 10.70)	2.31 (1.46, 3.66)	2.09 (1.31, 3.31)‡
3	7.40 (3.57, 15.37)	5.32 (2.60, 10.91)	1.98 (1.31, 2.99)	1.99 (1.31, 3.01)†	3.48 (2.01, 6.00)	2.86 (1.66, 4.92)†‡	6.19 (3.57, 10.73)	4.64 (2.71, 7.93)	2.25 (1.40, 3.60)	2.04 (1.27, 3.27)‡

4	2.26 (1.08, 4.76)	1.94 (0.93, 4.03)	1.41 (0.93, 2.14)	1.41 (0.93, 2.15)†	1.77 (1.03, 3.07)	1.63 (0.95, 2.80)†‡	2.46 (1.41, 4.29)	2.21 (1.29, 3.81)	1.34 (0.82, 2.19)	1.30 (0.80, 2.11)‡
5: highest	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Wealth fifths										
1: lowest	36.11 (18.07, 72.15)	36.50 (18.60, 71.63)†	3.81 (2.60, 5.60)	3.79 (2.58, 5.56)	11.96 (7.04, 20.33)	12.05 (7.17, 20.25)†‡	21.74 (12.82, 36.86)	21.63 (13.01, 35.96)	4.43 (2.81, 6.97)	4.38 (2.79, 6.87)
2	15.64 (7.78, 31.45)	14.93 (7.57, 29.44)†	2.35 (1.60, 3.45)	2.33 (1.59, 3.42)	5.12 (3.02, 8.66)	4.95 (2.97, 8.27)†‡	8.07 (4.76, 13.68)	7.51 (4.52, 12.45)	2.92 (1.86, 4.58)	2.85 (1.83, 4.45)
3	5.06 (2.45, 10.45)	4.48 (2.21, 9.07)†	1.73 (1.16, 2.57)	1.71 (1.15, 2.54)	2.87 (1.68, 4.91)	2.64 (1.56, 4.48)†‡	4.06 (2.36, 6.98)	3.61 (2.14, 6.08)	1.92 (1.20, 3.07)	1.83 (1.14, 2.91)
4	3.43 (1.64, 7.15)	3.20 (1.58, 6.54)†	1.37 (0.91, 2.04)	1.35 (0.90, 2.02)	2.25 (1.30, 3.88)	2.15 (1.26, 3.67)†‡	2.58 (1.48, 4.51)	2.38 (1.39, 4.07)	1.80 (1.12, 2.90)	1.74 (1.09, 2.78)
5: highest	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Area-level deprivation fifths										
5: most deprived	8.44 (4.42, 16.13)	11.55 (6.11, 21.82)†	2.42 (1.65, 3.56)	2.48 (1.69, 3.65)	3.31 (1.94, 5.65)	4.00 (2.34, 6.73)†‡	6.33 (3.81, 10.50)	8.20 (5.00, 13.43)†‡	2.52 (1.59, 3.99)	2.78 (1.76, 4.40)
4	3.86 (2.08, 7.19)	4.83 (2.63, 8.86)†	1.65 (1.15, 2.37)	1.69 (1.17, 2.43)	1.80 (1.09, 2.98)	2.05 (1.25, 3.35)†‡	3.56 (2.19, 5.79)	4.28 (2.67, 6.86)†‡	1.33 (0.87, 2.03)	1.44 (0.94, 2.20)
3	1.45 (0.77, 2.73)	1.62 (0.89, 2.99)†	1.04 (0.72, 1.49)	1.05 (0.73, 1.51)	1.18 (0.72, 1.94)	1.25 (0.77, 2.04)†‡	1.75 (1.07, 2.86)	1.92 (1.20, 3.09)†‡	1.19 (0.78, 1.83)	1.25 (0.82, 1.90)
2	1.76 (0.95, 3.27)	1.93 (1.06, 3.52)†	1.31 (0.91, 1.87)	1.32 (0.92, 1.89)	1.46 (0.89, 2.40)	1.54 (0.95, 2.50)†‡	2.14 (1.32, 3.46)	2.31 (1.45, 3.68)†‡	1.45 (0.95, 2.20)	1.50 (0.98, 2.27)
1: least deprived	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Obesity										
Obesity	3.51 (2.37, 5.20)	3.06 (2.14, 4.37)	2.06 (1.63, 2.59)	1.74 (1.39, 2.19)	3.92 (2.86, 5.37)	3.21 (2.40, 4.28)	3.18 (2.35, 4.31)	2.68 (2.05, 3.52)	2.77 (2.11, 3.63)	2.39 (1.83, 3.12)
Non-obesity	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
BMI per 1 kg/m^2 increment	1.14 (1.10, 1.17)	1.13 (1.09, 1.16)	1.08 (1.06, 1.10)	1.06 (1.04, 1.08)	1.56 (1.12, 1.19)	1.14 (1.11, 1.16)	1.12 (1.09, 1.14)	1.11 (1.08, 1.13)	1.12 (1.10, 1.15)	1.11 (1.08, 1.14)

BMI, body mass index; CI, confidence interval; National Vocational Qualification; OR, odds ratio; RDCI, rheumatic disease comorbidity index; ref, reference category. SEP indicators adjusted for age and gender. Obesity/BMI adjusted for age, gender, SEP and RDCI. †Significant interaction with gender (0.001>p<0.05); therefore these estimates were only adjusted for age. ‡Significant interaction between SEP and obesity (0.01>p<0.05). Stratified analyses for gender and obesity are shown in Tables S2 and S3. No evidence of interaction between obesity and gender (0.09>p<0.87).

Table 3: Linear mixed effects models for the relationships of socioeconomic indicators and obesity with difficulties in activities in daily living score (0–6, 0 = no difficulties)

Predictors	Regression coefficient* (95% CI)	
	Unadjusted	Adjusted
Education		
No qualification	0.36 (0.17, 0.54)	0.31 (0.11, 0.48)†
Other	0.06 (-0.17, 0.28)	0.03 (-0.20, 0.25)†
CSE / NVQ1	0.23 (-0.07, 0.52)	0.18 (-0.11, 0.47)†
O-level / NVQ2 / GCE	0.14 (-0.07, 0.35)	0.14 (-0.07, 0.34)†
A-level / NVQ3	0.03 (-0.23, 0.28)	0.05 (-0.21, 0.30)†
Higher education / <degree	-0.14 (-0.36, 0.09)	-0.15 (-0.37, 0.08)†
Degree / NVQ4/5	ref	ref
Occupation		
Semi-routine	0.44 (0.30, 0.58)	0.45 (0.31, 0.60)
Lower supervisory / technical	0.32 (0.12, 0.51)	0.30 (0.10, 0.49)
Small employers	0.38 (0.19, 0.58)	0.36 (0.17, 0.56)
Intermediate	0.16 (-0.03, 0.35)	0.19 (-0.00, 0.38)
Managerial / professional	ref	ref
Income fifths		
1: lowest	0.42 (0.24, 0.60)	0.39 (0.21, 0.56)
2	0.50 (0.32, 0.69)	0.43 (0.25, 0.62)
3	0.34 (0.15, 0.53)	0.28 (0.09, 0.47)
4	0.08 (-0.11, 0.27)	0.05 (-0.14, 0.25)
5: highest	ref	ref
Wealth fifths		
1: lowest	0.75 (0.58, 0.92)	0.75 (0.58, 0.92)
2	0.52 (0.34, 0.70)	0.51 (0.33, 0.69)
3	0.21 (0.03, 0.40)	0.19 (0.01, 0.38)
4	0.17 (-0.02, 0.36)	0.16 (-0.02, 0.35)
5: highest	ref	ref
Area-level deprivation fifths		
5: most deprived	0.60 (0.42, 0.77)	0.65 (0.48, 0.83)†
4	0.37 (0.20, 0.54)	0.41 (0.25, 0.58)†
3	0.14 (-0.03, 0.31)	0.16 (-0.01, 0.33)†
2	0.21 (0.04, 0.38)	0.22 (0.06, 0.39)†
1: least deprived	ref	ref
Obesity		
Obesity	0.21 (0.10, 0.32)	0.16 (0.06, 0.27)
Non-obesity	ref	ref
BMI per 1 kg/m^2 increment	0.02 (0.01, 0.03)	0.02 (0.01, 0.03)

BMI, body mass index; CI, confidence interval; CSE, certificate of secondary education; NVQ, National Vocational Qualification; OR, odds ratio; RDCI, rheumatic disease comorbidity index; ref, reference category. SEP indicators adjusted for age and gender. Obesity/BMI adjusted for age, gender, SEP and RDCI. No evidence of interactions (0.08>p<0.83), except for education and gender (p=0.001) and IMD and gender (p=0.008).*Regression coefficient is interpreted as: for every one unit increase in the predictors, the outcome will increase/decrease by the regression coefficient. †As interaction terms between education/area-level deprivation and gender were statistically significant, these estimates are not adjusted for gender; instead, stratified analyses for these are shown in Table S4).

Table 4: Cox proportional hazard regression for the relationships of socioeconomic indicators and obesity with knee joint replacement surgery

Predictors	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Education		
No qualification	0.77 (0.43, 1.37)	0.71 (0.39, 1.28)
Other	1.42 (0.76, 2.68)	1.34 (0.71, 2.55)
NVQ1 / CSE	1.23 (0.53, 2.84)	1.17 (0.51, 2.73)
O-level / NVQ2 / GCE	0.91 (0.49, 1.70)	0.90 (0.48, 1.68)
A-level / NVQ3	1.05 (0.50, 2.20)	1.06 (0.51, 2.22)
Higher education / <degree	1.28 (0.69, 2.39)	1.25 (0.67, 2.34)
Degree / NVQ4/5	ref	ref
Occupation		
Semi-routine	0.69 (0.45, 1.05)	0.69 (0.45, 1.06)
Lower supervisory / technical	1.07 (0.63, 1.84)	1.07 (0.62, 1.83)
Small employers	1.03 (0.60, 1.79)	1.03 (0.60, 1.79)
Intermediate	0.80 (0.46, 1.39)	0.79 (0.45, 1.39)
Managerial / professional	ref	ref
Income fifths		
1: lowest	0.66 (0.40, 1.09)	0.64 (0.38, 1.06)
2	0.65 (0.39, 1.07)	0.60 (0.36, 1.00)
3	0.74 (0.44, 1.25)	0.70 (0.41, 1.19)
4	0.73 (0.44, 1.23)	0.72 (0.43, 1.21)
5: highest	ref	ref
Wealth fifths		
1: lowest	0.54 (0.32, 0.91)	0.55 (0.33, 0.93)
2	0.52 (0.30, 0.89)	0.52 (0.30, 0.89)
3	0.95 (0.58, 1.56)	0.95 (0.58, 1.55)
4	0.74 (0.44, 1.24)	0.74 (0.44, 1.24)
5: highest	ref	ref
Index of multiple deprivation fifths		
5: most deprived	0.36 (0.18, 0.70)	0.37 (0.19, 0.73)
4	0.80 (0.50, 1.30)	0.83 (0.51, 1.34)
3	0.80 (0.49, 1.30)	0.81 (0.49, 1.31)
2	0.88 (0.56, 1.40)	0.89 (0.56, 1.41)
1: least deprived	ref	ref
Obesity		
Obesity	1.56 (1.12, 2.17)	1.87 (1.32, 2.66)
Non-obesity	ref	ref
BMI per 1 kg/m^2 increment	1.05 (1.02, 1.07)	1.07 (1.04, 1.10)

BMI, body mass index; CI, confidence interval; HR, hazard ratio; NVQ, National Vocational Qualification; RDCI, rheumatic disease comorbidity index; ref, reference category. SEP indicators adjusted for age and gender. Obesity/BMI adjusted for age, gender, SEP, RDCI and time-varying HbA1c. Some indication of interaction for education and gender (p=0.06) and occupation and gender (p=0.07), but not for other SEP indicators (p>0.32). Stratified analyses by gender for education and occupation are shown in Tables S7. No evidence of interactions between obesity and gender (p=0.961) and SEP indicators (p>0.081).

5.4.4 Mediation of obesity for the relationship between lower socioeconomic position and functional limitations

The fit indices of the confirmatory factor analyses and SEMs are shown in Table S9. A small proportion of the association between lower SEP and functional limitations was mediated by obesity: 12.5% (95% CI 8.3%, 17.3%) for mobility and 6.2% (95% CI 2.2%, 11.7%) for ADL (Table 5 and Figure 1). Stratified analyses by gender indicated that the proportion mediated by obesity was higher among women (19.4% (95% CI 11.0%, 29.4%) for mobility and 11.7% (95% CI 4.8%, 22.9%) for ADL) compared with men (5.5% (95% CI 1.6%, 10.9%) for mobility and no indirect effect for ADL) (Table 5). As there was no clear association between lower SEP and increased hazards of knee JRS, no mediation analyses were performed for knee JRS as an outcome.

Table 5: The total, direct and indirect effect via BMI of socioeconomic position as a latent variable on functional limitations (as indicated by difficulties in mobility and activities of daily living) in people with knee OA, adjusted for age and gender

	Total		Direct		Indirect		Proportion mediated (95% CI)*
	β-coefficient (95% CI)	p-value	β-coefficient (95% CI)	p-value	β-coefficient (95% CI)	p-value	
Mobility							
Total	0.483 (0.394, 0.572)	p<0.001	0.423 (0.336, 0.509)	p<0.001	0.061 (0.038, 0.083)	p<0.001	12.5% (8.3%, 17.3%)
Men	0.609 (0.460, 0.758)	p<0.001	0.576 (0.428, 0.723)	p<0.001	0.034 (0.009, 0.058)	p=0.008	5.5% (1.6%, 10.9%)
Women	0.400 (0.289, 0.511)	p<0.001	0.322 (0.216, 0.428)	p<0.001	0.078 (0.043, 0.122)	p<0.001	19.4% (11.0%, 29.4%)
Activities of daily living							
Total	0.224 (0.171, 0.277)	<0.001	0.210 (0.157, 0.264)	<0.001	0.014 (0.004, 0.024)	0.006	6.2% (2.2%, 11.7%)
Men	0.292 (0.207, 0.377)	<0.001	0.287 (0.200, 0.374)	<0.001	0.005 (-0.009, 0.019)	0.476	-
Women	0.177 (0.112, 0.243)	<0.001	0.157 (0.091, 0.222)	<0.001	0.021 (0.006, 0.035)	0.007	11.7% (4.8%, 22.9%)

CI, confidence interval. *Calculated by indirect effect/total effect*100%. 95% CI estimated with bootstrapping. For ADL in men, there was no indirect effect so the proportion mediated was not calculated.

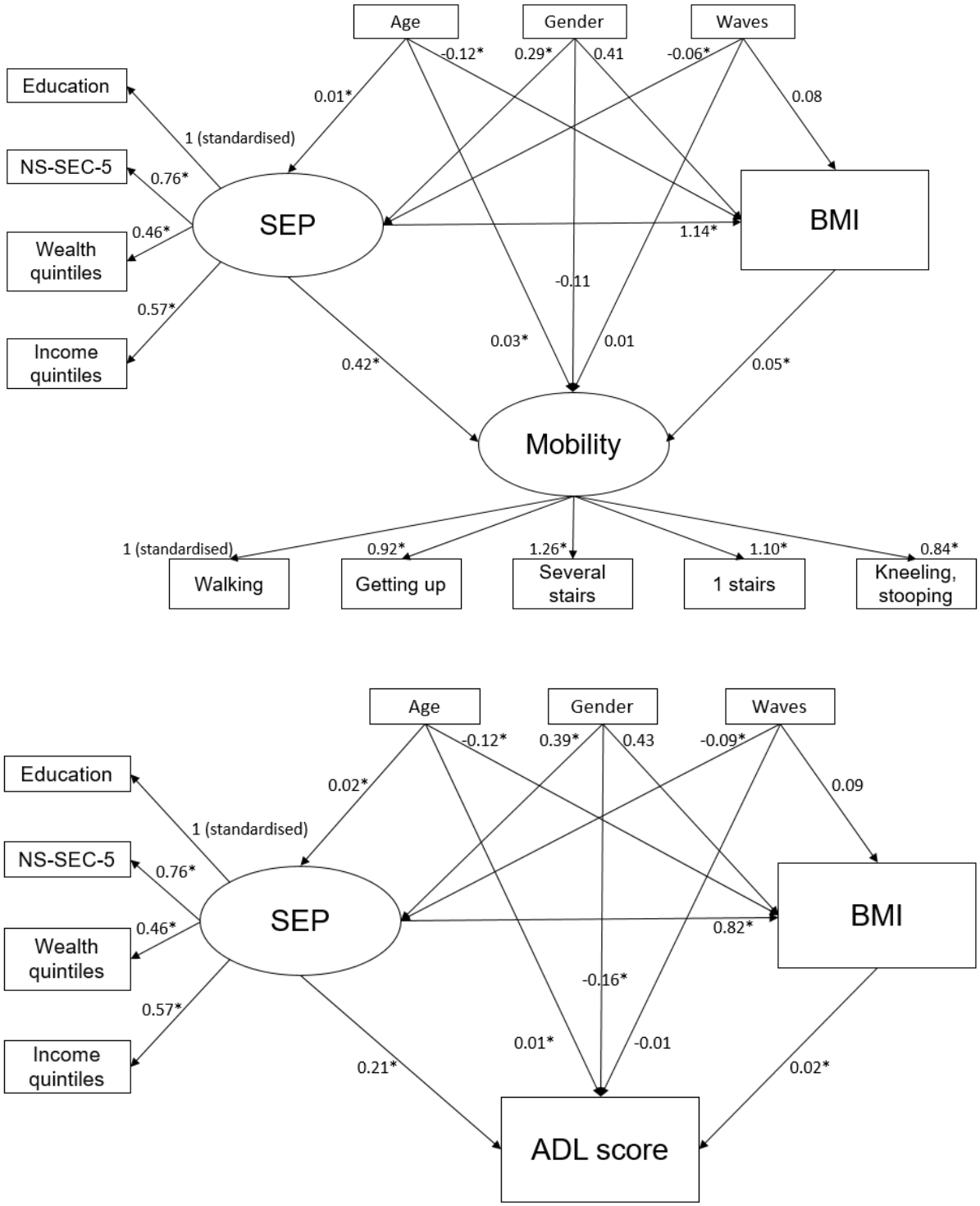

Figure 1: The structural equation models for the relationships between socioeconomic position, BMI and mobility / ADL score, adjusted for age, gender and number of waves attended

*statistically significant ($p<0.05$). ADL, activities of daily living; BMI, body mass index; NS-SEC, national statistics socioeconomic classification; SEP, socioeconomic position.

5.5 Discussion

This study indicates that both lower SEP and obesity at baseline were associated with greater odds of functional limitations, measured by mobility and ADL, in people with symptomatic knee OA participating in a large national longitudinal panel study of adults aged ≥50 years in England. A small proportion of the association between lower SEP and functional limitations could be explained by obesity (6.2% for ADL and 12.5% for mobility). Despite this, those with a lower income, lower wealth and higher deprivation were less likely to undergo knee JRS.

In our study among those with symptomatic knee OA a range of SEP indicators were associated with more functional limitations over time. Our findings are consistent with research suggesting that lower SEP is associated with functional limitations in knee and hip OA[9, 10, 33, 34]; however, most of these studies were cross-sectional[9, 10, 33] making it difficult to determine the temporal nature of the association. Although the mechanisms are unclear, in our study obesity contributed in part to the association between a lower SEP and functional limitations. However, other factors may also contribute, such as a higher prevalence of comorbidities, lifestyle factors (e.g. physical activity)[35] and local factors (e.g. access to primary care services and less safe places to exercise in deprived areas)[36]. There may also be inequalities regarding delivery of care. For example, research has indicated that people with OA with a lower education were less likely to receive advice on exercise compared to those with a higher education[37]. Whether these factors mediate the rest of the association between lower SEP and adverse outcomes in symptomatic knee OA should be investigated in future studies.

Similar to our findings, obesity has also been associated with increased functional limitations in people with OA in both cross-sectional[38] and longitudinal studies[39, 40]. In general, the relationship between a lower SEP and mobility was stronger for men versus women; however, a larger proportion of this association was mediated by BMI for women versus men. This indicates that obesity may be a more important factor leading to mobility limitations for women with lower SEP than men. This might be driven by the relationship between a lower SEP and obesity, which generally appears to be stronger for women than men[22]. For men, other factors may play a role, such as occupational exposures: previous studies have found that occupational exposures (i.e. pollution and physically demanding jobs) explained the association between SEP and functional limitations in men but not for women[41]. To our knowledge, gender differences for this relationship in OA populations have not been assessed previously.

Although the rates of knee JRS among different educational and occupational groups were similar, the relationships appeared to be gender dependent. In lower educational and occupational groups, women were less likely to have knee JRS and men were more likely to have knee JRS compared to higher educational and occupational groups. For income, wealth and deprivation, the lower fifths were less likely to undergo knee JRS compared to the higher fifths and there were no gender differences observed. Other studies in England[11], Sweden[12] and Denmark[13] also found that there was either an inverse (i.e. those with

a lower SEP are less likely to undergo knee JRS) or no relationship between SEP and knee JRS. In general, gender differences have been found previously, where women undergo less knee JRS compared with men despite their potentially greater need[42]. Our study adds that the gender differences may be more marked in lower SEP groups.

Given the association between a lower SEP and functional limitations, this may indicate underutilisation of knee JRS in lower SEP groups and specifically in women. Despite free medical care at the point of use in England, there are still socioeconomic inequalities in healthcare[43]. Reasons may include that those with lower SEP are less likely to be referred to specialists care[44], fewer clinics and public transport to access clinical appointments and surgery are present in deprived communities[36], and less social support among the lower SEP potentially impacting the willingness to undergo surgery[13]. Those with lower SEP may also not be able to take time off work to accommodate the surgery and recovery. Reasons for gender differences have been attributed to women being less willing to undergo surgery (more willing to accept functional decline, less willing to accept the risk of surgery) and specialists are more likely to recommend surgery to men than women[42]. Moreover, in line with previous studies[20, 45, 46], our study confirmed the association between obesity and a higher risk of knee JRS. What our study added was that there was no interaction between obesity and SEP indicators for knee JRS; however, this may be because the two factors cancel each other out, i.e. lower SEP associated with lower rates of surgery and obesity with increased rates of surgery.

Strengths of the study include the fact that it was based on a national population sample and included data on serial assessments for up to 16 years. It also included detailed information concerning a range of SEP indicators including education, occupation, income, wealth and area-level deprivation. However, there are a number of limitations that need to be considered in interpreting the findings. The occurrence of OA was based on self-report and therefore subject to errors of recall and potential misclassification. Data from a systematic review including 11 studies comparing OA self-report (at any site) with medical records or American College of Rheumatology criteria, suggest a sensitivity of 0.75 and specificity of 0.89 for self-report[47]. We attempted to minimise misclassification by including a requirement for both self-reported diagnosis and self-reported knee pain; however, this does not exclude it. Therefore, caution is required in interpreting the frequency of OA; however, any misclassification is more likely to reduce the chance of finding significant biological associations (bias towards the null). Moreover, the prevalence of self-reported knee OA in our sample was 12.7% (1,804 out of an eligible sample of ELSA of 14,228 in waves 2–8); this is in line with previously reported symptomatic knee OA prevalence estimates in the US of similar age groups (16.7% of people aged ≥45 years in the Johnston County OA project[48]; 12.1% of people aged ≥60 years in NHANES III[49]). Selection bias may have occurred by only including those with a BMI measurement in the main analyses; however, sensitivity analyses where BMI measurements were imputed did not change our findings. Data concerning JRS was also obtained based on self-report, though given the nature of the procedure it seems less likely that this would be subject to errors of recall. Furthermore, JRS data were

obtained relatively contemporaneously to the procedure. ADLs and level of mobility are subject to variation over time and possibly prone to recall bias, although our use of data over multiple time points provides a more robust indicator of functional ability over time. In our study, we did not have any information concerning the severity of the underlying OA or its treatment which may have influenced outcome. It is possible, for example, that those with lower SEP may have had more severe disease or were less likely to have therapy and this may in part explain their more severe disability. Finally, our findings were based on a predominantly white English population and caution is needed in generalising the findings beyond this setting.

Functional limitations are associated with impaired quality of life[50], work productivity[51] and mortality[4] in people with OA. Weight reduction and physical therapy interventions are effective in reducing functional limitations in OA, though there are few data concerning the impact of such interventions in disadvantaged groups for which further research is indicated[52]. JRS is effective in relieving pain and improving function in those with knee OA and the lower frequency of surgery in those with lower wealth and living in deprived areas is of concern particularly given the higher levels of disability in these areas. Mediation studies are needed to understand the reasons why those with a lower SEP, and particularly women, are less likely to have JRS even though they appear to have higher disability levels.

To conclude, knee OA in England is expected to rise due to an increase in the number of people with obesity coupled with population ageing. It is important for public health policy to identify predictors of disability and knee JRS. Our results showed that among those with symptomatic knee OA, lower SEP is associated with increased functional limitations and a reduced likelihood of receiving JRS. The increased functional limitations may in part be due to levels of obesity. Further research is required to understand the mechanisms linking lower SEP and adverse outcomes in knee OA and also the reduced likelihood of JRS.

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5.7 Supplementary material

Table S1: Results of the Schoenfeld test to test proportional hazard assumption

Exposure variables	**Schoenfeld test (p-value)**
Education	0.40
Occupation	0.55
Income	0.08
Wealth	0.71
IMD	0.81
Obesity	0.51
BMI	0.14

*A p-value >0.05 indicates that the proportional hazard assumption is met. BMI, body mass index; IMD, index of multiple deprivation; OA, osteoarthritis; RA, rheumatoid arthritis; WC, waist circumference.

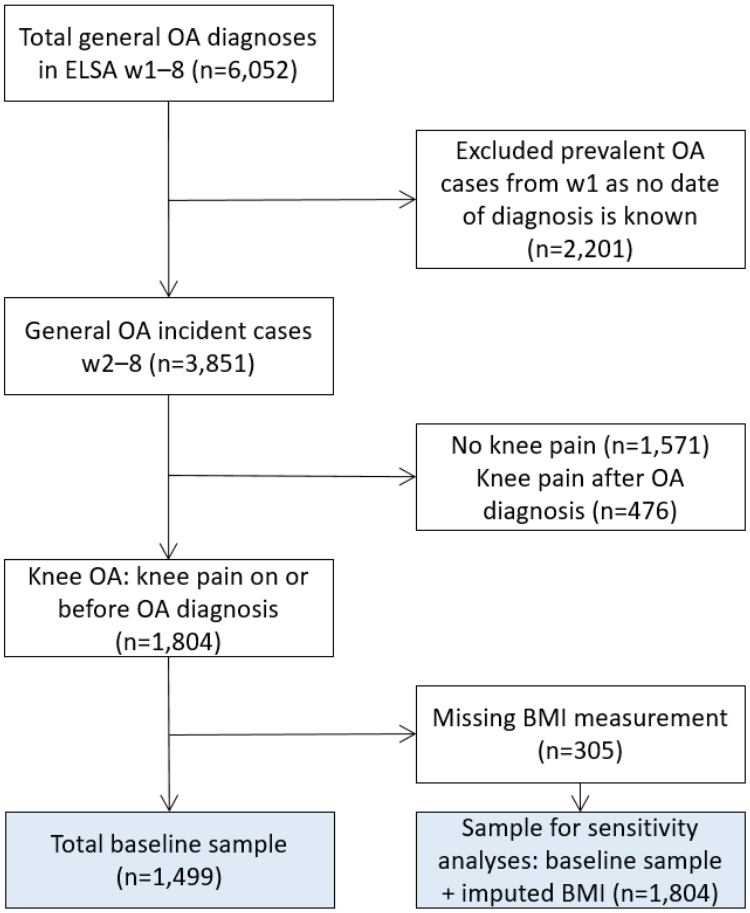

Figure S1: Flowchart of sample selection for this study

Table S2: Stratified analyses for the relationships between socioeconomic indicators and difficulties in mobility by gender

Predictors	Mobility: difficulty (yes)									
	Walking 100 yards		Getting up from chair		Several stairs		One stair		Stooping, kneeling, crouching	
	Men (OR (95% CI))	Women (OR (95% CI))	Men (OR (95% CI))	Women (OR (95% CI))	Men (OR (95% CI))	Women (OR (95% CI))	Men (OR (95% CI))	Women (OR (95% CI))	Men (OR (95% CI))	Women (OR (95% CI))
Education										
No qualification	20.16 (7.13, 56.99)	1.42 (0.58, 3.49)	5.21 (2.75, 9.89)	2.15 (1.26, 3.37)	17.53 (7.16, 42.90)	3.12 (1.60, 6.08)	17.88 (7.20, 44.38)	3.49 (1.78, 6.86)	7.20 (3.68, 14.10)	1.16 (0.60, 2.22)
Other	3.79 (1.01, 14.25)	0.55 (0.19, 1.62)	2.53 (1.12, 5.72)	1.54 (0.82, 2.88)	4.86 (1.58, 14.93)	1.64 (0.75, 3.59)	8.02 (2.61, 24.61)	1.28 (0.58, 2.82)	4.42 (1.88, 10.43)	0.78 (0.37, 1.67)
CSE / NVQ1	10.25 (2.77, 37.91)	0.53 (0.09, 3.04)	3.84 (1.65, 8.93)	2.44 (0.90, 6.63)	11.17 (3.50, 35.68)	1.40 (0.41, 4.79)	6.85 (2.21, 21.25)	1.27 (0.36, 4.46)	3.86 (1.61, 9.25)	1.79 (0.52, 6.17)
O-level / NVQ2 / GCE	5.49 (1.75, 17.18)	1.72 (0.27, 1.91)	4.22 (2.05, 8.68)	1.57 (0.89, 2.79)	5.70 (2.14, 15.16)	1.59 (0.78, 3.23)	5.07 (1.88, 13.71)	1.50 (0.73, 3.09)	3.90 (1.85, 8.23)	0.90 (0.45, 1.80)
A-level / NVQ3	2.47 (0.67, 9.11)	0.98 (0.27, 3.52)	1.36 (0.61, 3.05)	2.62 (1.23, 5.57)	3.18 (1.07, 9.49)	2.16 (0.84, 5.52)	2.96 (0.96, 9.12)	1.75 (0.69, 4.45)	2.26 (1.00, 5.11)	0.79 (0.32, 1.92)
Higher education / <degree	2.97 (0.93, 9.47)	0.36 (0.12, 1.09)	1.86 (0.91, 3.81)	1.65 (0.87, 3.15)	4.51 (1.70, 11.96)	1.15 (0.52, 2.55)	5.14 (1.90, 13.91)	0.47 (0.20, 1.10)	3.86 (1.84, 8.12)	0.58 (0.27, 2.26)
Degree / NVQ4/5	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Occupation (NSSEC-5)										
Semi-routine	8.63 (4.01, 18.57)	2.84 (1.47, 5.49)	2.76 (1.68, 4.53)	1.57 (1.07, 2.30)	5.71 (2.79, 11.70)	1.96 (1.20, 3.19)	7.50 (3.89, 14.46)	4.26 (2.61, 6.93)	2.45 (1.44, 4.16)	1.87 (1.18, 2.96)
Lower supervisory / technical	3.39 (1.41, 8.13)	3.21 (1.16, 8.92)	1.58 (0.89, 2.80)	1.86 (1.00, 3.46)	2.85 (1.27, 6.36)	1.78 (0.80, 3.93)	3.30 (1.57, 6.97)	3.61 (1.70, 7.68)	2.45 (1.32, 4.55)	2.27 (1.04, 4.95)
Small employers	3.88 (1.53, 9.83)	1.15 (0.42, 3.17)	2.94 (1.58, 5.47)	0.98 (0.55, 1.74)	4.59 (1.95, 10.83)	0.98 (0.47, 2.04)	4.13 (1.88, 9.06)	1.26 (0.60, 2.64)	2.66 (1.37, 5.17)	1.26 (0.64, 2.51)
Intermediate	2.24 (0.50, 9.97)	0.75 (0.32, 1.74)	1.80 (0.67, 4.84)	0.82 (0.52, 1.31)	1.29 (0.34, 4.96)	1.26 (0.70, 2.27)	2.19 (0.61, 7.85)	1.50 (0.82, 2.72)	0.86 (0.31, 2.40)	1.29 (0.74, 2.25)
Managerial / professional	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Income quintiles										
1: lowest	10.22 (3.39, 30.77)	6.24 (2.59, 15.03)	4.01 (2.05, 7.87)	1.71 (1.05, 2.77)	7.51 (2.86, 19.75)	2.17 (1.19, 3.97)	5.70 (2.30, 14.10)	6.87 (3.62, 13.03)	2.28 (1.10, 4.74)	1.43 (0.80, 2.53)

2	5.28 (1.93, 14.43)	7.10 (2.87, 17.52)	2.69 (1.43, 5.06)	1.69 (1.03, 2.79)	5.55 (2.33, 13.23)	3.53 (1.82, 6.84)	5.72 (2.50, 13.11)	6.83 (3.54, 13.17)	2.73 (1.37, 5.42)	1.70 (0.92, 3.15)
3	5.66 (1.92, 16.73)	5.00 (1.97, 12.74)	2.20 (1.13, 4.26)	1.85 (1.09, 3.13)	3.25 (1.28, 8.24)	2.57 (1.34, 4.92)	4.54 (1.84, 11.19)	4.74 (2.41, 9.31)	2.13 (1.03, 4.40)	1.96 (1.04, 3.69)
4	1.38 (0.46, 4.13)	2.41 (0.92, 6.29)	1.43 (0.73, 2.80)	1.43 (0.85, 2.43)	1.71 (0.68, 4.30)	1.68 (0.87, 3.24)	1.38 (0.56, 3.40)	2.95 (1.49, 5.82)	1.40 (0.69, 2.85)	1.23 (0.65, 2.31)
5: highest	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Wealth quintiles										
1: lowest	76.53 (26.17, 223.85)	22.17 (9.35, 52.58)	5.04 (2.72, 9.34)	3.22 (1.98, 5.23)	23.90 (9.85, 58.00)	7.51 (4.02, 14.04)	29.54 (12.29, 70.97)	18.13 (9.73, 33.77)	4.84 (2.50, 9.37)	3.96 (2.17, 7.22)
2	23.50 (8.12, 67.99)	10.97 (4.53, 26.53)	2.71 (1.44, 5.10)	2.14 (1.32, 3.46)	6.05 (2.57, 14.25)	4.18 (2.23, 7.80)	10.76 (4.43, 26.08)	6.14 (3.29, 11.47)	3.30 (1.69, 6.47)	2.48 (1.38, 4.46)
3	10.30 (3.45, 30.72)	2.50 (0.99, 6.28)	2.04 (1.06, 3.93)	1.50 (0.91, 2.48)	3.41 (1.39, 8.37)	2.14 (1.14, 4.04)	5.50 (2.25, 13.45)	2.81 (1.46, 5.41)	3.06 (1.52, 6.15)	1.30 (0.70, 2.42)
4	4.61 (1.50, 14.14)	2.48 (0.98, 6.26)	1.36 (0.70, 2.65)	1.31 (0.80, 2.17)	2.03 (0.82, 5.05)	1.96 (1.04, 3.69)	3.42 (1.36, 8.62)	1.95 (1.01, 3.76)	2.74 (1.34, 5.59)	1.28 (0.70, 2.34)
5: highest	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Index of multiple deprivation quintiles										
5: most deprived	16.98 (6.20, 46.52)	8.88 (3.91, 20.14)	3.91 (2.03, 7.53)	1.96 (1.22, 3.15)	11.29 (4.37, 29.17)	2.40 (1.30, 4.43)	14.57 (6.17, 34.42)	6.11 (3.36, 11.12)	3.19 (1.53, 6.67)	2.50 (1.39, 4.50)
4	5.78 (2.24, 14.90)	4.24 (1.93, 9.32)	1.95 (1.07, 3.57)	1.57 (1.00, 2.46)	2.98 (1.26, 7.04)	1.88 (1.04, 3.38)	4.95 (2.22, 11.04)	4.16 (2.33, 7.44)	1.41 (0.72, 2.74)	1.44 (0.84, 2.49)
3	1.86 (0.72, 4.81)	1.48 (0.66, 3.29)	0.83 (0.45, 1.52)	1.23 (0.78, 1.94)	1.61 (0.69, 3.76)	1.23 (0.69, 2.20)	2.37 (1.06, 5.29)	1.80 (1.00, 3.21)	0.93 (0.48, 1.78)	1.56 (0.90, 2.70)
2	1.15 (0.44, 3.04)	2.62 (1.21, 5.65)	1.25 (0.68, 2.30)	1.38 (0.89, 2.15)	1.63 (0.69, 3.83)	1.63 (0.92, 2.88)	1.65 (0.73, 3.71)	2.81 (1.60, 4.93)	1.46 (0.75, 2.85)	1.50 (0.88, 2.55)
1: least deprived	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref

BMI, body mass index; CI, confidence interval; CSE, certificate of secondary education; NS-SEC, National Statistics Socio-economic classification; NVQ, National Vocational Qualification; OR, odds ratio; RDCI, rheumatic disease comorbidity index; ref, reference category. Adjusted for age.

Table S3: Stratified analyses for the relationships of socioeconomic indicators and difficulties in mobility by obesity status

Predictors	Mobility: difficulty (yes)									
	Walking 100 yards		Getting up from chair		Several stairs		One stair		Stooping, kneeling, crouching	
	Obesity (OR (95% CI))	No obesity (OR (95% CI))	Obesity (OR (95% CI))	No obesity (OR (95% CI))	Obesity (OR (95% CI))	No obesity (OR (95% CI))	Obesity (OR (95% CI))	No obesity (OR (95% CI))	Obesity (OR (95% CI))	No obesity (OR (95% CI))
Education										
No qualification	2.10 (0.77, 5.73)	5.76 (2.36, 14.03)	2.11 (1.17, 3.80)	3.48 (1.98, 6.14)	1.77 (0.84, 3.71)	10.79 (5.27, 22.11)	3.27 (1.58, 6.78)	9.75 (4.48, 21.22)	0.80 (0.38, 1.68)	4.48 (2.48, 8.11)
Other	0.85 (0.25, 2.86)	1.68 (0.56, 5.00)	1.74 (0.86, 3.53)	1.94 (0.98, 3.84)	1.67 (0.68, 4.10)	3.04 (1.29, 7.15)	2.11 (0.89, 5.04)	2.79 (1.11, 7.05)	0.78 (0.32, 1.89)	2.41 (1.18, 4.92)
CSE / NVQ1	1.12 (0.27, 4.69)	2.92 (0.68, 12.53)	2.54 (1.09, 5.90)	2.55 (0.98, 6.59)	2.21 (0.76, 6.43)	3.34 (1.04, 10.74)	1.58 (0.56, 4.45)	2.77 (0.79, 9.64)	1.00 (0.35, 2.88)	2.02 (0.75, 5.40)
O-level / NVQ2 / GCE	0.89 (0.30, 2.62)	2.17 (0.79, 5.95)	1.76 (0.94, 3.29)	2.47 (1.31, 4.66)	1.16 (0.53, 2.54)	3.55 (1.61, 7.82)	1.48 (0.68, 3.21)	3.04 (1.28, 7.22)	0.57 (0.26, 1.26)	2.85 (1.47, 5.52)
A-level / NVQ3	1.19 (0.32, 4.39)	0.93 (0.26, 3.39)	1.96 (0.91, 4.22)	1.54 (0.71, 3.35)	1.51 (0.58, 3.95)	2.36 (0.89, 6.24)	1.88 (0.74, 4.78)	1.53 (0.52, 4.49)	0.79 (0.30, 2.04)	1.26 (0.57, 2.78)
Higher education / <degree	0.54 (0.16, 1.84)	1.34 (0.48, 3.79)	1.59 (0.79, 3.23)	1.81 (0.95, 3.47)	0.82 (0.34, 1.98)	3.55 (1.59, 7.96)	1.02 (0.42, 2.45)	1.56 (0.63, 3.83)	0.45 (0.19, 1.08)	2.63 (1.35, 5.14)
Degree /NVQ4/5	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Occupation (NSSEC-5)										
Semi-routine	3.58 (1.74, 7.36)	3.81 (1.96, 7.39)	1.76 (1.16, 2.66)	1.79 (1.16, 2.76)	1.94 (1.15, 3.27)	2.82 (1.58, 5.03)	4.22 (2.53, 7.03)	4.81 (2.68, 8.63)	1.50 (0.91, 2.46)	2.18 (1.37, 3.48)
Lower supervisory / technical	1.88 (0.73, 4.83)	3.29 (1.29, 8.41)	1.26 (0.73, 2.19)	1.59 (0.84, 3.00)	1.16 (0.59, 2.30)	2.24 (0.96, 5.24)	2.67 (1.38, 5.19)	2.47 (1.09, 5.63)	1.46 (0.74, 2.88)	2.53 (1.28, 5.01)
Small employers	2.30 (0.79, 6.68)	1.91 (0.80, 4.56)	1.82 (0.97, 3.39)	1.56 (0.89, 2.76)	1.72 (0.79, 3.76)	2.31 (1.09, 4.88)	2.24 (1.06, 4.76)	2.19 (1.05, 4.58)	1.46 (0.68, 3.12)	2.09 (1.14, 3.82)
Intermediate	1.36 (0.50, 3.73)	0.72 (0.28, 1.83)	0.96 (0.54, 1.70)	0.95 (0.53, 1.69)	1.17 (0.57, 2.38)	1.54 (0.73, 3.24)	1.91 (0.96, 3.80)	1.28 (0.59, 2.79)	1.35 (0.68, 2.68)	1.09 (0.60, 2.00)
Managerial / professional	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Income quintiles										
1: lowest	8.44 (3.26, 21.83)	5.00 (1.97, 12.72)	2.33 (1.39, 3.91)	1.94 (1.10, 3.41)	2.08 (1.08, 3.98)	3.73 (1.83, 7.63)	6.65 (3.48, 12.71)	4.84 (2.19, 10.69)	1.78 (0.63, 2.22)	2.05 (1.13, 3.72)

2	7.13 (2.73, 18.61)	4.80 (1.96, 11.76)	1.97 (1.17, 3.32)	1.98 (1.13, 3.48)	1.77 (0.91, 3.46)	7.73 (3.72, 16.05)	5.44 (2.83, 10.44)	6.73 (3.14, 14.43)	1.30 (0.68, 2.48)	2.82 (1.55, 5.14)
3	5.60 (2.10, 14.96)	3.90 (1.48, 10.31)	1.60 (0.94, 2.73)	2.21 (1.22, 4.02)	1.72 (0.88, 3.34)	3.41 (1.61, 7.22)	4.23 (2.16, 8.30)	4.14 (1.84, 9.32)	1.24 (0.65, 2.36)	2.66 (1.42, 5.01)
4	2.54 (0.88, 7.36)	1.34 (0.51, 3.56)	1.69 (0.96, 2.98)	1.19 (0.66, 2.16)	1.59 (0.78, 3.27)	1.76 (0.85, 3.65)	2.64 (1.31, 5.30)	1.73 (0.76, 3.95)	1.13 (0.57, 2.23)	1.45 (0.77, 2.71)
5: highest	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Wealth quintiles										
1: lowest	24.62 (9.03, 67.18)	25.89 (10.63, 63.07)	2.86 (1.66, 4.93)	3.60 (2.10, 6.16)	3.74 (1.85, 7.59)	13.75 (6.63, 28.51)	11.18 (5.61, 22.28)	24.26 (11.48, 51.27)	2.63 (1.33, 5.18)	3.86 (2.12, 7.04)
2	7.41 (2.69, 20.42)	18.15 (7.51, 43.89)	1.50 (0.86, 2.64)	2.84 (1.68, 4.81)	1.37 (0.68, 2.79)	7.88 (3.92, 15.83)	4.11 (2.04, 8.29)	9.34 (4.51, 19.33)	1.26 (0.63, 2.52)	3.75 (2.10, 6.71)
3	3.42 (1.20, 9.76)	3.50 (1.42, 8.61)	1.41 (0.79, 2.50)	1.65 (0.95, 2.87)	0.93 (0.45, 1.93)	3.62 (1.80, 7.30)	2.61 (1.26, 5.41)	3.30 (1.58, 6.90)	1.14 (0.56, 2.32)	1.81 (1.00, 3.29)
4	2.25 (0.75, 6.76)	2.96 (1.19, 7.38)	1.41 (0.78, 2.54)	1.05 (0.60, 1.82)	0.95 (0.45, 2.04)	2.25 (1.11, 4.58)	1.88 (0.88, 4.00)	2.07 (0.96, 4.45)	1.11 (0.54, 2.29)	1.77 (0.98, 3.18)
5: highest	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Index of multiple deprivation quintiles										
5: most deprived	10.15 (4.31, 23.90)	11.44 (4.74, 27.61)	2.14 (1.31, 3.50)	2.85 (1.60, 5.09)	2.17 (1.15, 4.08)	6.76 (3.11, 14.68)	4.91 (2.69, 8.95)	13.72 (6.42, 29.32)	3.37 (1.81, 6.26)	2.17 (1.15, 4.11)
4	5.76 (2.49, 13.31)	3.79 (1.67, 8.59)	1.85 (1.14, 2.98)	1.54 (0.91, 2.61)	1.44 (0.78, 2.66)	3.02 (1.50, 6.11)	3.71 (2.05, 6.70)	4.98 (2.47, 10.05)	1.74 (0.98, 3.11)	1.23 (0.69, 2.19)
3	2.14 (0.91, 5.02)	1.21 (0.53, 2.75)	1.26 (0.78, 2.06)	0.91 (0.54, 1.54)	1.08 (0.58, 2.01)	1.64 (0.83, 3.24)	2.07 (1.14, 3.78)	1.81 (0.90, 3.64)	1.44 (0.80, 2.57)	1.14 (0.64, 2.02)
2	3.89 (1.66, 9.10)	1.05 (0.47, 2.33)	1.82 (1.11, 2.97)	1.07 (0.65, 1.78)	1.72 (0.92, 3.23)	1.71 (0.88, 3.33)	3.04 (1.67, 5.53)	1.88 (0.95, 3.69)	2.07 (1.14, 3.74)	1.29 (0.74, 2.26)
1: least deprived	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref

BMI, body mass index; CI, confidence interval; CSE, certificate of secondary education; NS-SEC, National Statistics Socio-economic classification; NVQ, National Vocational Qualification; OR, odds ratio; RDCI, rheumatic disease comorbidity index; ref, reference category. Adjusted for age and gender.

Table S4: Stratified analysis for the relationships of education and deprivation with difficulties in activities of daily living scores (0–6, 0 = no difficulties) by gender

Predictors	Age-adjusted regression coefficient (95% CI)	
	Men	Women
Education		
No qualification	0.69 (0.42, 0.97)	0.03 (-0.22, 0.28)
Other	0.26 (-0.10, 0.62)	-0.16 (-0.45, 0.14)
CSE / NVQ1	0.41 (0.05, 0.78)	-0.04 (-0.51, 0.42)
O-level / NVQ2 / GCE	0.37 (0.06, 0.69)	-0.04 (-0.31, 0.23)
A-level / NVQ3	0.10 (-0.26, 0.45)	0.02 (-0.34, 0.37)
Higher education / <degree	0.08 (-0.24, 0.39)	-0.34 (-0.65, -0.03)
Degree / NVQ4/5	ref	ref
Index of multiple deprivation quintiles		
5: most deprived	0.85 (0.57, 1.13)	0.53 (0.31, 0.75)
4	0.39 (0.13, 0.66)	0.41 (0.20, 0.63)
3	0.12 (-0.15, 0.39)	0.17 (-0.04, 0.39)
2	-0.04 (-0.31, 0.23)	0.37 (0.16, 0.58)
1: least deprived	ref	ref

CI, confidence interval; CSE, certificate of secondary education; NVQ, National Vocational Qualification; ref, reference category.

Table S5: Sensitivity analysis – random-effect generalised linear mixed models for the relationships of socioeconomic indicators and obesity with difficulties in mobility

Predictors	Mobility: difficulty (yes)									
	Walking 100 yards		Getting up from chair		Several stairs		One stair		Stooping, kneeling, crouching	
	Unadjusted (OR (95% CI))	Adjusted (OR (95% CI))	Unadjusted (OR (95% CI))	Adjusted (OR (95% CI))	Unadjusted (OR (95% CI))	Adjusted (OR (95% CI))	Unadjusted (OR (95% CI))	Adjusted (OR (95% CI))	Unadjusted (OR (95% CI))	Adjusted (OR (95% CI))
Education										
No qualification	7.89 (4.04, 15.42)	4.69 (2.37, 9.27)	2.85 (1.95, 4.14)	2.82 (1.92, 4.13)	7.79 (4.72, 12.85)	5.56 (3.39, 9.10)	9.69 (5.72, 16.49)	6.77 (4.03, 11.36)	3.21 (2.10, 4.91)	2.87 (1.87, 4.41)
Other	1.54 (0.67, 3.53)	1.41 (0.61, 3.25)	1.74 (1.09, 2.76)	1.72 (1.08, 2.74)	2.72 (1.47, 5.02)	2.18 (1.19, 3.97)	2.99 (1.58, 5.64)	2.39 (1.28, 4.47)	2.04 (1.21, 3.44)	1.91 (1.13, 3.23)
CSE / NVQ1	3.67 (1.31, 10.28)	2.62 (0.92, 7.46)	2.62 (1.45, 4.74)	2.66 (1.47, 4.82)	3.49 (1.59, 7.63)	3.53 (1.65, 7.58)	3.51 (1.58, 7.80)	3.12 (1.43, 6.82)	2.24 (1.15, 4.38)	2.18 (1.12, 4.27)
O-level / NVQ2 / GCE	1.82 (0.87, 3.81)	1.78 (0.84, 3.78)	2.07 (1.37, 3.14)	2.06 (1.36, 3.12)	2.51 (1.46, 4.31)	2.29 (1.35, 3.89)	2.37 (1.33, 4.21)	2.23 (1.27, 3.92)	1.97 (1.24, 3.14)	1.92 (1.21, 3.06)
A-level / NVQ3	1.06 (0.42, 2.67)	1.43 (0.57, 3.61)	1.64 (0.98, 2.73)	1.64 (0.98, 2.74)	1.73 (0.88, 3.40)	1.88 (0.97, 3.63)	1.72 (0.85, 3.47)	1.85 (0.93, 3.68)	1.25 (0.71, 2.21)	1.28 (0.72, 2.25)
Higher education / <degree	1.17 (0.52, 2.62)	0.96 (0.42, 2.17)	1.73 (1.10, 2.72)	1.73 (1.10, 2.72)	1.90 (1.06, 3.41)	1.85 (1.04, 3.27)	1.52 (0.81, 2.84)	1.43 (0.77, 2.66)	1.70 (1.03, 2.82)	1.67 (1.01, 2.76)
Degree / NVQ4/5	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Occupation (NSSEC-5)										
Semi-routine	5.25 (3.20, 8.61)	5.30 (3.26, 8.62)	2.02 (1.52, 2.69)	1.99 (1.49, 2.64)	3.36 (2.29, 4.93)	2.92 (2.01, 4.25)	5.34 (3.62, 7.86)	5.05 (3.47, 7.35)	2.18 (1.58, 3.01)	2.11 (1.53, 2.91)
Lower supervisory / technical	3.63 (1.83, 7.20)	3.30 (1.69, 6.43)	1.55 (1.05, 2.30)	1.56 (1.05, 2.31)	1.72 (1.00, 2.96)	1.81 (1.07, 3.06)	2.90 (1.68, 5.01)	2.87 (1.69, 4.85)	2.08 (1.30, 3.32)	2.08 (1.30, 3.31)
Small employers	2.77 (1.40, 5.49)	2.40 (1.23, 4.69)	1.72 (1.17, 2.55)	1.72 (1.16, 2.54)	1.85 (1.09, 3.15)	1.79 (1.07, 2.99)	2.50 (1.47, 4.26)	2.31 (1.38, 3.86)	1.86 (1.18, 2.92)	1.83 (1.17, 2.88)
Intermediate	0.97 (0.50, 1.91)	1.00 (0.51, 1.96)	1.00 (0.69, 1.46)	0.96 (0.66, 1.41)	2.05 (1.24, 3.37)	1.54 (0.94, 2.53)	1.85 (1.11, 3.09)	1.64 (0.99, 2.72)	1.48 (0.97, 2.26)	1.37 (0.89, 2.11)
Managerial / professional	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Income quintiles										
1: lowest	9.50 (4.68, 19.29)	7.77 (3.84, 15.72)	2.21 (1.51, 2.25)	2.18 (1.48, 3.21)	3.79 (2.26, 6.36)	2.97 (1.78, 4.96)	8.07 (4.68, 13.91)	6.42 (3.74, 10.99)	1.84 (1.19, 2.85)	1.70 (1.10, 2.64)

2	9.90 (5.02, 19.49)	6.59 (3.38, 12.85)	1.93 (1.30, 2.86)	1.91 (1.28, 2.86)	4.75 (2.82, 8.03)	3.77 (2.23, 6.39)	8.37 (4.89, 14.32)	6.07 (3.58, 10.29)	2.27 (1.47, 3.50)	2.06 (1.32, 3.21)
3	8.91 (4.45, 17.84)	6.22 (3.14, 12.31)	1.92 (1.31, 2.82)	1.90 (1.29, 2.81)	3.32 (1.98, 5.59)	2.58 (1.54, 4.32)	6.44 (3.79, 10.95)	4.68 (2.78, 7.88)	2.20 (1.40, 3.47)	2.01 (1.26, 3.18)
4	2.10 (1.05, 4.22)	1.85 (0.93, 3.68)	1.31 (0.88, 1.94)	1.31 (0.88, 1.94)	1.58 (0.93, 2.68)	1.50 (0.89, 2.53)	2.34 (1.37, 4.02)	2.16 (1.27, 3.67)	1.38 (0.88, 2.17)	1.35 (0.86, 2.11)
5: highest	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Wealth quintiles										
1: lowest	38.25 (19.00, 77.01)	37.50 (19.09, 73.65)	3.60 (2.51, 5.17)	3.58 (2.49, 5.14)	10.94 (6.68, 17.93)	10.33 (6.41, 16.65)	19.48 (11.60, 32.69)	18.71 (11.37, 30.80)	4.53 (3.01, 6.82)	4.44 (2.95, 6.67)
2	16.62 (8.23, 33.57)	15.30 (7.67, 30.49)	2.41 (1.64, 3.52)	2.38 (1.63, 3.49)	4.77 (2.88, 7.90)	4.31 (2.63, 7.05)	7.76 (4.58, 13.17)	6.93 (4.13, 11.62)	2.92 (1.91, 4.46)	2.82 (1.85, 4.32)
3	4.94 (2.38, 10.25)	4.24 (2.11, 8.52)	1.69 (1.16, 2.46)	1.66 (1.14, 2.43)	2.53 (1.52, 4.20)	2.21 (1.35, 3.60)	3.48 (2.03, 5.97)	3.00 (1.79, 5.03)	1.91 (1.21, 2.99)	1.81 (1.56, 2.83)
4	3.44 (1.63, 7.25)	3.19 (1.56, 6.54)	1.35 (0.92, 1.97)	1.33 (0.91, 1.95)	1.98 (1.19, 3.31)	1.79 (1.10, 2.92)	2.24 (1.30, 3.86)	2.05 (1.22, 3.44)	1.74 (1.14, 2.66)	1.69 (1.11, 2.58)
5: highest	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Index of multiple deprivation quintiles										
5: most deprived	10.11 (5.42, 18.88)	14.20 (7.68, 26.24)	2.42 (1.69, 3.45)	2.50 (1.75, 3.57)	3.66 (2.23, 6.00)	4.56 (2.82, 7.39)	6.78 (4.18, 11.02)	9.07 (5.66, 14.54)	2.61 (1.71, 3.99)	2.85 (1.87, 4.35)
4	4.15 (2.27, 7.59)	5.18 (2.87, 9.33)	1.68 (1.19, 2.36)	1.72 (1.22, 2.41)	1.95 (1.22, 3.11)	2.29 (1.45, 3.61)	3.64 (2.28, 5.83)	4.48 (2.85, 7.06)	1.43 (0.96, 2.12)	1.52 (1.03, 2.25)
3	1.48 (0.80, 2.72)	1.66 (0.92, 3.02)	0.95 (0.68, 1.34)	0.97 (0.69, 1.36)	1.18 (0.74, 1.88)	1.31 (0.84, 2.05)	1.56 (0.97, 2.50)	1.76 (1.12, 2.78)	1.23 (0.83, 1.82)	1.27 (0.86, 1.88)
2	1.94 (1.07, 3.55)	2.12 (1.18, 3.80)	1.36 (0.97, 1.91)	1.37 (0.98, 1.92)	1.42 (0.89, 2.25)	1.50 (0.96, 2.34)	2.06 (1.30, 3.29)	2.23 (1.42, 3.48)	1.44 (0.98, 2.13)	1.47 (1.00, 2.17)
1: least deprived	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Obesity										
Obesity	3.23 (2.13, 4.88)	2.87 (1.96, 4.20)	1.90 (1.52, 2.38)	1.64 (1.31, 2.04)	3.33 (2.41, 4.62)	2.88 (2.13, 3.90)	2.87 (2.10, 3.94)	2.52 (1.89, 3.34)	2.50 (1.92, 3.25)	2.21 (1.70, 2.87)
Non-obesity	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
BMI per 1 kg/m^2 increment	1.12 (1.09, 1.16)	1.12 (1.09, 1.15)	1.07 (1.05, 1.09)	1.06 (1.04, 1.08)	1.13 (1.10, 1.16)	1.12 (1.09, 1.15)	1.10 (1.08, 1.13)	1.10 (1.07, 1.12)	1.11 (1.08, 1.13)	1.10 (1.07, 1.12)

BMI, body mass index; CI, confidence interval; CSE, certificate of secondary education; NS-SEC, National Statistics Socio-economic classification; NVQ, National Vocational Qualification; OR, odds ratio; RDCI, rheumatic disease comorbidity index; ref, reference category. SEP indicators adjusted for age and gender. Obesity/BMI adjusted for age, gender, SEP and RDCI.

Table S6: Sensitivity analysis – random-effect linear mixed models for the relationships of socioeconomic indicators and obesity with difficulties in activities in daily living score (0–6, 0= no difficulties)

Predictors	Unadjusted Regression coefficient (95% CI)	Adjusted Regression coefficient (95% CI)
Education		
No qualification	0.43 (0.24, 0.61)	0.36 (0.17, 0.54)
Other	0.09 (-0.15, 0.33)	0.06 (-0.18, 0.29)
CSE / NVQ1	0.25 (-0.04, 0.55)	0.19 (-0.10, 0.49)
O-level / NVQ2 / GCE	0.14 (-0.07, 0.35)	0.14 (-0.07, 0.35)
A-level / NVQ3	-0.01 (-0.26, 0.25)	0.01 (-0.25, 0.26)
Higher education / <degree	-0.06 (-0.29, 0.17)	-0.08 (-0.31, 0.15)
Degree / NVQ4/5	ref	ref
Occupation (NSSEC-5)		
Semi-routine	0.42 (0.29, 0.56)	0.43 (0.29, 0.57)
Lower supervisory/technical	0.36 (0.16, 0.56)	0.34 (0.14, 0.54)
Small employers	0.32 (0.13, 0.52)	0.30 (0.11, 0.49)
Intermediate	0.12 (-0.07, 0.31)	0.14 (-0.05, 0.33)
Managerial / professional	ref	ref
Income quintiles		
1: lowest	0.44 (0.25, 0.64)	0.40 (0.21, 0.60)
2	0.54 (0.36, 0.73)	0.46 (0.27, 0.65)
3	0.38 (0.18, 0.57)	0.31 (0.11, 0.50)
4	0.05 (-0.14, 0.25)	0.03 (-0.17, 0.23)
5: highest	ref	ref
Wealth quintiles		
1: lowest	0.78 (0.59, 0.96)	0.77 (0.59, 0.95)
2	0.56 (0.38, 0.75)	0.55 (0.37, 0.73)
3	0.22 (0.03, 0.41)	0.19 (-0.00, 0.37)
4	0.23 (0.04, 0.42)	0.21 (0.03, 0.40)
5: highest	ref	ref
Index of multiple deprivation quintiles		
5: most deprived	0.68 (0.50, 0.85)	0.75 (0.57, 0.92)
4	0.36 (0.19, 0.53)	0.40 (0.23, 0.57)
3	0.13 (-0.04, 0.30)	0.15 (-0.02, 0.32)
2	0.26 (0.09, 0.43)	0.27 (0.10, 0.44)
1: least deprived	ref	ref
Obesity		
Obesity	0.21 (0.08, 0.34)	0.17 (0.04, 0.30)
Non-obesity	ref	ref
BMI per 1 kg/m^2 increment	0.02 (0.01, 0.03)	0.02 (0.01, 0.03)

BMI, body mass index; CI, confidence interval; CSE, certificate of secondary education; NS-SEC, National Statistics Socio-economic classification; NVQ, National Vocational Qualification; OR, odds ratio; RDCI, rheumatic disease comorbidity index; ref, reference category. SEP indicators adjusted for age and gender. Obesity/BMI adjusted for age, gender, SEP and RDCI.

Table S7: Stratified analyses for the relationships of education and occupation with knee joint replacement surgery by gender

	Men Age-adjusted HR (95% CI)	Women Age-adjusted HR (95% CI)
Education		
No qualification	2.00 (0.65, 6.14)	0.39 (0.19, 0.79)
Other	3.36 (1.01, 11.17)	0.79 (0.37, 1.71)
CSE / NVQ1	2.56 (0.68, 9.61)	0.73 (0.21, 2.58)
O-level / NVQ2 / GCE	1.56 (0.44, 5.53)	0.64 (0.31, 1.31)
A-level / NVQ3	2.56 (0.72, 9.10)	0.62 (0.24, 1.63)
Higher education / <degree	3.11 (0.99, 9.79)	0.72 (0.33, 1.55)
Degree / NVQ4/5	ref	ref
Occupation		
Semi-routine	1.12 (0.55, 2.25)	0.53 (0.31, 0.91)
Lower supervisory/technical	1.12 (0.51, 2.46)	1.05 (0.49, 2.23)
Small employers	1.40 (0.64, 3.04)	0.79 (0.36, 1.74)
Intermediate	n/a*	0.81 (0.45, 1.48)
Managerial/ professional	ref	ref

CI, confidence interval; CSE, certificate of secondary education; HR, hazard ratio; NS-SEC, National Statistics Socio-economic classification; NVQ, National Vocational Qualification. *No knee JRS in this group.

Table S8: Sensitivity analysis – Cox regression analysis for the relationships of socioeconomic indicators and obesity with knee joint replacement surgery

Predictors	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Education		
No qualification	0.71 (0.41, 1.23)	0.64 (0.37, 1.13)
Other	1.47 (0.81, 2.66)	1.39 (0.76, 2.53)
CSE/NVQ1	1.05 (0.46, 2.39)	1.01 (0.44, 2.31)
O-level/NVQ2/ GCE	0.87 (0.48, 1.58)	0.86 (0.47, 1.56)
A-level NVQ3	0.93 (0.45, 1.91)	0.94 (0.46, 1.94)
Higher education/<degree	1.36 (0.76, 2.43)	1.32 (0.74, 2.37)
Degree/NVQ4/5	ref	ref
Occupation (NSSEC-5)		
Semi-routine	0.72 (0.48, 1.08)	0.71 (0.47, 1.07)
Lower supervisory/technical	1.13 (0.68, 1.89)	1.12 (0.67, 1.88)
Small employers	1.09 (0.65, 1.83)	1.09 (0.65, 1.83)
Intermediate	0.80 (0.47, 1.35)	0.78 (0.45, 1.33)
Managerial/ professional	ref	ref
Income quintiles		
1: lowest	0.65 (0.40, 1.07)	0.63 (0.38, 1.04)
2	0.68 (0.41, 1.14)	0.63 (0.38, 1.07)
3	0.73 (0.43, 1.25)	0.69 (0.40, 1.18)
4	0.76 (0.45, 1.29)	0.76 (0.45, 1.28)
5: highest	ref	ref
Wealth quintiles		
1: lowest	0.53 (0.31, 0.88)	0.53 (0.32, 0.89)
2	0.55 (0.32, 0.95)	0.55 (0.32, 0.95)
3	1.06 (0.65, 1.72)	1.04 (0.64, 1.70)
4	0.83 (0.50, 1.37)	0.83 (0.50, 1.37)
5: highest	ref	ref
Index of multiple deprivation quintiles		
5: most deprived	0.32 (0.16, 0.61)	0.33 (0.17, 0.64)
4	0.78 (0.49, 1.24)	0.80 (0.50, 1.28)
3	0.87 (0.55, 1.37)	0.87 (0.55, 1.38)
2	0.89 (0.57, 1.38)	0.89 (0.57, 1.39)
1: least deprived	ref	ref
Obesity		
Obesity	1.50 (1.06, 2.13)	1.81 (1.30, 2.51)
Non-obesity	ref	ref
BMI per 1 kg/m^2 increment	1.04 (1.02, 1.07)	1.07 (1.04, 1.10)

BMI, body mass index; CI, confidence interval; cm, centimetres; CSE, certificate of secondary education; HR, hazard ratio; NS-SEC, National Statistics Socio-economic classification; NVQ, National Vocational Qualification; RDCI, rheumatic disease comorbidity index; ref, reference category. SEP indicators adjusted for age and gender. Obesity/BMI adjusted for age, gender, SEP, RDCI and time-varying HbA1c.

Table S9: Fit indices of the structural equation models

	CFI	RMSEA	SRMSR
Model fit of latent variables			
SEP	0.998	0.039	0.007
Mobility	0.994	0.064	0.016
Model fit for structural equation models			
ADL	0.931	0.071	0.035
Mobility	0.941	0.060	0.040

CFA, confirmatory factor analysis; CFI, comparative fit index; OA, osteoarthritis; RA, rheumatoid arthritis; RMSEA, root mean square error of approximation; SEP, socioeconomic position; SRMSR, standardised root mean square residual.

Chapter 6

6. The relationship between socioeconomic position, obesity and the progression of rheumatoid arthritis

Publications

Witkam, R., Gwinnutt, J. M., D.A, Cooper, R., Humphreys, J.; RAMS Co-Investigators, Verstappen, S. M. M. (2022). Is the relationship between deprivation and outcomes in rheumatoid arthritis mediated by body mass index? A longitudinal cohort study. *Rheumatology.* Epub ahead of print.

6.1 Abstract

Objectives: To understand the relationships between deprivation and obesity with self-reported disability and disease activity in people with RA; and whether BMI mediates the relationship between area-level deprivation and these outcomes.

Methods: Data came from the Rheumatoid Arthritis Medication Study (RAMS), a one-year multi-centre prospective observational cohort of people with RA recruited from rheumatology centres across England commencing methotrexate for the first time. 1529 and 1626 people were included who had a baseline and at least one follow-up measurement at 6 or 12 months of Health Assessment Questionnaire – Disability Index (HAQ-DI) and Disease Activity Score-28 (DAS28), respectively. Linear mixed models estimated the associations of deprivation and obesity with repeated measures HAQ-DI and DAS28. Causal mediation analyses estimated the mediating effect of BMI on the relationship between deprivation and RA outcomes.

Results: Higher deprivation and obesity were associated with higher disability (adjusted regression coefficients highest vs lowest deprivation fifths 0.32 (95% CI 0.19, 0.45); obesity vs no obesity 0.13 (95% CI 0.06, 0.20)) and higher disease activity (adjusted regression coefficients highest vs lowest deprivation fifths 0.34 (95% CI 0.11, 0.58); obesity vs no obesity 0.17 (95% CI 0.04, 0.31)). BMI mediated part of the association between higher deprivation and self-reported disability (14.24%) and disease activity scores (17.26%).

Conclusions: People with RA living in deprived areas have a higher burden of disease, which is partly mediated through obesity. Weight-loss strategies in RA could be better targeted towards those living in deprived areas.

6.2 Introduction

RA is a progressive degenerative autoimmune disease, which if untreated can result in painful, swollen joints, severe disability and premature mortality[1]. Understanding risk factors associated with these poor outcomes in people with RA is important. If risk factors are modifiable, they can be targeted early in the disease process and if they are not easily modified, those most at risk for severe disease can be closely monitored by their clinicians.

Evidence from cross-sectional[2-5] and longitudinal[6-9] studies suggest that there are socioeconomic disparities in outcomes for people with RA. In order to address the worse disease outcomes among those from with lower socioeconomic position (SEP), it is important to understand why these discrepancies exist. The relationship between lower SEP and RA outcomes is likely (at least partly) indirect, with SEP influencing other intermediary factors, such as lifestyle and environmental factors, which in turn influence disability and disease activity. Understanding which factors mediate the relationship between lower SEP and RA outcomes may help to identify targets for intervention strategies.

A potential mediator for the relationship between a lower SEP and RA outcomes is obesity. Obesity rates are rising worldwide. In the UK, the latest estimates suggest that the majority of the adult population aged ≥16 years (68% (95% CI 66%, 70%) for men and 60% (95% CI 59%, 62%) for women) was either overweight or obese[10]. It is well-known that obesity is socially patterned: those with lower SEP are more likely to be obese[11]. Recent research also suggests a relationship between obesity and worse disability and disease activity[12-17] and a reduced chance of achieving remission in obese people with RA[12], potentially through the accumulation of pro-inflammatory cytokines in adipose tissue[18]. However, most of these studies did not adjust for socioeconomic factors and failed to acknowledge the complex interaction of SEP and obesity with RA outcomes.

As previous literature has suggested that both SEP and obesity increase the risk for worse outcomes in RA[2-9, 12-16], it is of clinical importance to understand how these factors interact. We hypothesised that obesity is a mediator for the relationship between deprivation and worse disease outcomes in RA; however, this has not yet been investigated. Therefore, this study aimed to understand 1) the relationships between area-level deprivation and disability and disease activity, separately; 2) the relationships between obesity and disability and disease activity; and 3) the mediating effect of body mass index (BMI) on the relationship between area-level deprivation and disability and disease activity in people with RA.

6.3 Methods

6.3.1 Study population

Data came from the Rheumatoid Arthritis Medication Study (RAMS), a one-year prospective observational cohort of people with RA recruited between August 2008 and July 2019 from 38 rheumatology centres across England, who were about to start methotrexate (MTX) for the first time. Inclusion criteria for RAMS were: being 18 years or older, having a medical diagnosis of RA, and were about to start MTX (either as monotherapy or combined with other conventional synthetic disease-modifying anti rheumatic drugs (csDMARDs)) for the first time. Participants were excluded if they previously used biological DMARDs (bDMARDs). Baseline assessment was just before participants started MTX and follow-up assessments were at 6 and 12 months after commencing MTX.

Participants were included for this study if they either had a HAQ-DI or DAS28 available at baseline and at least one follow-up (either at 6 or 12 months) and weight and height were measured at baseline to calculate BMI. Written informed consent was acquired from all participants. Ethical approval was obtained from Central Manchester Research Ethics Committee (REC number 08/H1008/25).

6.3.2 Measurements

Data were obtained by a research nurse interviewing the participant (using case report forms (CRF)), patient questionnaires and by extracting information from participants' clinical records. The patient questionnaires were sent to the co-ordinating centre in Manchester in a pre-paid envelope by either the study nurse or participants for entry into a secure database; however, both the CRF and information from clinical records were entered in the database locally by a study nurse.

6.3.2.1 Exposure variables

Height and weight were self-reported in the CRF at baseline, at 6 months and 12 months. BMI was then calculated by dividing each participant's weight in kilograms by their height in metres squared (kg/m^2). Obesity was defined as having a BMI of 30 or more.

Area-level deprivation was used as a proxy for SEP, and was measured using the Index of Multiple Deprivation (IMD) fifths. Using the participants' postcode at baseline, the most recent IMD calculation (2010, 2015 or 2019) was used after participants' baseline date. The IMD is a measure of small-area deprivation in England based on seven indicators of deprivation (income; employment; education; skills and training; health deprivation and disability; crime; barriers to housing and services; living environment)[19].

6.3.2.2 Outcome variables

At baseline, 6 months and 12 months, participants completed the Health Assessment Questionnaire – Disability Index (HAQ-DI) in the patient questionnaire, which measures self-reported disability[20]. Disease Activity Score in 28 joints (DAS28) was also calculated at baseline, 6 months and 12 months, incorporating information regarding the number of tender joints out of 28 joints, the number of swollen joints out of 28

joints and self-reported general wellbeing using the visual analogue scale (VAS) (0–100 mm, where 100 is the worst score) recorded in the CRF during the visit to the research nurse[21]. Blood samples for the measurement of C-reactive protein (CRP) (mg/L) to measure inflammation were taken and sent to the UK Biobank, Stockport, UK. If blood samples were not available, CRP levels were taken from participants' clinical records.

6.3.2.3 Covariates / additional variables

Demographic and lifestyle covariates were recorded at baseline. Covariates relevant to this study included: age, gender, ethnicity (white, non-white) smoking status (never, current, ex-smoker), alcohol intake (yes/no) and physical activity (compared to people your own age – much more, more, the same, less, much less). Additional clinical variables included the American College of Rheumatology (ACR) 1987 criteria[22], symptom duration (years), MTX starting dose (mg/wk) and history of comorbidities from a predefined table (hypertension, diabetes, cardiovascular disease, asthma, chronic obstructive pulmonary disease, peptic ulcer disease, liver disease, renal disease, depression and cancer) (categorised into: no comorbidities, one comorbidity, two or more comorbidities). All variables were captured in the CRF, except for physical activity which was recorded in the patient questionnaire.

6.3.3 Statistical analysis

Baseline characteristics of the study sample were reported for categorical and continuous data using frequencies (%) and means with standard deviation (SD), respectively.

Linear mixed models (LMM) were used to estimate longitudinal associations between IMD fifths (reference group: least deprived fifth) and repeated measures of HAQ-DI and DAS28 (adjusted for age and gender) and between obesity (reference group no obesity) and repeated measures of HAQ-DI and DAS28 (adjusted for age, ethnicity, IMD, smoking, physical activity and alcohol consumption). As a sensitivity analysis, we also investigated the four separate components of the DAS28 (i.e. tender joints, swollen joints, inflammation level and VAS wellbeing score). Mixed models incorporate both fixed and random-effects, taking into account the correlation between an individual's repeated measures. To investigate whether associations differed for subgroups (i.e. by gender, obesity status or IMD group), interaction terms between (1) IMD and gender, (2) IMD and obesity and (3) obesity and gender were included in the models. Where meaningful interaction effects were identified from inspection of the p-values of interaction terms, subgroup analyses were performed. As some of the exposure variables and covariates had missing data (all <5.5%), multiple imputation using chained equation was performed with 10 cycles[23]. These analyses were performed using Stata v14.

The mediating effect of BMI on the relationship between deprivation and HAQ-DI/DAS28 was estimated using the Causal Mediation Analysis package in R[24]. This method uses a counterfactual approach, and assigns all participants first as exposed and then unexposed to the exposure variable (e.g. deprivation). The causal total (i.e. total effect of deprivation on HAQ-DI/DAS28), indirect (i.e. the effect mediated by BMI)

and direct (i.e. effect not explained by BMI) effects are then defined as the difference between the two potential outcomes[25, 26]. Listwise deletion was used to deal with missing data in the mediation analyses. Sensitivity analyses were performed to test exposure-mediator interaction and the assumption of sequential ignorability (i.e. the degree of unmeasured confounding)[26].

6.4 Results

6.4.1 Description of the cohort

Of the 2431 people consenting to RAMS with a baseline record, 1641 and 1770 had HAQ-DI and DAS28 scores at baseline with at least one follow-up at 6 or 12 months, respectively. After excluding those with missing (110 for HAQ-DI sample; 140 for DAS28 sample) or extreme BMI values (BMI<12 or BMI>60) (2 for HAQ-DI sample; 4 for DAS28 sample), the final samples comprised of 1529 people for the HAQ-DI analyses and 1626 for the DAS28 analyses (Supplementary Figure S1). The sample characteristics for the HAQ-DI and DAS28 were similar. For the HAQ-DI and DAS28 samples respectively, the majority were female (67.0% and 66.2%), had a white ethnicity (95.4% and 90.4%), 494 participants (32.3%) and 541 participants (33.3%) were obese and the mean ages were 59.92 (standard deviation (SD) 12.94) and 58.77 (SD 13.42) (Table 1). In terms of clinical characteristics, 76% fulfilled the 1987 ACR criteria in both samples, mean symptom duration was 2.2 years (SD 4.7 and 4.6 for HAQ-DI and DAS28 samples, respectively), mean MTX start dose was 12.1 (SD 3.0) mg/week for both samples and 28.4% and 28.5% had two or more comorbidities in the HAQ-DI and DAS28 samples, respectively.

Table 1: Baseline characteristics of the sample for the analysis of HAQ-DI (N=1529) and DAS28 (n=1626)

Characteristics	Frequencies (%) / mean (SD)			
	HAQ-DI sample (N=1529)	Missing	DAS28 sample (N=1626)	Missing
Demographic and lifestyle factors				
Age, *years*	59.92 (12.94)	0 (0%)	58.77 (13.42)	0 (0%)
Gender, *female*	1025 (67.0%)	0 (0%)	1076 (66.2%)	0 (0%)
Ethnicity, *white*	1458 (95.4%)	13 (0.9%)	1470 (90.4%)	97 (5.9%)
BMI, kg/m²	28.25 (5.96)	0 (0%)	28.37 (6.04)	0 (0%)
BMI categories†:				
Underweight	16 (1.0%)		22 (1.4%)	
Normal weight	492 (32.2%)		505 (31.1%)	
Overweight	527 (34.5%)		558 (34.3%)	
Obesity	494 (32.3%)		541 (33.3%)	
Alcohol intake, *Yes*	1,055 (69.0%)	26 (1.7%)	1,108 (68.1%)	24 (1.5%)
IMD fifths:		55 (3.6%)		64 (3.9%)
1: most deprived	164 (10.7%)		181 (11.1%)	
2	263 (17.2%)		285 (17.5%)	
3	295 (19.3%)		318 (19.6%)	
4	371 (24.3%)		384 (23.6%)	
5: least deprived	381 (24.9%)		394 (24.2%)	
Smoking status:		6 (0.4%)	645 (39.7%)	7 (0.4%)
Never	627 (41.0%)			
Former	249 (16.3%)		308 (18.9%)	
Current	647 (42.3%)		666 (41.0%)	
Physical activity:		10 (0.7%)	67 (4.1%)	91 (5.5%)
Much more	74 (4.8%)			
More	246 (16.1%)		234 (14.4%)	
The same	381 (24.9%)		378 (23.2%)	
Less	544 (35.6%)		559 (34.4%)	
Much less	274 (17.9%)		297 (18.3%)	
Clinical factors				
Fulfilled 1987 ACR criteria	1163 (76.0%)	133 (8.7%)	1236 (76.0%)	130 (7.9%)
Symptom duration, years	2.23 (4.70)	141 (9.2%)	2.18 (4.55)	153 (9.4%)
MTX starting dose, mg/week	12.09 (2.99)	17 (1.1%)	12.11 (2.99)	15 (0.9%)
Comorbidities, two or more	434 (28.4%)	0 (0.0%)	463 (28.5%)	0 (0.0%)
HAQ-DI score (0–3)	1.07 (0.73)	0 (0%)	1.09 (0.74)	92 (5.7%)
DAS28-CRP (0.96–10)	4.16 (1.34)	65 (4.3%)	4.23 (1.34)	0 (0%)
Tender joint count (0–28)	7.57 (7.37)	43 (2.8%)	7.96 (7.56)	0 (0%)
Swollen joint count (0–28)	6.01 (5.57)	45 (2.9%)	6.18 (5.71)	0 (0%)
CRP value, mg/L	14.36 (23.50)	13 (0.9%)	14.32 (23.13)	0 (0%)
VAS general wellbeing (0–100 mm)	40.4 (23.7)	8 (0.5%)	41.8 (23.7)	0 (0%)

ACR, American College of Rheumatology; BMI, body mass index; CRP, c-reactive protein; DAS28, 28-joint Disease Activity Score; HAQ-DI, health assessment questionnaire – disability index; IMD, index of multiple deprivation; kg, kilograms; m, meters; mg, milligrams; MTX, methotrexate; SD, standard deviation; VAS, visual analogue scale. †BMI categories defined as: underweight (BMI <18.5 kg/m²), normal weight (BMI 18.5–24.9 kg/m²), overweight (BMI 25.0–29.9 kg/m²), obesity (BMI ≥ 30.0 kg/m²).

6.4.2 The relationship between area-level deprivation and HAQ-DI and DAS28 scores

Those living in the most deprived areas were more likely to have higher self-reported disability scores (measured through HAQ-DI) (adj regression coefficient 0.32 (95% CI 0.19, 0.45)) and disease activity scores (measured through DAS28) (adj regression coefficient 0.34 (95% CI 0.11, 0.58)) over the subsequent year, compared with those living in the least deprived areas (Table 2). Stratified analyses indicated that the relationship between higher deprivation and DAS28 was stronger for obese versus non-obese people with RA (adj regression coefficients 0.39 (95% CI 0.02, 0.76) for obese people and 0.22 (95% CI -0.09, 0.52) for non-obese people) (Table 3). Out of the different components of DAS28, area-level deprivation was only associated with more tender joints and higher VAS general wellbeing score (Supplementary Table S1).

6.4.3 The relationship between obesity and HAQ-DI and DAS28 scores

Over time, obese people with RA at baseline were more likely to have higher HAQ-DI scores (adj regression coefficient 0.13 (95% CI 0.06, 0.20) and DAS28 scores (adj regression coefficient 0.17 (95% CI 0.04, 0.31) over the subsequent year, compared with non-obese people with RA (Table 2). A 1-unit BMI increment was also associated with a 0.01 (95% CI 0.00, 0.01) increase in HAQ-DI score and a 0.01 (95% CI 0.00, 0.02) increase in DAS28 score. Stratified analyses indicated that the relationship between obesity and DAS28 was dependent on gender: adj regression coefficients 0.14 (95% CI -0.11, 0.39) for men and 0.20 (95% CI 0.03, 0.36) for women (Table 4). However, no substantial gender differences were observed for the different components of the DAS28 (Supplementary Table S2).

Table 2: Linear mixed effect models for the relationships of deprivation and obesity with HAQ-DI and DAS28 score

	HAQ-DI score (0–3) Regression coefficient (95% CI)		DAS28 score (0.96–10) Regression coefficient (95% CI)	
	Unadjusted	Adjusted	Unadjusted	Adjusted
Index of Multiple Deprivation quintiles				
1: most deprived	**0.38 (0.25, 0.50)**	**0.32 (0.19, 0.45)**	**0.51 (0.31, 0.71)**	**0.34 (0.11, 0.58)**
2	**0.18 (0.07, 0.28)**	**0.14 (0.03, 0.25)**	**0.36 (0.19, 0.52)**	**0.30 (0.09, 0.51)**
3	0.02 (-0.08, 0.12)	0.03 (-0.07, 0.14)	0.16 (-0.01, 0.32)	0.15 (-0.06, 0.35)
4	-0.06 (-0.16, 0.03)	-0.12 (-0.22, -0.03)	0.03 (-0.13, 0.18)	-0.01 (-0.19, 0.17)
5: least deprived	ref	ref	ref	ref
Obesity				
Obesity	**0.19 (0.13, 0.24)**	**0.13 (0.06, 0.20)**	**0.41 (0.30, 0.51)**	**0.17 (0.04, 0.31)**
Non-obesity	ref	ref	ref	ref
BMI per 1 kg/m^2 increment	**0.02 (0.02, 0.03)**	**0.01 (0.00, 0.01)**	**0.04 (0.03, 0.05)**	**0.01 (0.00, 0.02)**

BMI, body mass index; CI, confidence interval; DAS28, disease activity score 28; HAQ-DI, health assessment questionnaire; kg, kilograms; m, meters. Obesity analyses adjusted for age, gender, ethnicity, deprivation, smoking, physical activity and alcohol consumption. Socioeconomic position analyses adjusted for age and gender. Bold values indicate statistical significance. For HAQ-DI, no interaction between obesity and gender (p=0.273), obesity and IMD (p=0.188) and IMD and gender (p=0.909). For DAS28, evidence of interaction between obesity and IMD (p=0.020), but not for obesity and gender (p=0.676) and IMD and gender (p=0.377).

Table 3: Linear mixed effect models for the relationship between deprivation and HAQ-DI and DAS28 score by obesity status

	HAQ-DI score (0–3) Regression coefficient (95% CI)		DAS28 score (0–10) Regression coefficient (95% CI)	
	No obesity	Obesity	No obesity	Obesity
Index of Multiple Deprivation quintiles				
1: most deprived	**0.31 (0.14, 0.47)**	**0.25 (0.04, 0.45)**	0.22 (-0.09, 0.52)	**0.39 (0.02, 0.76)**
2	0.09 (-0.04, 0.22)	0.17 (-0.02, 0.37)	0.15 (-0.10, 0.40)	**0.49 (0.14, 0.83)**
3	0.01 (-0.12, 0.13)	0.07 (-0.13, 0.26)	0.19 (-0.05, 0.43)	0.02 (-0.32, 0.37)
4	-0.10 (-0.22, 0.01)	-0.15(-0.34, 0.04)	0.06 (-0.16, 0.28)	-0.17 (-0.51, 0.17)
5: least deprived	ref	ref	ref	ref

CI, confidence interval; DAS28, disease activity score 28; HAQ-DI, health assessment questionnaire. Adjusted for age and gender. Bold values indicate statistical significance.

Table 4: Linear mixed effect models for the relationship between obesity and DAS28 score by gender

	HAQ-DI score (0–3) Regression coefficient (95% CI)		DAS28 score (0–10) Regression coefficient (95% CI)	
	Men	Women	Men	Women
Obesity				
Obesity	**0.18 (0.06, 0.30)**	**0.11 (0.03, 0.19)**	0.14 (-0.11, 0.39)	**0.20 (0.03, 0.36)**
Non-obesity	ref	ref	ref	ref
BMI per 1 kg/m^2 increment	0.01 (-0.00, 0.02)	**0.01 (0.00, 0.02)**	0.01 (-0.02, 0.03)	**0.01 (0.00, 0.02)**

BMI, body mass index; CI, confidence interval; DAS28, disease activity score 28; kg, kilograms; m, meters. Adjusted for age, ethnicity, deprivation, smoking, physical activity and alcohol consumption. Bold values indicate statistical significance.

6.4.4 The mediating effect of body mass index for the relationship between area-level deprivation and HAQ-DI and DAS28 scores

BMI mediated part of the association between higher deprivation and HAQ-DI scores (14.24%) and DAS28 scores (17.26%) in the total study population (men and women combined). However, there were no indirect effects when restricting the sample to men only. For women, the mediating effect of BMI were 17.79% and 25.56% for HAQ-DI and DAS28 respectively (Table 5).

Results from the sensitivity analysis to test sequential ignorability indicated that the degree of unmeasured confounding required to explain way the observed mediation effect for both HAQ-DI and DAS28 was a ρ of 0.2.

Table 5: The total, direct and indirect effect (via BMI) of area-level deprivation on average HAQ-DI and DAS28 scores

	β-coefficient (95% CI)			Proportion mediated (95% CI)*
	Total	Direct	Indirect	
Average HAQ-DI score (0–3)				
Total	**0.097 (0.067, 0.120)**	**0.083 (0.054, 0.110)**	**0.014 (0.007, 0.020)**	14.24% (7.77%, 23.00%)
Men	**0.098 (0.049, 0.145)**	**0.091 (0.042, 0.136)**	0.007 (-0.001, 0.019)	-
Women	**0.095 (0.065, 0.130)**	**0.078 (0.050, 0.110)**	**0.017 (0.008, 0.030)**	17.79% (8.67%, 30.00%)
Average DAS28 score (0–10)				
Total	**0.122 (0.083, 0.162)**	**0.101 (0.062, 0.140)**	**0.021 (0.012, 0.032)**	17.26% (9.72%, 29.00%)
Men	**0.123 (0.055, 0.190)**	**0.119 (0.051, 0.190)**	0.004 (-0.002, 0.020)	-
Women	**0.120 (0.007, 0.170)**	**0.089 (0.039, 0.130)**	**0.031 (0.018, 0.046)**	25.56% (14.35%, 44.00%)

CI, confidence interval; DAS28, disease activity score 28; HAQ-DI, health assessment questionnaire; *Calculated by indirect effect/total effect*100%. 95% CI estimated with bootstrapping. For men, there were no indirect effects so the proportion mediated was not calculated. The exposure-mediator interaction was non-significant for both HAQ-DI (p=0.83) and DAS28 (p=0.09), indicating that the no exposure-mediator interaction assumption holds.

6.5 Discussion

In this study of adults with RA starting MTX for the first time, we found that area-level deprivation was associated with worse disability and disease activity over the subsequent year. We found that a proportion of these associations could be explained by obesity.

The temporal relationship between a lower SEP (measured through both individual indicators and area-level measures) and worse outcomes in RA has been found previously[6-9]. However, longitudinal studies performed in England are limited. Given the complex interactions between SEP and obesity, it was important to investigate the interactions between area-level deprivation and obesity on RA disease outcomes. We found that the association between deprivation and DAS28 was stronger among those with obesity versus those without, indicating that in people who live in more deprived areas, having obesity is associated with worse disease outcomes. We further found that part of the association between deprivation and RA outcomes can be explained by BMI. Notably, when restricting the sample to men or women only, the mediating effect of BMI was only observed among women for both disability and disease activity. This may partly be explained by the stronger relationship between lower SEP and obesity among women compared with men in the general population[11]. Another explanation may be that we found that the association between obesity and DAS28 was stronger among women than men; however, no gender differences were observed for the separate components of DAS28. It is therefore also possible that our sample size for men was too small to find an effect. It is also possible that fibromyalgia may play a role; obesity is associated with fibromyalgia[27], it is generally more common among women[28] and it has been associated with worse RA outcomes[29]. However, this needs further investigation. Gender differences for the relationship between obesity and RA outcomes have not been studied extensively; however, a Swedish clinical trial assessing MTX also found that obese women were less likely to achieve remission compared to non-obese women or obese men[30]. These gender differences for the relationship between BMI and functional limitations have also been found in the general population[31]. Although the exact reasons for this are unclear, a potential explanation is that men are more likely to underreport limitations whereas women are more willing to report, or even overestimate, their physical limitations[32].

In general, a large part of the association between area-level deprivation and worse RA outcomes could not be explained by obesity, indicating that other factors may be important too. For example, it has been suggested that differences in disease progression could be due to lower patient participation (i.e. less rheumatologist visits)[33] and treatment delays[34] in people with RA with lower SEP. Potentially this may lead people with RA to missing the "window of opportunity" in the early stages of disease[35], resulting in worse outcomes over time among those with a lower SEP[36].

The relationship between obesity and worse RA outcomes has been reported in previous studies[12-16]. Although it is uncertain what the exact mechanisms for this relationship are, there are a few potential explanations. Firstly, inflammation and immunological changes instigated by adipose tissue may drive

disease activity[18]; however, in our study we did not find an association between obesity and CRP levels in people with RA. Secondly, obese people with RA may be less responsive to rheumatic medications, including MTX, and therefore have higher disease activity than those without obesity[37]. It has been hypothesised that this may also be due to higher levels of pro-inflammatory cytokines in obese individuals[37]. Thirdly, self-reported musculoskeletal pain is higher in obese people with RA[38], which may be partly explained by disrupted neurotransmitters and hormones[27]. In line with this third point, we found that the higher DAS28 scores in obese individuals were driven by the subjective components, tender joint count and VAS general wellbeing, rather than swollen joint counts or CRP levels. Higher pain may further impact daily activities in the HAQ-DI.

Strengths of this study includes that it is a prospective cohort study with measurements of HAQ-DI and DAS28 at two or more time points, allowing the analysis of temporal associations between deprivation, obesity and RA outcomes. Unfortunately, we only had data about area-level deprivation which we used as a proxy for SEP. Area-level deprivation measures have sometimes been criticised as they misclassify people who experience deprivation but do not live in deprived areas[39]. Therefore, these results need to be validated in future studies where individual-based indicators, such as education, occupation, income or wealth, are used. Although educational level was recorded in RAMS, 41% of the sample had missing values; hence, it was decided to not include this in our analyses. Furthermore, BMI is an imperfect measure of adiposity[40]. It would have been interesting to investigate waist circumference (WC), as WC has a stronger association with inflammatory factors than BMI[41] which may contribute to worse progression of disease. Unfortunately, WC was not recorded in RAMS. RAMS has a short follow-up (max 12 months), which may be too short to investigate the longitudinal effects of socioeconomic factors and obesity on RA disease progression. Lastly, the criteria for selecting the study samples may have resulted in selection bias. The DAS28 sample is slightly larger than the HAQ-DI sample, as the DAS28 components were measured during the CRF and HAQ-DI components were recorded in the patient questionnaire which required the additional steps of completing it and sending it to the co-ordinating research centre by the study nurse or the participant. However, baseline characteristics between the two groups did not differ substantially, except in terms of ethnicity (Table 1). Moreover, loss to follow-up was differential (Supplementary Table S3 shows the characteristics of people who were lost to follow-up); those from more deprived areas were more likely to not have at least one follow-up measurement and were therefore excluded from this study. In addition to this, people in disadvantaged groups are less likely to participate in research generally[42]. Therefore, it is possible that our study population may not represent the whole RA population in England.

With these limitations in mind, there are some important implications of the findings of this study. We cannot definitely conclude that the relationships found in this study are causal due to the observational nature of our study; however, we did find that obesity is an important factor for social disparities in RA outcomes. Recently updated NICE guidelines suggest that multicomponent treatment interventions should be the first choice of treatment, which includes behaviour change strategies to improve people's diet and

increase physical activity[43]. If lifestyle interventions are ineffective, medication or bariatric surgery can be considered[43]. Studies assessing the impact of weight loss interventions in people with RA are limited. A retrospective study indicated that weight loss of ≥5 kg was associated with reduced disease activity[44]. More recently, a pilot randomised clinical trial including 50 participants reported that a weight and pain management programme is effective in improving function and reducing pain in obese people with established RA[45]. There is also emerging evidence that disease activity is reduced after bariatric surgery[46-48]. These studies show potential for weight loss interventions to improve RA outcomes. However, it is unknown whether weight loss interventions in obese people with RA are effective in different socioeconomic groups, for which further research is indicated.

To conclude, improving disease outcomes is a key aim for the management of RA. In order to address socioeconomic disparities in RA outcomes, it is important to understand why these discrepancies exist and whether they are modifiable. We found that part of the association between area-level deprivation and both disease activity and functional disability in RA is mediated through obesity. Further research is needed to understand whether weight loss interventions for obese people with RA are effective in lower socioeconomic groups.

6.6 References

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6.7 Supplementary material

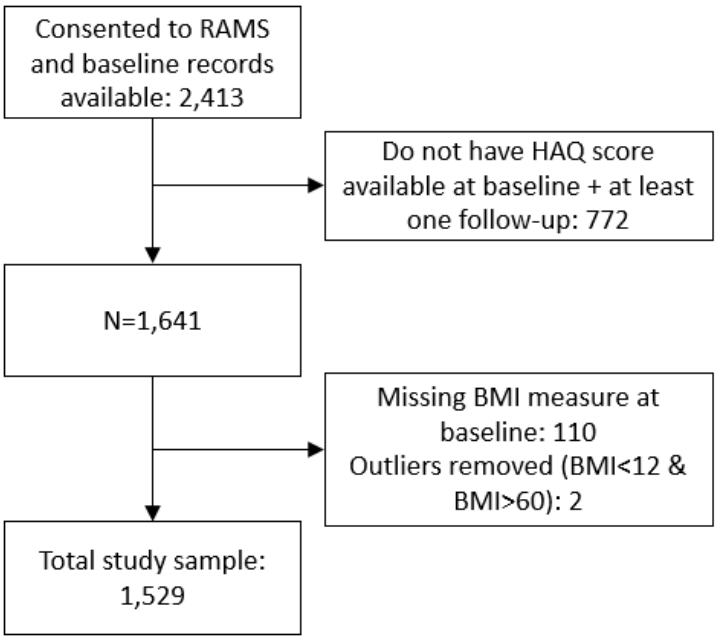

Figure S1: Flowchart of participant selection for HAQ analyses

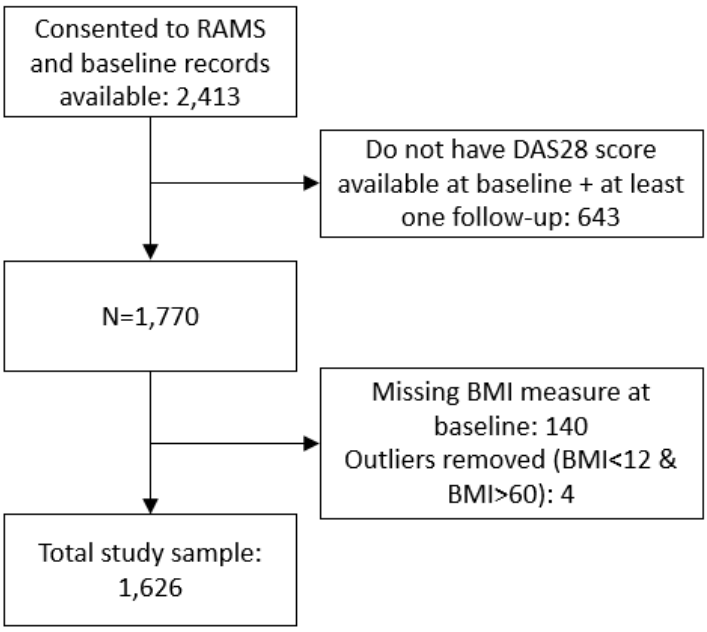

Figure S2: Flowchart of participant selection for DAS28 analyses

Table S1: Linear mixed effect models for the relationships of deprivation and obesity with separate DAS28 components (tender joint counts, swollen joint counts, CRP levels and VAS general wellbeing)

	Regression coefficient (95% CI)							
	Tender joint count (0–28)		Swollen joint count (0–28)		CRP levels		VAS general wellbeing (0-100)	
	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted
Index of Multiple Deprivation quintiles								
1: most deprived	**2.31 (1.27, 3.34)**	**2.16 (0.83, 3.49)**	0.29 (-0.37, 0.95)	-0.23 (-1.25, 0.79)	1.02 (-1.27, 3.31)	0.93 (-3.28, 5.14)	**9.51 (6.32, 12.69)**	**7.95 (3.81, 12.09)**
2	**2.01 (1.12, 2.91)**	**1.57 (0.39, 2.76)**	**0.64 (0.09, 1.19)**	0.53 (-0.36, 1.42)	-0.42 (-2.41, 1.57)	-0.47 (-4.11, 3.17)	**6.08 (3.37, 8.78)**	**7.07 (3.57, 10.57)**
3	**1.23 (0.38, 2.09)**	**1.19 (0.10, 2.28)**	0.24 (-0.30, 0.78)	0.14 (-0.71, 0.99)	0.64 (-1.29, 2.57)	1.85 (-1.70, 5.40)	1.18 (-1.50, 3.85)	2.15 (-1.37, 5.67)
4	0.17 (-0.64, 0.98)	-0.15 (-1.19, 0.88)	-0.10 (-0.61, 0.40)	-0.49 (-1.29, 0.31)	0.46 (-1.38, 2.31)	0.94 (-2.37, 4.24)	0.16 (-2.36, 2.68)	1.08 (-2.14, 4.30)
5: least deprived	ref	ref	ref	ref	ref	ref	ref	ref
Obesity								
Obesity	**1.50 (0.95, 2.04)**	**0.90 (0.12, 1.69)**	**0.65 (0.29, 1.02)**	0.52 (-0.09, 1.12)	1.23 (-0.10, 2.57)	-1.41 (-3.94, 1.12)	**5.65 (3.89, 7.42)**	1.43 (-0.99, 3.84)
Non-obesity	ref	ref	ref	ref	ref	ref	ref	ref
BMI per 1 kg/m^2 increment	0.16 (0.11, 0.20)	0.07 (0.01, 0.13)	**0.06 (0.03, 0.09)**	0.03 (-0.01, 0.08)	**0.11 (0.00, 0.21)**	-0.17 (-0.37, 0.03)	**0.47 (0.33, 0.61)**	0.00 (-0.19, 0.19)

BMI, body mass index; CI, confidence interval; DAS28, disease activity score 28; kg, kilograms; m, meters. Obesity analyses adjusted for age, gender, ethnicity, deprivation, smoking, physical activity and alcohol consumption. Socioeconomic position analyses adjusted for age and gender. Bold values indicate statistical significance.

Table S2: Linear mixed effect models for the relationships of deprivation and obesity with separate DAS28 components (tender joint counts, swollen joint counts, CRP levels and VAS general wellbeing) by gender

	Regression coefficient (95% CI)							
	Tender joint count (0–28)		Swollen joint count (0–28)		CRP levels		VAS general wellbeing (0-100)	
	Men	Women	Men	Women	Men	Women	Men	Women
Index of Multiple Deprivation quintiles								
1: most deprived	1.81 (-0.42, 4.03)	**2.14 (0.50, 3.78)**	-0.56 (-2.46, 1.35)	-0.25 (-1.45, 0.95)	4.51 (-3.65,	-0.33 (-5.43, 4.77)	**11.17 (3.82, 18.51)**	**6.62 (1.70, 11.54)**
2	**3.00 (1.17, 4.83)**	0.79 (-0.67, 2.25)	1.17 (-0.37, 2.71)	0.11 (-0.95, 1.17)	-3.28 (-9.83, 3.28)	0.83 (-3.59, 5.25)	**7.84 (1.98, 13.70)**	**6.47 (2.11, 10.82)**
3	0.74 (-0.94, 2.42)	**1.43 (0.00, 2.85)**	-0.16 (-1.60, 1.29)	0.31 (-0.72, 1.35)	2.24 (-3.91, 8.40)	1.65 (-2.62, 5.93)	-0.21 (-5.89, 5.47)	3.50 (-0.83, 7.82)
4	-0.32 (-1.90, 1.27)	-0.15 (-1.52, 1.21)	-0.57 (-1.93, 0.79)	-0.53 (-1.54, 0.47)	-0.39 (-6.22, 5.45)	1.61 (-2.50, 5.73)	4.98 (-0.30, 10.27)	-0.99 (-5.10, 3.13)
5: least deprived	ref	ref	ref	ref	ref	ref	ref	ref
Obesity								
Obesity	1.03 (-0.21, 2.27)	0.84 (-0.16, 1.84)	0.55 (-0.53, 1.63)	0.53 (-0.23, 1.29)	-3.68 (-8.22, 0.86)	0.33 (-2.68, 3.33)	3.36 (-0.83, 7.55)	0.58 (-2.38, 3.54)
Non-obesity	ref	ref	ref	ref	ref	ref	ref	ref
BMI per 1 kg/m^2 increment	0.06 (-0.05, 0.18)	0.07 (-0.00, 0.15)	0.02 (-0.08, 0.12)	0.04 (-0.02, 0.10)	-0.64 (-1.07, -0.21)	-0.01 (-0.23, 0.22)	0.27 (-0.11, 0.65)	-0.07 (-0.29, 0.14)

BMI, body mass index; CI, confidence interval; DAS28, disease activity score 28; kg, kilograms; m, meters. Obesity analyses adjusted for age, gender, ethnicity, deprivation, smoking, physical activity and alcohol consumption. Socioeconomic position analyses adjusted for age and gender. Bold values indicate statistical significance.

Table S3: Characteristics of people who were excluded due to missing BMI or follow-ups for the HAQ analyses

Characteristics	Frequencies (%) / mean (SD)			
	Excluded due to missing follow-up (N=772)	Missing	Excluded due to missing BMI values N=112	Missing
Age, *years*	54.66 (14.26)	6 (0.78%)	60.94 (12.13)	0 (0.0%)
Gender, *female*	510 (66.06%)	6 (0.78%)	77 (68.8%)	0 (0.0%)
Ethnicity, *white*	491 (92.6%)	242 (31.3%)	105 (93.8%)	1 (0.9%)
IMD fifths, *1: most deprived*	139 (18.0%)	33 (4.3%)	14 (12.5%)	5 (4.5%)
2	160 (20.7%)		22 (19.6%)	
3	149 (19.3%)		26 (23.2%)	
4	150 (19.4%)		19 (17.0%)	
5: least deprived	141 (18.3%)		26 (23.2%)	
Smoking status, *Never*	234 (30.3%)	32 (4.1%)	44 (39.3%)	6 (5.4%)
Former	272 (35.2%)		39 (34.8%)	
Current	234 (30.3%)		23 (20.5%)	
Physical activity, *Much more*	21 (2.7%)	236 (30.6%)	8 (7.1%)	0 (0.0%)
More	68 (8.8%)		18 (16.1%)	
The same	129 (16.7%)		35 (31.3%)	
Less	194 (25.1%)		36 (32.1%)	
Much less	124 (16.1%)		15 (13.4%)	
Alcohol intake, *Yes*	454 (58.8%)	46 (6.0%)	76 (67.9%)	11 (9.8%)
BMI, kg/m²	28.59 (6.39)	131 (17.0%)	-	-
Underweight	16 (2.1%)			
Normal weight	190 (24.6%)			
Overweight	209 (27.1%)			
Obesity	226 (29.3%)			
HAQ-DI score (0–3)	1.12 (0.77)	246 (31.9%)	1.14 (0.79)	0 (0.0%)

Chapter 7

7. Discussion

The main aim of this thesis was to advance the understanding of the relationships between SEP, obesity and the development and progression of arthritis. As described in the Introduction, previous studies have reported socioeconomic inequalities in the development and progression of arthritis; however, it was unknown whether this could be explained by higher obesity levels in lower socioeconomic groups. A better understanding of pathways of disease onset and progression may help to inform targeted prevention and intervention strategies.

Within the main aim, four objectives were defined: 1) To summarise the current understanding of the relationship between SEP and obesity, 2) To understand the associations between SEP, obesity and incident arthritis, 3) To understand the associations between SEP, obesity and the progression of OA and 4) To understand the associations between SEP, obesity and the progression of RA. The first objective was addressed through a SLR. The second and third objectives were examined using data from ELSA, a representative population of adults aged 50 years and older in England. The fourth objective was addressed using data from RAMS, a cohort of people with RA in England who were starting MTX therapy.

7.1 Summary of the findings

The following sections will summarise the results into four main themes:

I. The relationship between SEP and obesity
II. The relationship between SEP and arthritis incidence and progression of disease
III. The relationship between obesity and arthritis incidence and progression of disease
IV. The mediating effect of BMI for the relationships between SEP and the development and progression of arthritis

7.1.1 The relationship between socioeconomic position and obesity

The SLR, in Chapter 3, summarised the current understanding of the relationship between SEP and obesity. The results have been published in the journal *Social Science & Medicine - Population Health*[410]. The review provided new insights into whether the association between educational attainment and obesity differed by measure of obesity (total versus central obesity) and by gender. In line with previous SLRs[109-112, 114, 115], an association was found between having a lower education and total and central obesity, and this relationship was stronger among women than men. A novel finding of this review was that, only in men, the relationship was found to be stronger for total compared to central obesity.

A possible explanation for these results may relate to occupational differences between men and women. Lower SEP men engage in more occupational physical activity than women[116], potentially reducing their obesity levels. This may also explain why there is a stronger relationship for total obesity compared with central obesity among men, as occupational physical activity may lead to increased muscle mass, increasing BMI but not WC[411]. This study only focussed on one indicator of SEP, educational attainment. Although the indicators of SEP are interrelated, education does not capture the full spectrum of SEP. Therefore, further research is needed to explore possible associations between other SEP indicators (e.g. occupation) and total and central obesity.

7.1.2 The relationship between socioeconomic position and the development and progression of arthritis

7.1.2.1 Incidence

The relationship between multiple indicators of SEP and incident arthritis was examined in Chapter 4. Only the results of incident OA have been published in the journal *Seminars in Arthritis and Rheumatism*[412], as there were concerns regarding potential misclassification for RA cases (as discussed in more detail in section 7.2.6). However, as the misclassification is likely non-differential, and will thus underestimate the true effect, this section will still discuss the results of the RA analysis (which were provided in Appendix F).

Using data from ELSA, the results showed that in an older population in England, those with lower individual-level SEP (education, occupation, income and wealth) and area-level SEP (deprivation) were more likely to develop both OA and RA over time compared to those from less deprived backgrounds or areas. Although previous cross-sectional and case-control studies had linked a lower SEP with RA[288-290] and

OA[182-185], prospective cohort studies were lacking. Prospective cohort studies were needed to ascertain the direction of the relationship. Therefore, this study using longitudinal data provided important insights about the fact that lower SEP at baseline increases the risk of developing arthritis over time.

As mentioned in the Introduction, SEP is considered a distal factor, affecting health indirectly via more proximal factors, such as lifestyle and environmental factors[413]. Understanding what these proximal factors are is important for targeted prevention strategies in those who are most vulnerable to developing arthritis. This study demonstrated that the relationship between lower SEP and increased arthritis incidence can partly be explained by higher obesity rates in those with lower SEP (which is further discussed in section 7.1.4). However, other factors may also play a role. For example, manual occupations are more common among those with lower SEP[116] and are associated with increased risk for the development of OA through heavy physical work load and increased risks for work-related joint trauma[188]. Moreover, smoking and exposure to environmental pollutants, which may be more common among those with lower SEP, have been associated with the development of RA[260-263, 267-269].

7.1.2.2 Progression

The relationships between SEP and the progression of OA and RA was investigated in Chapters 5 and 6, respectively. Chapter 5 highlighted that lower individual- and area-level SEP was associated with worse functional disability (measured through ADLs and mobility indicators) in people with OA aged 50 years and older over time. Although previous studies indicated a link between SEP and worse progression of OA[226-229], this study shed a light on the direction of the relationship, i.e. lower SEP leading to worse disability. Importantly, the study further elucidated that obesity mediates some of the relationship between lower SEP and disability, but not all. Therefore, higher disability rates among people with OA in lower SEP groups may also be explained by other lifestyle factors[414] (such as comorbidities, smoking and lower physical activity) and community factors[415] (such as fewer clinics and less safe places to exercise in deprived areas) leading to functional limitations. Evidence also points to socioeconomic inequities in receiving education on self-care and weight management[416]. For instance, a study in Canada has shown that in people with OA, having a lower education was associated with receiving less advice on exercise compared with people with a higher education[417]. Lastly, this study highlighted that those with lower SEP are less likely to have knee JRS compared to those with higher SEP; as knee JRS is associated with improved outcomes in OA[134], this may make socioeconomic inequalities in OA outcomes even worse.

The finding of inequalities in knee JRS may be expected in a fully privatised healthcare system, where people need to fund medical care or health insurance themselves. However, the NHS is free at the point of use, which means that in theory everyone should be able to use the full breadth of medical care regardless of SEP. Nonetheless, the results of this study align with studies from other countries with government-funded healthcare systems[232-234]. This points towards barriers experienced by those with lower SEP that are not just related to the cost of the procedure. Other potential barriers include fewer specialised clinics

in deprived communities[415], reduced social support needed to recover from surgery[234], and physician bias, where those from a lower SEP are less likely to be referred to specialist care[418].

Chapter 6 provided insights into the relationships between area-level deprivation and progression of RA. In line with previous literature from other countries[336-339], the results indicated that people with RA living in the most deprived areas had higher disability rates (measured through HAQ-DI) and higher disease activity scores (measured through DAS28) compared with those living in the least deprived areas. Importantly, the results highlighted that a proportion of these relationships could be explained by higher obesity rates among those living in deprived communities. However, as obesity did not explain the full associations, other factors may be important too. It has been suggested that lower patient participation among the lower SEP[341] may be responsible for treatment delays[419], and missing the opportunity for early treatment may result in worse outcomes over time[420].

7.1.3 The relationship between obesity and the development and progression of arthritis

7.1.3.1 Incidence

The association between obesity and incident arthritis was investigated in Chapter 4. Previous studies on this topic mostly focused on total obesity only. However, central obesity has a stronger association with pro-inflammatory factors than total obesity, and it has been shown that pro-inflammatory factors may lead to joint inflammation and joint damage[177, 178]. Therefore, importantly, my investigation focused on both types of obesity.

The results of Chapter 4 showed that both total and central obesity were independently associated with incident OA and RA, irrespective of gender. Surprisingly, there were no notable differences in the strength of the effect sizes between the two measures. This may be because they are highly correlated, and may measure the same construct: adiposity.

Both total and central obesity have been linked to incident OA[170]; however, the majority of research to date on central obesity was cross-sectional and did not account for SEP[179, 180], which is a potential confounder for the relationship. This study, therefore, confirmed that there is a temporal relationship between both total and central obesity and incident OA, independent of SEP. The results of Chapter 4 support the idea that, in addition to mechanical stress on joints, inflammation brought on by central adiposity may potentially play a role in the development of OA. However, further research is necessary to determine the processes by which both types of obesity are associated with incident OA and whether they differ from one another.

The relationship between total obesity and RA, independent of SEP, has also been demonstrated previously[274, 281]. However, few studies investigated central obesity and the findings were inconsistent. Two Scandinavian studies found no association between central obesity and incident RA in women (but did in men)[284] and in both men and women[285]. A potential reason for not finding an association was that the

number of cases of RA was too low to detect an association for both these studies. In contrast, in a larger cohort using data from the Nurses' Health Study, central obesity was associated with incident RA in women (incident cases = 844)[421]. Chapter 4 confirmed that there is a temporal association between both total and central obesity and incident RA among both men and women.

7.1.3.2 Progression

In Chapter 5 and 6, I studied the relationship between obesity and the progression of OA and RA, respectively. The results in Chapter 5 showed that, in people with knee OA, total obesity was associated with increased functional disability and higher risk of knee JRS; these findings were in line with previous longitudinal studies[220-222, 422, 423]. There are some explanations why obese OA patients may have a higher disease burden. Firstly, being overweight or obese puts pressure on joints, potentially leading to increased joint degeneration[424]. Secondly, it is thought that low-grade inflammation in obese people with OA contributes to synovial inflammation and progression of pain in OA[38]. Lastly, reduced mobility caused by being obese may result in reduced physical activity and muscle strength; this could lead to a vicious cycle of being obese -> reduced physical activity -> reduced mobility -> disability -> weight gain[425]. Interestingly, Chapter 5 found that there was no interaction between obesity and SEP indicators for knee JRS. However, it was hypothesised that this could be because the two factors cancel each other out, i.e. lower SEP associated with lower rates of surgery and obesity with increased rates of surgery. This compounds poor outcomes for people from lower SEP, because they are more likely to be obese and have OA, but less likely to receive beneficial surgery (section 7.1.2.2 explained potential reasons for lower surgery rates among lower SEP).

Similarly, the results in Chapter 6 indicated that total obesity was associated with increased disability and higher disease activity in people with RA starting MTX for the first time. This finding is in line with what has been reported in previous studies[321-325]. Although specific processes underlying this association are unknown, several possible reasons include: 1) obese people with RA are less responsive to MTX leading to higher disease activity[426]; 2) adipose tissue is associated with inflammation, potentially increasing disease activity[427]; and 3) higher musculoskeletal pain levels in general in obese people with RA, impacting daily activities in the HAQ[331].

7.1.4 The mediating effect of body mass index for the relationship between socioeconomic position and the development and progression of arthritis

Previous sections discussed the different relationships studied in this PhD: section 7.1.1 described the relationship between lower SEP and obesity, section 7.1.2 highlighted the relationship between lower SEP and the development and progression of arthritis, and section 7.1.3 illustrated the relationship between obesity and the development and progression of arthritis. The novel part of this PhD project was to bring all these relationships together. It was hypothesised that obesity was a mediator for the relationship between lower SEP and the development and progression of arthritis (Figure 15). I investigated the

mediating effects of BMI on the relationship between lower SEP and incident arthritis in Chapter 4, the progression of OA in Chapter 5 and the progression of RA in Chapter 6.

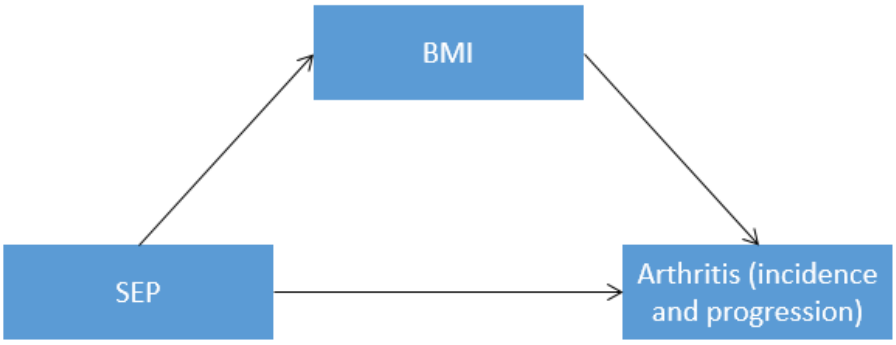

Figure 15: The mediating effect of BMI for the relationship between SEP and the development and progression of arthritis
BMI, body mass index; SEP, socioeconomic position

7.1.4.1 Incidence

In Chapter 4, it was found that the relationship between lower SEP and incident OA and RA was mediated through BMI (proportion mediated: for OA, not calculated as there was only an indirect effect; for RA, 16.8% in women and 10.0% in men). For RA, the direct effect (independent from BMI) was also statistically significant, whereas this was not the case for OA. Two previous studies investigated whether BMI mediated the relationship between lower SEP and incident OA and RA using Mendelian Randomisation techniques[186, 292]. Mendelian Randomisation suffers less from confounding than observational studies, as genetic variants are randomly allocated at conception. Similar to our study, Zhao et al found that 17% of the relationship between genetically-predicted lower educational attainment and having RA was mediated through BMI[292]. However, Gill et al found that this was 23% for OA[186]. This is a smaller effect than what was found in our study. It is possible that BMI has a larger effect on OA via measured variables of SEP than genetically-predicted education. Another potential reason is that both BMI and education cannot be fully predicted using genes, resulting in non-differential misclassification and an underestimation of effect in the study of Gill et al. Nonetheless, the conclusion is the same: both Gill et al and my study indicate an important mediating effect of BMI on the relationship between lower SEP and OA.

In addition, Chapter 4 found that the indirect, or mediating, effects of BMI were slightly higher for women than men. This may be underpinned by the finding in Chapter 3: the relationship between a lower SEP and obesity is also stronger among women compared to men. As a result, for the SEP -> BMI -> arthritis relationship, BMI plays a greater role in women than men. It may also be the case that the sample size for men was too small to find an effect.

7.1.4.2 Progression

BMI also mediated the relationship between lower SEP and the progression of arthritis, as outlined in Chapter 5 for OA and Chapter 6 for RA. Importantly, and similar to the results of incident arthritis, there

were gender differences for the mediating effect of BMI. In Chapter 5, the results highlighted that a proportion of the relationship between lower SEP and mobility (19.4% for women and 5.5% for men) and activities of daily living (11.7% for women and no mediating effect for men) was mediated by BMI in people with knee OA. The results in Chapter 6 showed that, among women with RA, 17.3% and 29.1% of the associations between higher area-level deprivation and disability and disease activity scores were mediated by BMI, respectively. However, no mediating effect was observed among men. These results highlight the critical finding that obesity may be a more important factor leading to functional disability for women with lower SEP than men in an older population with knee OA. Reasons for these gender differences may be attributed to the aforementioned considerations, including gender-differences in the SEP-obesity relationship or the smaller sample size among men. These are novel findings; to my knowledge, no previous studies researching the mediating effect of BMI on the relationship between lower SEP and progression of arthritis have been performed.

Nonetheless, a large part of the association between lower SEP and OA and RA outcomes could not be explained by obesity, indicating that other factors are relevant too, such as other lifestyle factors, community factors, inequities in delivery of care or lower patient participation (e.g. number of visits to the rheumatologist or treatment adherence) among the lower SEP. Potential reasons for social disparities in OA and RA burden independent of obesity were explained in more detail previously in section 7.1.2.

7.2 Strengths and limitations of the analyses

The findings of this PhD thesis need to be interpreted in context of the strengths and limitations of the different studies. Specific strengths and limitations of the different studies are discussed in the Discussion sections of Chapters 3, 4, 5 and 6. This section will describe the factors that may have impacted the overall internal validity (the ability of the study to measure what it is meant to measure) and the external validity (the ability of the findings to be generalisable to the population it is meant to study) of this PhD thesis.

7.2.1 Choice of datasets

This PhD study used two different longitudinal datasets. Chapters 4 and 5 used data from ELSA, a large longitudinal cohort study with a maximum follow-up of 16 years, generalisable to the older English population (with the use of probability weights). Chapter 6 used data from RAMS, a longitudinal cohort of people with RA starting MTX for the first time with a follow-up of one year. Strengths of longitudinal studies include the ability to analyse incident cases, changes over time and temporal relationships between predictors and outcome variables. Nonetheless, due to the observational nature of longitudinal studies, it is not possible to conclude with absolute certainty that the relationships that were found in this PhD study are causal. An effort was made to adjust the analyses for relevant confounders, increasing the credence of a causal interpretation, but unmeasured confounding cannot be ruled out. Normally, RCTs are considered the gold standard for drawing conclusions about causality in medical research[79]. Randomisation of the study population balances observed and unobserved participant characteristics, and thus potential

confounders. As a result, differences in the outcome of the study can be attributed to the intervention. However, observational studies are the only way in which we can study the relationships between SEP, obesity and arthritis, as it would be impossible to do an experiment based on these exposures. Another strength was that in each study, a large sample size was included (n>1,499), allowing for more precise estimates and reducing the risk for the results to be due to chance. On the other hand, stratifying the analyses based on gender reduced the sample sizes and power to find statistical effects. This may in part explain some of the null findings for men.

7.2.2 Selection bias

Selection bias can impact external validity and thus the generalisability of the findings. Specifically for this PhD study, it is important to consider the potential lack of inclusion of under-served population groups in the study samples. Under-served populations are groups of people that are less likely to be included in studies due to physical barriers, language barriers, cognitive barriers or a general lack of interest in participating in research[428]. Often under-served populations are from ethnic minorities and lower socioeconomic backgrounds[428]. Unfortunately, study samples in this PhD study also suffered from selection bias.

For example, participants in our analyses were mostly from Caucasian backgrounds (97.5% in Chapter 4, 96.1% in Chapter 5, and 95.3% in Chapter 6). These proportions are not in line with estimates of the general population in England: according to Census estimates from 2019, 84.8% were from Caucasian backgrounds[429]. In Chapter 4, survey weights were used to account for this and to improve the generalisability of the sample; however, this was not possible for Chapter 5 and 6 when determining specific OA and RA population groups. Although there is limited information about the prevalence of OA and RA among different ethnicities in the UK, studies in the US have suggested that the prevalence of both type of arthritis is higher among African and Native Americans compared to Caucasians[164, 258]. This may be similar in the UK, indicating that there is selection bias in our samples. It is therefore plausible that the results from Chapter 5 and 6 are not fully generalisable to the wider OA and RA populations in the UK.

Furthermore, the baseline samples of Chapters 5 and 6 were selected based on a variety of criteria. For example, in Chapter 5, people were included in the main analyses if they had a self-reported OA diagnosis, recorded knee pain (to validate the self-reported OA diagnosis and to focus specifically on knee OA rather than OA at any site) and had a BMI measurement. Participants with a BMI measurement were different than those without. People who had no BMI measurement were more often from a non-white ethnicity and lived in more deprived areas; they also had more missing values in general. Because of this, sensitivity analyses were performed where BMI measurements were imputed for those with missing values. The results from the sensitivity analyses did not change our findings. In Chapter 6, people were included if they had at least one follow-up assessment. People who were excluded due to loss to follow-up after baseline lived more often in the most deprived areas compared to people who were included in the study, indicating

differential loss to follow-up. Although the participants included in the study were from a range of deprivation quintiles and I was able to look at associations, it is likely that the study population did not fully represent the RA population in the UK.

Index event bias may be an issue when studying risk factors for progression of OA and RA in Chapters 5 and 6. This type of bias was explained in detail in section 1.2.5.2, but in short it happens when the sample is selected based on having the disease (e.g. OA or RA) and its causes become correlated. If these causes are unmeasured (e.g. a certain genetic factor), this may lead to unmeasured confounding and an underestimation of the association between a certain measured risk factor and progression of disease. As it was impossible to adjust for unmeasured or unknown confounders, it may be possible that the observed associations between SEP/obesity and the progression of OA and RA were underestimated.

7.2.3 Missing data and attrition

Missing data from people not completing certain questions were addressed using multiple imputation by chained equations. However, it is possible that the missing data may still have biased the results due to the imputation models being incorrectly specified or if the missing data were MNAR instead of MAR. Moreover, attrition may attenuate the generalisability of the sample over time and decrease power. Selective attrition happens when, for example, people from a lower SEP are more likely to leave the study than people with a higher SEP. ELSA aims to maintain generalisability by using weights based on demographic and social factors taking selective attrition into account. However, RAMS experienced selective attrition, as explained in section 7.2.2, impacting the external validity of Chapter 6.

7.2.4 Operationalisation of socioeconomic position

Operationalising the concept of SEP to get a complete overview of the relationship between SEP and the development and progression of arthritis was an important aspect of this PhD project. In ELSA, many SEP indicators were recorded, including education, occupation, income, wealth and deprivation. Specifically for the older population, having a mixture of these measures is essential to capture a complete overview of how SEP influences arthritis. Wealth was particularly a strength as it is a stronger predictor of future mortality compared with other SEP measures in ELSA[100]. Using structural equation modelling, I was able to capture all these different indicators of SEP into one latent variable, improving the precision of the measurement of SEP as a concept.

However, in RAMS, I was only able to use area-level deprivation measured through IMD as a SEP indicator. As mentioned in section 1.1.3.3.5, IMD combines multiple indicators (such as the proportion of unemployed/manual workers, average income levels, education, crime, housing and services) into a composite score and classifies neighbourhoods on a scale of relative deprivation. These scores can be ranked on a national level, making it easy to compare the most deprived versus the least deprived areas. This is useful for governments to inform which areas need additional resources or services[430]. Given the

complexity of SEP, the use of multiple components in one score can be viewed as an advantage over other simpler indicators, such as education level[107].

However, area-level deprivation measures have been criticised. Firstly, area-level deprivation does not mean that each individual living in that neighbourhood experiences personal deprivation, and people experiencing deprivation may not live in deprived neighbourhoods classified by IMD. Therefore, it is a crude measure, and it may miss out on a substantial amount of people who experience deprivation[107]. Moreover, IMDs are based on Lower Layer Super Output Areas (LSOA), which are areas consistent in size (approximately 1500 residents) created to improve small-area statistics in England[60]. This is useful to compare different areas; however, in reality LSOAs may cut through different neighbourhoods and communities. Because of this, boundaries of LSOAs may be blurry and in one LSOA, there may be deprived communities and wealthy communities. Moreover, LSOA may change quickly over time, for instance, in cities. Although the IMD changes every 3–4 years, this may not be often enough to fully capture changing LSOAs. These concerns highlight that the IMD is merely a partial measure of SEP and it is preferable to use multiple proxies for SEP. Therefore, one of the main limitations of Chapter 6 was the over-reliance on area-level deprivation as a proxy for SEP. This means that the results of Chapter 6 can only be interpreted based on area-level SEP, rather than individual-level SEP.

7.2.5 Definitions of obesity

In addition to SEP, obesity was an important exposure variable for this PhD project. Chapters 4 and 5 used nurse-measured height, weight and WC. However, in Chapter 6, height and weight were self-reported. Self-reported height and weight have been subject to misclassification, where people tend to underestimate their BMI category (underestimate their weight and/or overestimate their height)[431]. This is particularly common among men, older people (aged >60 years), the overweight and people with lower SEP[431]. A potential reason for underestimation of weight include the "peer-effect", where being overweight is considered a normal weight because other "peers" are also overweight[431]. Another reason is social desirability bias, where a weight or height is reported conforming to social norms[432]. Indeed, it has been reported that self-reported obesity estimates are lower than obesity rates based on measured weight and height[433]. In Chapter 6, it is therefore possible that obesity rates were underestimated, possibly particularly among the lower SEP. This downward bias in obesity rates may lead to obese people being classified as non-obese and, consequently, lead to an underestimation of the effects of obesity on RA outcomes. Nurse-measured height, weight and WC in Chapters 4 and 5 are therefore a strength of this PhD.

Whilst total obesity (measured through BMI) is a practical measure and most commonly used in scientific studies, it is an imperfect measure. Specifically, as mentioned in the Introduction (section 1.1.1.1), the WHO cut-off points for BMI categories may not be valid for every population group, such as the elderly, athletes or people from different ethnic groups. Therefore, this PhD thesis did not rely on the categories alone, but also used BMI as a continuous variable. The conclusions for BMI as a continuous variable were,

however, in line with those from BMI as a categorical variable. Furthermore, a strength of this PhD project was that I also incorporated central obesity (measured through WC) in Chapters 3 and 4. Central obesity is a better measure of adiposity in the abdominal area and has a stronger association with inflammatory factors. It was hypothesised that central obesity would be particularly important for RA, given it is a form of inflammatory arthritis. Bearing the limitations of RA cases in Chapter 4 in mind (section 7.2.6), differences were not found between total and central obesity. Unfortunately, I was unable to test differences in total and central obesity in Chapter 6 as RAMS did not record WC. For incident OA (Chapter 4), there were no major differences between central and total obesity; therefore, Chapter 5 (about the progression of OA) only included the BMI measure. In addition to BMI and WC, there are other measures that may be more precise. For instance, the most recent NICE guidelines now recommend the use of waist-to-height ratios to define central obesity (section 1.1.1.2.2). As it incorporates the height of people, it may be a more appropriate measure to assess populations with different heights and ethnicities. Lastly, both ELSA and RAMS did not have early life data on total and central obesity. Therefore, it was not possible to study life course effects of BMI/WC on the development and progression of arthritis.

7.2.6 Definitions of arthritis diagnoses

One of the main limitations of the ELSA dataset is that arthritis diagnoses were self-reported and not clinically verified. This self-reported data may be inaccurate due to recall bias leading to misclassified diagnoses. Initially, the objective of Chapter 4 was to investigate the associations between SEP, obesity and incident RA and OA. However, due to the considerably higher incidence rate of self-reported RA in ELSA (1417 per 100,000 persons years) than would be expected in a similar population of older adults (not higher than 100 per 100,000[239]), there was a substantial risk of misclassification of RA cases. Although it is uncertain what the exact reason is for the misclassification in ELSA, it is possible that some people mistake RA for other forms of arthritis or fibromyalgia. The misclassification was likely to be non-differential, which means that it is equally distributed among obese versus non-obese and high versus low SEP. Non-differential misclassification increases the similarity between exposed and non-exposed groups, resulting in an underestimation of the true effect. This is in contrast to differential misclassification, where the misclassification is not equally distributed among different groups; this type of misclassification can lead to either an overestimate or underestimate of the true effect. Even though it was expected that the misclassification of RA cases was non-differential, the potential extent of the RA misclassification was concerning. Therefore, it was decided to remove the incident RA analyses from the publication and focus instead on the incident OA analyses. In spite of that, the results of the RA analyses are presented in this PhD thesis in Appendix F, as the results may still contribute to the knowledge gap of the pathways between SEP, obesity and incident RA.

Self-reported OA diagnoses were still used in Chapters 4 and 5 as the overestimation and misclassification for OA was thought to be minimal as OA incidence and prevalence rates were comparable to other studies. For example, in Chapter 4, the incidence rate of OA in ELSA was estimated to be 3622 per 100,000 person

years. This is comparable to a recent meta-analysis pooling the incidence rates of four UK studies: 3150 per 100,000 person years[152]. In Chapter 5, participants were classified as having symptomatic knee OA when they self-reported both an OA diagnosis and knee pain in an effort to reduce misclassification. The prevalence of self-reported knee OA in the sample of Chapter 5 was 12.7% (1,804 out of an eligible sample of ELSA of 14,228 in waves 2–8). This estimate is consistent with previously reported prevalence of symptomatic knee OA for similar age groups: 16.7% of people aged ≥45 years in the Johnston County OA project[139] and 12.1% of people aged ≥60 years in NHANES III[164]. Nonetheless, I acknowledge that this does not entirely exclude potential misclassification bias. Because of this, caution is required when interpreting the frequency of OA in Chapters 4 and 5, but any remaining misclassifications are likely to cause an underestimate of our findings. Furthermore, a 2015 systematic review and meta-analysis by Peeters et al studied the sensitivity and specificity of self-reported OA compared with medical records or clinical ACR criteria[151]. This study showed a reasonably high sensitivity and specificity for OA self-report (0.75 and 0.89, respectively). In Chapter 6, using RAMS data, RA cases were defined using a physician's diagnosis of RA. Therefore, it is likely that the identified RA cases in Chapter 6 are true RA cases.

7.2.7 Mediation analyses

A strength of this PhD thesis is that two types of mediation analysis techniques (SEM and causal mediation analyses) were used. However, using SEM and causal mediation analyses I was not able to analyse the repeated outcomes longitudinally as that was not supported in the respected packages. Instead, I averaged the scores over the different time points and adjusted for the number of follow-ups. In the future, it would be desirable to explore the opportunities to incorporate the repeated measures longitudinally for more precise estimates.

In addition, using a latent variable for SEP in the SEM was a strength, where multiple observed indicators attempted to define the underlying construct of SEP. Nonetheless, it is important to keep in mind that the latent variable might not be an exact representation of the underlying construct; this depends on the accuracy of the observed indicators, and there might be additional indicators that are relevant for the construct but are not included in the dataset.

Lastly, the mediation analyses were only adjusted for age and gender as they are known confounders for each pathway. However, there may be other variables (e.g. smoking) that are a confounder for one pathway (e.g. obesity – arthritis) and a mediator for another pathway (e.g. SEP – arthritis). To avoid added complexities in the interpretation and overadjustment, it was decided to only adjust for variables affecting each pathway. This may have biased the results. Specifically with regards to smoking, this may have underestimated the association between obesity and arthritis and thus obesity's mediating effect.

7.3 Implications for policy, public health and clinical practice

Keeping the aforementioned strengths and limitations in mind, there are relevant implications for policy, public health and clinical practice. These can be divided into two main themes: 1) efforts to prevent/reduce

obesity in the general population and within arthritis cohorts and 2) efforts to reduce social inequalities in arthritis incidence and progression.

7.3.1 Efforts to prevent obesity / reduce obesity prevalence

The results of this thesis highlighted that obesity was associated with the development of OA and RA, and with the progression of both diseases. Obesity also partly explained the relationship between a lower SEP and the development and progression of arthritis. Therefore, it is important to focus on efforts to prevent obesity in the general population and focus on interventions to reduce obesity in people with prevalent arthritis to reduce the progression of disease.

7.3.1.1 Population-based interventions

Since the UK formally recognised obesity as a public health concern in 1991, 14 government strategies with the aim to reduce obesity have been published[434]. However, a recent review assessing the effectiveness of these policies concluded that these policies have mostly failed[434]. Suggested reasons why these strategies were largely ineffective include a lack of a clear implementation strategy, not learning from past successes and failures, and a general focus on personal responsibility (e.g. promoting a healthy diet and physical activity) rather than changing the obesogenic environment through fiscal and regulatory policies.

More recent policies, such as the *Childhood Obesity: A plan for action (2016 and 2018)*[435, 436] and *Tackling Obesity (2020)*[437] contain more restrictive policies, such as the Soft Drinks Industry Levy, restricting price promotions of unhealthy food and drinks, ending TV advertising for unhealthy products before 9pm, and mandatory calorie labelling on restaurant menus. The Soft Drinks Industry Levy, since its implementation in 2018, has been shown to be effective in reducing sugar in drinks and thus reducing the consumption of sugar in UK households[438]. However, the reduction in sugar in soft drinks in the UK may also have led to increased use of artificial sweeteners[439] (the safety of artificial sweeteners should be further explored).

Although the *Tackling Obesity (2020)* strategy contains some structural measures (mentioned previously, of which the effectiveness are yet to be explored), it still focusses largely on personal responsibility. For example, it states "we owe it to the NHS to move towards a healthier weight" and "you can play your part to protect the NHS and save lives". This type of language is stigmatising and can lead to people having an unhealthy relationship with food[440]. Moreover, the document fails to acknowledge the complex drivers of obesity mentioned in the Introduction (section 1.1.3), including environmental and socioeconomic factors. Future public health policy should focus on reducing obesogenic environments, particularly in deprived communities, including: improving the safety and accessibility of active transport (i.e. walking, biking), reducing unhealthy fast food restaurants (especially nearby schools), and providing better access to green spaces[440]. These strategies may help to prevent and reduce obesity levels in the general population, subsequently reducing the risk for chronic diseases, including OA and RA.

7.3.1.2 Weight-reduction programmes for arthritis patients

This thesis has shown that obesity is associated with worse outcomes in both OA and RA. Therefore, weight loss may help to improve outcomes of both diseases. Whilst NICE recommends general weight loss for obese people with OA[206], it is not mentioned in their management guidelines for RA[301]. However, 2021 EULAR recommendations do advise that people with rheumatic and musculoskeletal diseases "should aim for a healthy weight"[441].

A systematic review including 22 trials indicated that weight loss interventions (combined diet and physical activity interventions) are effective in reducing weight, pain and disability in people with OA[442]. Moreover, across the NHS, "prehabilitation" programmes improving health through modifying lifestyle and behavioural factors have been set up to reduce complication risks after surgery[443]. A recent study found that the programmes containing specific BMI policies reduced knee and hip JRS rates based on data from the National Joint Registry for England; however, it was unclear what the exact mechanisms were (a decrease in need or inappropriate restriction to access in surgery)[444]. Evidence for weight-loss programmes for RA patients is limited. One retrospective study (n=117) found that RA patients who were overweight or obese and lost ≥5 kg of weight, were more likely to experience disease activity improvement (OR 3.03 (95% CI 1.18, 7.83)) compared to those who did not lose weight[445].

It is important that these programmes are disease specific as people with OA and RA suffer from pain and disabilities which may impact the ability to successfully engage with the programme (especially for the physical activity component[446]). Therefore, lifestyle behavioural weight management programmes need to incorporate pain coping strategies[446]. Some people may ease pain by eating high-calorie foods[447]; therefore, pain coping skills learned during the programme may serve as an alternative for using unhealthy foods for pain relief. A programme combining behavioural weight management and pain coping strategies has been shown to be more effective (in terms of reducing BMI and disability) compared with behavioural management alone in obese OA patients[448]. A recent small pilot feasibility trial of 50 primarily female RA patients[449] found similar results for patients with RA; however, this needs to be validated on a larger scale.

To my knowledge, no specific weight loss programme has been set up in the UK for people with OA or RA. It would benefit patients if they could be referred to weight loss programmes that are disease specific (i.e. incorporating pain coping strategies). This may be particularly important for those with lower SEP as they experience the worst disease outcomes. As mentioned in section 7.2.2, under-served populations, such as those with lower SEP, are more difficult to reach and may face physical or cognitive barriers to access health services. Therefore, weight loss programmes need to specifically focus on targeting the lower SEP and understanding how to overcome any barriers for the lower SEP to access healthcare services. The next section will elaborate on this further.

7.3.2 Efforts to reduce social inequalities in arthritis prevalence and progression

This thesis provided important insights into the relationship between lower SEP and the development and progression of arthritis. As Professor Margaret Whitehead, co-creator of the influential Dahlgren-Whitehead model of health determinants, stated: "health disparities are avoidable, unnecessary, unfair and unjust"[450]. The words "avoidable" and "unnecessary" suggest that socioeconomic disparities are not a given and that there are ways to decrease these inequalities in health outcomes. In his latest report, *Health Equity in England: The Marmot Review 10 years on* written in 2020[2], Professor Sir Michael Marmot concluded that health inequalities in England have widened since writing the 2010 Marmot Review, *Fair Society Healthy Lives*[1]. Marmot attributes this to deteriorating social and economic conditions, fuelled by widespread governmental funding cuts. The latest report recommends governmental policies to improve health across communities. They are described in detail in the report, but the general themes are as follows[2]: 1) Develop a national strategy on health inequalities; 2) Introduce policies and interventions proportionate to needs of areas; 3) Early intervention to prevent health inequalities (i.e. "give every child the best start in life"); 4) Develop the social determinants of health workforce; 5) Engage the public and improve the public's understanding of what factors drive health; 6) Develop whole systems monitoring and strengthening accountability for health inequalities.

As is evident from these policies, decreasing health inequalities requires a robust response from the government and they are not easily (and quickly) modified. Therefore, it is also important to focus on factors that may be modified more easily that can be targeted to prevent the development and/or progression of arthritis. One of these factors is obesity; policy interventions tackling obesity were explained previously in section 7.3.1. However, this PhD study showed that obesity does not fully explain the association between lower SEP and progression of disease. Therefore, it was hypothesised that other modifiable factors, for example in the access and delivery of healthcare services, may drive some of these inequalities in the burden of disease in people with arthritis.

The results of Chapter 5 suggested that there may be underutilisation of knee JRS in people from a lower SEP. As knee JRS are effective in relieving pain and improving function, this could lead to additional disability in people with lower SEP. This may indicate inequities in the delivery or access of care. In people with OA, inequity of care has been described previously: for example, lower educated people with OA were less likely to receive advice and comprehensive instructions on joint exercises than those with a higher education[417, 451]. Therefore, public health policy needs to focus on developing interventions with the aim to reduce inequities in healthcare. According to a systematic review[452], there are currently limited studies assessing interventions to improve healthcare quality for disadvantaged populations with OA: only 10 studies were included and they were all conducted in the US. Therefore, the results may not be directly applicable in a free at the point of access healthcare system, such as in the UK. Furthermore, this review highlighted that most interventions focus on patients or the healthcare system, but not on healthcare providers. From this, it seems that the role of healthcare providers in OA is an understudied field.

Therefore, my recommendation would be to increase awareness training for healthcare professionals about healthcare inequities and training in biases that influence decision-making in disadvantaged populations. It should further be recognised that people with a lower SEP may need more intensive primary care intervention, taking into account low literacy, cultural views and access to interventions (e.g. transportation).

7.4 Future work

The results presented in this thesis advanced the knowledge about the relationships between SEP, obesity and arthritis. Building on the findings and arising from some of the limitations of this thesis, there are several opportunities for future research.

7.4.1 Validating findings in different datasets

As mentioned in section 7.2.1, there were both strengths and limitations in the use of ELSA and RAMS in this thesis. Arising from some of these limitations, as a first step, findings from this PhD should be replicated using data from other datasets in the UK comprising a different population (i.e. younger and in different ethnic groups). This will help to understand whether the findings are generalisable to the wider population of the UK. Using a different dataset may also help to address some of the specific limitations of ELSA (e.g. self-reported diagnosis of OA and RA) and RAMS (e.g. short follow-up, only IMD as proxy for SEP and no WC recorded). Moreover, future studies should confirm whether gender differences that were found in this PhD are also observed in other datasets, or whether the findings were due to smaller sample sizes of men.

7.4.2 Investigating other mediating factors

This PhD focused on BMI as a mediator for the relationship between lower SEP and the development and progression of arthritis. As BMI did not explain the full associations, there are also other potential mediators that can be explored in future research, such as other lifestyle factors (e.g. smoking and physical activity) and community factors (e.g. number of clinics, safe places to exercise). All proposed factors can be added into the same mediation model to investigate the relative mediating effect of each factor, provided the sample size is large enough. In addition, qualitative research or a mixed-method approach may provide a deeper understanding about other potential mediating factors for the relationship between a lower SEP and arthritis from the view of patients or clinicians.

7.4.3 Investigating weight loss interventions specific for people with arthritis

As mentioned in section 7.3.1.2, future research should focus on how effective weight loss programmes specific for OA and RA can be implemented in the NHS. It is especially important to understand how to effectively engage people from lower SEP in these interventions as they appear to have the highest need.

7.4.4 Understanding disparities in knee joint replacement surgeries

An important finding of this PhD was that those from lower SEP are less likely to have knee JRS despite a potential greater need. This may indicate underutilisation of knee JRS. Future research should focus on

understanding why there are disparities in the utilisation of knee JRS. It is important to understand what the barriers are to receive knee JRS for people with lower SEP. This may ultimately help to inform health policy makers to improve the equitability of care.

7.5 Final conclusions

This thesis aimed to understand the complex relationships between SEP, obesity and the development and progression of arthritis. Chapter 3 confirmed that there are socioeconomic inequalities in the prevalence of obesity. The results of Chapters 4–6 have highlighted that both lower SEP and obesity are associated with the development and progression of arthritis. The results further provided novel insights about the mediating effect of BMI on the relationship between lower SEP and arthritis. The relationship between lower SEP and incident OA was fully mediated through BMI. The relationships between lower SEP and progression of OA and RA were partially mediated through BMI. These findings illustrate the need to investigate the effectiveness of weight management strategies in people with arthritis from lower SEP.

As I started this PhD thesis with a quote from Professor Sir Michael Marmot, I would also like to end with one from his book *The Health Gap*: "At the end of every scientific paper there is a familiar coda: more research is needed, more research is needed. What, I wondered, if we added a new coda: more action is needed." In addition to further research, most importantly, action is now needed to reduce the unfair socioeconomic inequalities in both OA and RA, which were observed in this PhD project.

8. References

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9. Appendices

9.1 Appendix A: List of OECD countries as per March 2020

List of OECD countries as per March 2020[453]

Australia
Austria
Belgium
Canada
Chile
Czech republic
Denmark
Estonia
Finland
France
Germany
Greece
Hungary
Iceland
Ireland
Israel
Italy
Japan
Korea
Latvia
Lithuania
Luxembourg
Mexico
Netherlands
New Zealand
Norway
Poland
Portugal
Slovak republic
Slovenia
Spain
Sweden
Switzerland
Turkey
United Kingdom
United States

9.2 Appendix B: Directed acyclic graphs for Chapters 4, 5 and 6

9.2.1 Chapter 4: The relationships between SEP, BMI and incident OA and RA

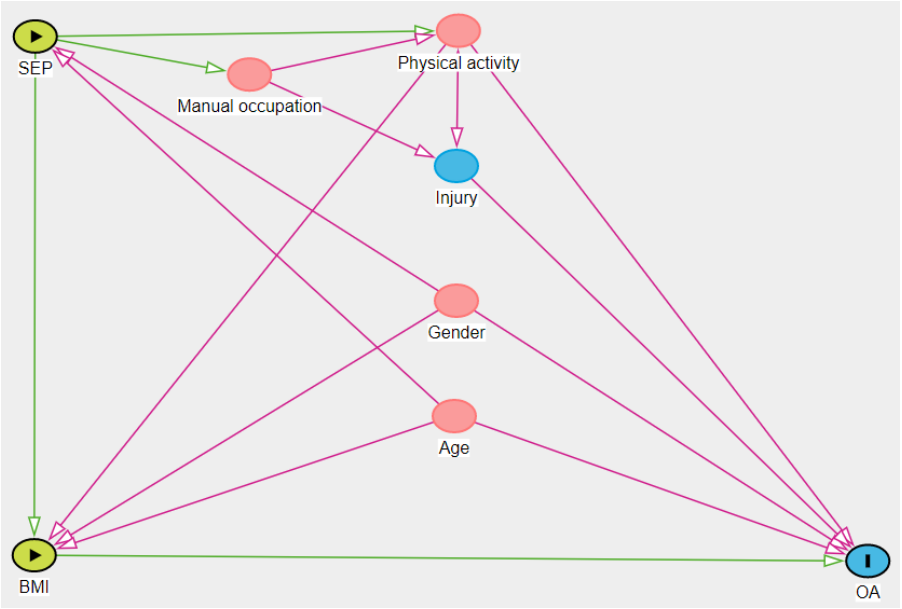

Figure S1: DAG for the relationships between SEP, BMI and incident OA

BMI, body mass index; DAG, directed acyclic graph; OA, osteoarthritis; SEP, socioeconomic position.
Green circle=exposure; blue circle with I=outcome; pink circle=ancestor of exposure and outcome; blue circle=ancestor of outcome; pink line=biasing pathway; green line=causal pathway.

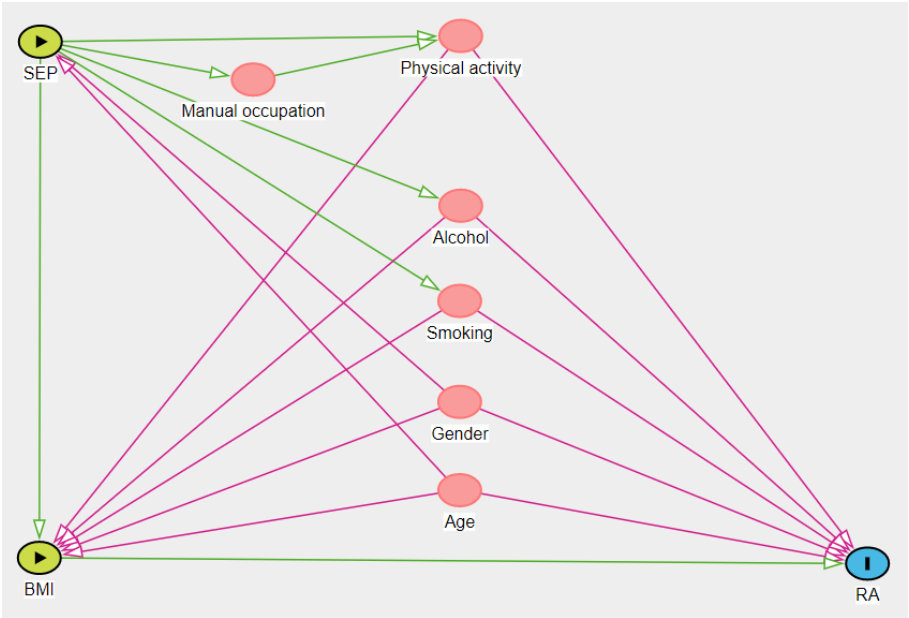

Figure S2: DAG for the relationships between SEP, BMI and incident RA

BMI, body mass index; DAG, directed acyclic graph; RA, rheumatoid arthritis; SEP, socioeconomic position.
Green circle=exposure; blue circle=outcome; pink circle=ancestor of exposure and outcome; pink line=biasing pathway; green line=causal pathway.

9.2.2 Chapter 5: The relationships between SEP, BMI and progression of OA

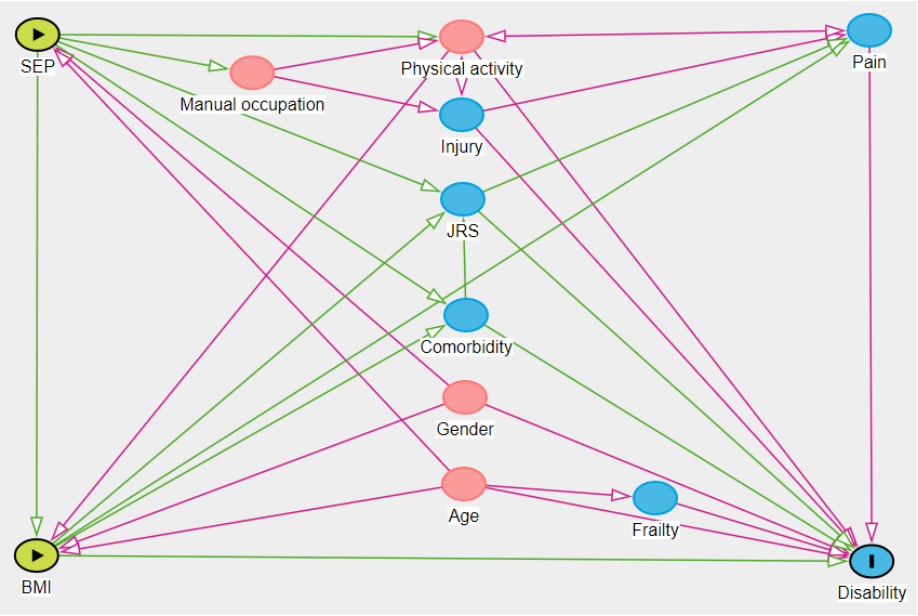

Figure S3: DAG for the relationships between SEP, BMI and disability in people with OA

BMI, body mass index; DAG, directed acyclic graph; JRS, joint replacement surgery; OA, osteoarthritis; SEP, socioeconomic position. Green circle=exposure; blue circle with I=outcome; pink circle=ancestor of exposure and outcome; blue circle=ancestor of outcome; pink line=biasing pathway; green line=causal pathway.

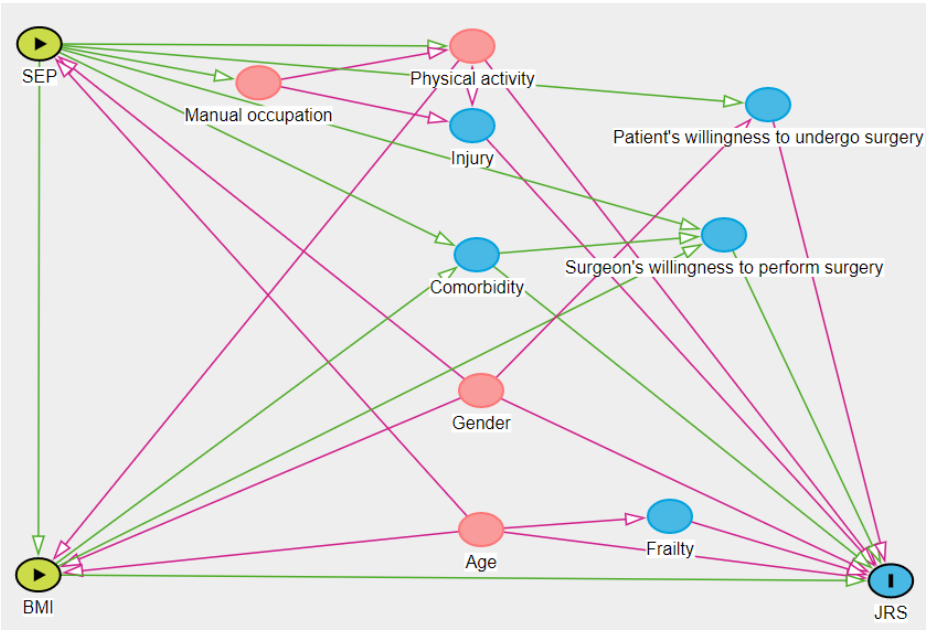

Figure S4: DAG for the relationships between SEP, BMI and JRS in people with OA

BMI, body mass index; DAG, directed acyclic graph; JRS, joint replacement surgery; OA, osteoarthritis; SEP, socioeconomic position. Green circle=exposure; blue circle with I=outcome; pink circle=ancestor of exposure and outcome; blue circle=ancestor of outcome; pink line= biasing pathway; green line=causal pathway.

9.2.3 Chapter 6: The relationships between SEP, BMI and progression of RA

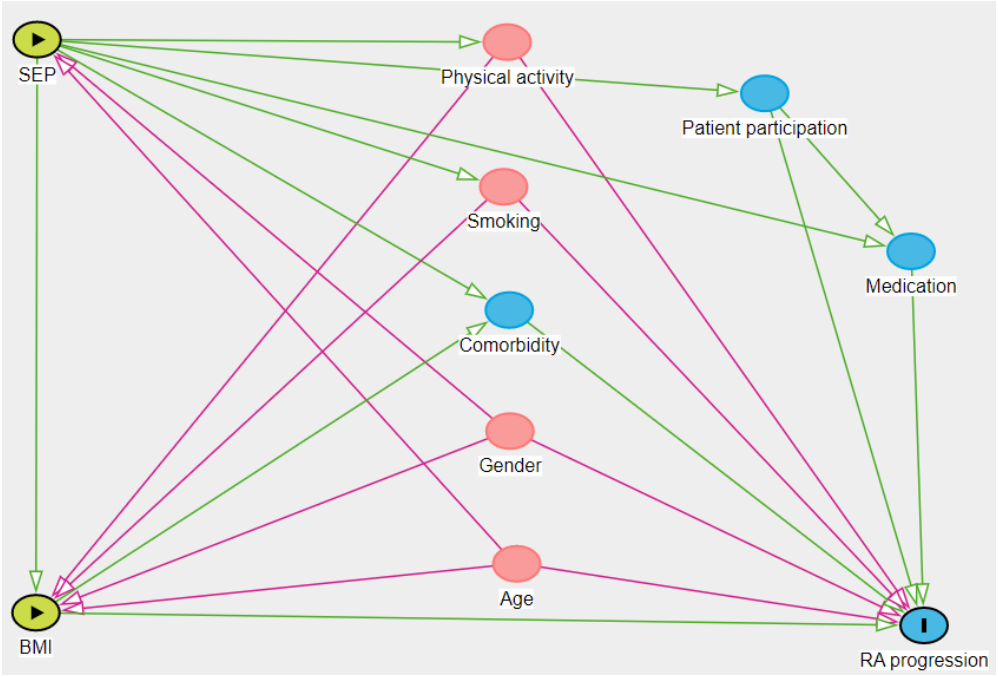

Figure S5: DAG for the relationships between SEP, BMI and progression of RA

BMI, body mass index; DAG, directed acyclic graph; RA, rheumatoid arthritis; SEP, socioeconomic position. Green circle=exposure; blue circle with I=outcome; pink circle=ancestor of exposure and outcome; blue circle=ancestor of outcome; pink line=biasing pathway; green line=causal pathway.

9.3 Appendix C: Content of the ELSA CAPI and self-completion interview at wave 6 (2012/13) sourced from Technical Report Wave 6[374]

Household demographics: collected or updated demographic information about everyone living in the household, including sex, age and relationships to each other, and collected or updated information about children living outside the household.

Individual demographics: collected or updated details about respondents' legal marital status, parents' age and cause of death, and number of living children.

Health: collected or updated self-reported general health, long-standing illness or disability, eyesight, hearing, specific diagnoses and symptoms, pain, difficulties with daily activities, smoking, mental health, urinary incontinence, falls and fractures, quality of care and cancer screening. New health questions at wave 6 included those on bowel incontinence. Questions on sleep and balance were included again at wave 6. Questions about dental health were omitted from wave 6.

Social care: new questions about receipt of social care were added at wave 6 to follow on from existing questions about ADLs and IADLs. These replaced previous questions about care received. Topics included the nature of care received, who it was received from, the amount received and payments made for care.

Social participation: covered the use of public transport.

Work and pensions: collected or updated current work activities, current and past pensions, reasons for job change, health-related job limitations and working beyond the state pension age and state pension deferral. At wave 6, questions about knowledge of the male state pension age were included.

Income and assets: assessed the income that respondents received from a variety of sources over the last 12 months: wages, state pensions, private pensions, other annuity income and state benefits; also collected financial and non-financial assets. Questions about perceived financial position relative to others were omitted from wave 6. Questions about lifetime receipt of gifts and inheritances were included in wave 6.

Housing: collected or updated current housing situation (including size and quality), housing-related expenses, adaptations to accommodation for those with physical impairments, ownership of durable goods and cars, and consumption including food in and out of home, fuel, durables and clothing.

Cognitive function: measured different aspects of the respondent's cognitive function, including memory, speed and mental flexibility.

Expectations: measured expectations for the future in a number of dimensions, financial decision-making and relative deprivation. Questions about movement into a nursing home and future housing and care needs were added at wave 6.

Effort and reward: assessed the relationship between effort and reward in relation to voluntary and caring activities. New questions on care provided to others were integrated into existing questions in this section.

Psychosocial health: measured how the respondent viewed his or her life across a variety of dimensions.

Walking speed: for respondents aged 60 and over, a 'timed walk' with the respondent walking a distance of 8 feet (244 cm) at their usual walking pace.

Final questions: collected any missing demographic information and updated contact details and consents.

Self-completion questionnaires: covered quality of life, social participation, altruism, control at work, life satisfaction, consumption of fruit and vegetables, social networks and alcohol consumption. There was also a new self-completion questionnaire introduced at wave 6 about sexual experience, attitudes and desire.

9.4 Appendix D: Content of the ELSA nurse interview at wave 6 (2012/13) sourced from Technical Report Wave 6[374]

The nurse visit included several standard measures including:

- **Blood pressure**
- **Lung function:** a measure of how much air respondents can blow out from lungs, measured using a spirometer.
- **Blood sample:** most respondents under the age of 80 were asked to fast before giving the sample. The uses to which the sample was put are listed in Box 5.4.
- **Hair sample:** respondents were asked to give a small sample of hair to measure cortisol, which is an indicator of stress.
- **Anthropometric measures:** weight, standing height and waist measurement (to assess the distribution of body fat across the body).

In addition, nurses took four physical performance measures. Taken together with the gait speed (or timed walk) measure carried out during the personal interview, these provide an excellent way of tracking change in physical well-being over time:

- **Grip strength:** a measure of upper body strength, during which the respondent was asked to squeeze a grip gauge up to three times with each hand.
- **Chair rises:** a measure of lower body strength, during which respondents were asked to stand up from a firm chair without using their arms. If they succeeded, they were asked to stand up and down as quickly as they can for either five rises if they are aged 70 years and over or up to ten rises if aged 69 years and under.
- **Balance:** respondents were asked to stand in three different positions for up to 30 seconds.
- **Leg raise:** respondents under 70 years old were asked to lift one foot off the ground for up to 30 seconds.

Questions about prescribed medication were introduced at wave 6, collecting the details of up to 40 prescribed medications currently being taken.

9.5 Appendix E: Content of the RAMS baseline questionnaire

The University of Manchester

MANCHESTER 1824

Arthritis Research UK

RHEUMATOID ARTHRITIS MEDICATION STUDY

RAMS
Rheumatoid Arthritis Medication Study

Patient questionnaire: Visit 0 = Baseline

We are interested in your views about your arthritis, daily activities, treatment and general health. We know that people may respond differently to the same treatment for a number of reasons. We are particularly interested in seeing if these differences can be explained by how a person perceives their illness and treatment.

This booklet contains a series of questionnaires.

Many questions will seem similar, but please try to answer every question in the booklet.

There are no right or wrong answers.

‼ All your answers will be kept confidential ‼

Questionnaire A : Demographic characteristics and working status

Today's date: D D M M Y Y Y Y

Which of these ethnic groups do you and your parents belong to?

Yourself:	*Your father:*	*Your mother:*
❍ White	❍ White	❍ White
❍ Black-African	❍ Black-African	❍ Black-African
❍ Black-Caribbean	❍ Black-Caribbean	❍ Black-Caribbean
❍ Black-British	❍ Black-British	❍ Black-British
❍ Black-other	❍ Black-other	❍ Black-other
❍ Indian	❍ Indian	❍ Indian
❍ Pakistani	❍ Pakistani	❍ Pakistani
❍ Bangladeshi	❍ Bangladeshi	❍ Bangladeshi
❍ Chinese	❍ Chinese	❍ Chinese
❍ Other: _____	❍ Other: _____	❍ Other: _____

What is the highest level of education that you completed?

❍ Primary school

❍ Some secondary school

❍ O Levels/GCSEs/Other secondary education qualification

❍ A/AS Levels/Other further education qualification

❍ Attended university but did not graduate

❍ University degree/Higher education qualification

3. Please tick the box which best describes you? *(please tick all boxes that apply)*

❍ Working full-time

❍ Working part-time

❍ Unable to work due to disability ("Work disability"), reason for work disability: _____

Date start work disability:

(please proceed to question 11 if work disabled and not working)

❍ Retired early due to arthritis
Date early retirement:

(please proceed to question 11)

❍ Working full-time in the home *(please proceed to question 11)*

❍ Unemployed but seeking paid work *(please proceed to question 11)*

❍ Retired *(please proceed to question 11)*

❍ Other, please describe: _____ *(please proceed to question 11)*

Please complete this section if you have paid work (please also complete if you are currently on sick leave)

4. What is your current occupation? _____

5a. How many hours per week do you have to work according to your contract? _____ **Hours / Week**

5b. Over how many days are these hours distributed? _____ **Days / Week**

6. Are you on sick leave at this time?

❍ No

❍ Yes, date sick leave started:

If yes, are you on sick leave because of your arthritis? ❍ Yes ❍ No

7. How many days in the last month did you miss work because of your arthritis? (If none, please write '0'). ?

_____ days

8. How many days in the last month was **your productivity at work reduced by half or more** because of your arthritis? (please don't include any days noted in the question above (question 8); if none please write '0')

_____ days

9. In the last month, how much has your arthritis **interfered with your work productivity** (paid work)?

- In the last month, how much has arthritis interfered with your work productivity (work outside of home) on a scale of 0-10, where 0=no interference and 10=complete interference (please circle number).

No interference _____ **Complete interference**

0 1 2 3 4 5 6 7 8 9 10

Questionnaire D : Daily activities in the past week

10. Since the start of your arthritis, did you need to change your occupation or was your working environment changed because of your arthritis?

❍ **No**

❍ **Yes**, *please describe these changes:* _____

❍ Never worked or stopped working before my arthritis

11. On average, how many cups of caffeinated coffee or tea do you drink per day? _____

Questionnaire B : Your symptoms

Below are two scales. Please mark on each scale how you feel.

1. How much pain have you had because of your illness over the past **WEEK.**

Please place a mark on the scale below to indicate the SEVERITY of the pain.

NO PAIN **SEVERE PAIN**

2. How much of a problem has fatigue or tiredness been for you in the past **WEEK?**

Place a mark on the line below.

NO PROBLEM **MAJOR PROBLEM**

3. Is your current condition satisfactory, when you take your general functioning and your current pain into consideration?

Questionnaire C : Physical activity

*The following three questions are about physical activity. Please answer the questions by ticking **ONE** box you think most closely applies to you.*

In comparison with others of your own age, do you think your physical activity is:

❍ Much more ❍ More ❍ The same ❍ Less ❍ Much less

During the **past month**, on average, on **how many days per week** have you taken exercise that has lasted **at least 20 minutes**?

❍ Every day ❍ 4 – 6 days ❍ 2 – 3 days ❍ 1 day ❍ None

During the **past month**, on average, on **how many days per week** have you taken exercise that has **made you sweat**?

❍ Every day ❍ 4 – 6 days ❍ 2 – 3 days ❍ 1 day ❍ None

Questionnaire D : Daily activities in the past week

Please tick one response for each question which best describes your usual abilities over the past week.

	Without ANY difficulty	With SOME difficulty	With MUCH difficulty	UNABLE to do
1. DRESSING and GROOMING				
Dress yourself, including tying shoelaces and doing buttons?	❍	❍	❍	❍
b. Shampoo your hair?	❍	❍	❍	❍
2. RISING				
a. Stand up from an armless straight chair?	❍	❍	❍	❍
b. Get in and out of bed?	❍	❍	❍	❍
3. EATING				
a. Cut your meat/food?	❍	❍	❍	❍
b. Lift a full cup or glass to your mouth?	❍	❍	❍	❍
c. Open a new carton of milk?	❍	❍	❍	❍
4. WALKING				
a. Walk outdoors on flat ground?	❍	❍	❍	❍
b. Climb up five steps?	❍	❍	❍	❍

PLEASE TICK ANY AIDS OR DEVICES THAT YOU USUALLY USE FOR ANY OF THESE ACTIVITIES:

❍ Cane ❍ Walking frame ❍ Built-up or special utensils

❍ Crutches ❍ Wheelchair ❍ Special or built-up chair

❍ Devices used for dressing (button hooks, zipper pull, shoe horn)

❍ Other (specify) .....

PLEASE TICK ANY CATEGORIES FOR WHICH YOU USUALLY NEED HELP FROM ANOTHER PERSON:

❍ Dressing and Grooming ❍ Eating

❍ Rising ❍ Walking

Questionnaire D: Daily activities in the past week (continued)

Please tick one response for each question which best describes your usual abilities over the past week.

	Without ANY difficulty	With SOME difficulty	With MUCH difficulty	UNABLE to do
5. HYGIENE				
a. Wash and dry your entire body?	❍	❍	❍	❍
b. Take a bath?	❍	❍	❍	❍
c. Get on and off the toilet?	❍	❍	❍	❍
6. REACH				
a. Reach and get down a 5 lb object (e.g. bag of potatoes) from just above your head?	❍	❍	❍	❍
b. Bend down to pick up clothing off the floor?	❍	❍	❍	❍
7. GRIP				
a. Open car doors?	❍	❍	❍	❍
b. Open jars which have been previously opened?	❍	❍	❍	❍
c. Turn taps on and off?	❍	❍	❍	❍
8. ACTIVITIES				
a. Run errands and shop?	❍	❍	❍	❍
b. Get in and out of a car?	❍	❍	❍	❍
c. Do chores such as vacuuming, housework or light gardening?	❍	❍	❍	❍

PLEASE TICK ANY AIDS OR DEVICES THAT YOU USUALLY USE FOR ANY OF THESE ACTIVITIES:

❍ Raised toilet seat ❍ Bath seat ❍ Bath rail

❍ Long handled appliances for reach ❍ Jar opener (for jars previously opened)

❍ Other (specify) .....

PLEASE TICK ANY CATEGORIES FOR WHICH YOU USUALLY NEED HELP FROM ANOTHER PERSON:

❍ Hygiene ❍ Gripping and opening things

❍ Reach ❍ Errands and housework

Questionnaire E (part I) : Your current health

We are interested in how you describe your current health state.

Please indicate for each of the five activities below which statements best describe your own health state today.

1. MOBILITY *Please tick one box*

- I have no problems in walking ❍
- I have some problems in walking ❍
- I am confined to bed ❍

2. SELF CARE *Please tick one box*

- I have no problems with self care ❍
- I have some problems washing or dressing ❍
- I am unable to wash or dress ❍

3. USUAL ACTIVITIES *Please tick one box*

- I have no problems performing my usual activities (e.g. work, study, housework) ❍
- I have some problems performing my usual activities ❍
- I am unable to perform my usual activities ❍

4. PAIN / DISCOMFORT *Please tick one box*

- I have no pain or discomfort ❍
- I have moderate pain or discomfort ❍
- I have extreme pain or discomfort ❍

5. ANXIETY / DEPRESSION *Please tick one box*

- I am not anxious or depressed ❍
- I am moderately anxious or depressed ❍
- I am extremely anxious or depressed ❍

6. Compared with my general level of health over the past 6 months, my health state today is:

Please tick one box

- Better ❍
- Much the same ❍
- Worse ❍

Questionnaire E (part II) : Your current health

1.

We would like you to indicate on this scale how good or bad is your health today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your current state is.

How do you feel today

BEST IMAGINABLE STATE

100

-

-

90

-

-

80

-

-

70

-

-

60

-

-

50

-

-

40

-

-

30

-

-

20

-

-

10

-

-

0

WORST IMAGINABLE STATE

Questionnaire F : How you have felt in the PAST WEEK

We are interested in how you have been feeling recently.

*Read each item and tick the relevant box to the reply that comes closest to how you have been feeling in the **PAST WEEK.** Your immediate response to each item will probably be more accurate than a long thought out response.*

1. I feel tense and 'wound up'

- ❍ Most of the time
- ❍ From time to time, occasionally
- ❍ A lot of the time
- ❍ Not at all

2. I still enjoy the things I used to enjoy

- ❍ Definitely as much
- ❍ Only a bit
- ❍ Not quite as much
- ❍ Hardly at all

3. I get a sort of frightened feeling as if something awful is about to happen

- ❍ Very definitely and quite badly
- ❍ A little, but it doesn't worry me
- ❍ Yes, but not too badly
- ❍ Not at all

4. I can laugh and see the funny side of things

- ❍ As much as I always could
- ❍ Definitely not as much now
- ❍ Not quite as much now
- ❍ Not at all

5. Worrying thoughts go through my mind

- ❍ A great deal of the time
- ❍ From time to time, but not too often
- ❍ A lot of the time
- ❍ Only occasionally

6. I feel cheerful

- ❍ Not at all
- ❍ Sometimes
- ❍ Not too often
- ❍ Most of the times

7. I can sit at ease and feel relaxed

- ❍ Definitely
- ❍ Not often
- ❍ Usually
- ❍ Not at all

Questionnaire F : How you have felt in the PAST WEEK (continued)

*How have you felt in the **PAST WEEK**?*

8. I feel as if I am slowed down

- ❍ Nearly all the time
- ❍ Sometimes
- ❍ Very often
- ❍ Not at all

---

9. I get a sort of frightened feeling like 'butterflies' in the stomach

- ❍ Not at all
- ❍ Quite often
- ❍ Occasionally
- ❍ Very often

---

10. I have lost interest in my appearances

- ❍ Definitely
- ❍ I may not take quite as much care
- ❍ I don't take as much care as I should
- ❍ I take just as much care as ever

---

11. I feel restless as I have to be on the move

- ❍ Very much indeed
- ❍ Not very much
- ❍ Quite a lot
- ❍ Not at all

---

12. I look forward with enjoyment to things

- ❍ As much as I ever did
- ❍ Definitely less than I used to
- ❍ Rather less than I used to
- ❍ Hardly at all

---

13. I get sudden feelings of panic

- ❍ Very often indeed
- ❍ Not very often
- ❍ Quite often
- ❍ Not at all

---

14. I can enjoy a good book or radio or TV programme

- ❍ Often
- ❍ Not often
- ❍ Sometimes
- ❍ Very seldom

Questionnaire G : Your views about your illness

We are interested in your own personal views of how you see your arthritis.

Please indicate how much you agree or disagree with the following statements about your arthritis by circling the appropriate number.

1. How much does your arthritis affect your life?

0	1	2	3	4	5	6	7	8	9	10
no affect at all										severely affects my life

2. How long do you think your arthritis will continue?

0	1	2	3	4	5	6	7	8	9	10
a very short time										forever

3. How much control do you feel you have over your arthritis?

0	1	2	3	4	5	6	7	8	9	10
absolutely no control										extreme control

4. How much do you think your treatment can help your arthritis?

0	1	2	3	4	5	6	7	8	9	10
not at all										extremely helpful

5. How much do you experience symptoms from your illness?

0	1	2	3	4	5	6	7	8	9	10
no symptoms at all										many severe symptoms

6. How concerned are you about your arthritis?

0	1	2	3	4	5	6	7	8	9	10
not at all concerned										extremely concerned

7. How well do you feel you understand your arthritis?

0	1	2	3	4	5	6	7	8	9	10
don't understand at all										understand very clearly

8. How much does your arthritis affect you emotionally (e.g. does it make you angry, scared, upset or depressed)?

0	1	2	3	4	5	6	7	8	9	10
not at all affected										extremely affected

Please list in rank-order the three most important factors that you believe caused <u>your illness.</u>

1. _____

2. _____

3. _____

Questionnaire H : Information received about Methotrexate

We are interested to know what kind of information you received or obtained yourselves about Methotrexate.

1. What kind of information did you receive or obtain yourselves about Methotrexate?

(please tick all boxes which apply)

- ❍ Verbal information given by a nurse or rheumatologist as part of a usual visit to the clinic
- ❍ Leaflet about MTX medication given by the nurse or rheumatologist
- ❍ Information from Arthritis Research UK (AR UK) website (searched website)
- ❍ Information from National Rheumatoid Arthritis Society (NRAS) website (searched website)
- ❍ NHS Direct website
- ❍ Information given by the pharmacist
- ❍ Search on internet
- ❍ Telephone help-lines (eg AR UK or NRAS)
- ❍ Local patient support group
- ❍ Other, please describe:

---

2. Would you have liked to have received more information?

- ❍ No
- ❍ Yes, please describe what kind of information you would have liked to have received:

Questionnaire J: Your views about your medication

We would like to ask you about your personal views about your medicines prescribed to you. These are statements other people have made about their medicines.

Please indicate for each statement how far you agree by ticking the appropriate box that reflects your opinion best. It is important you complete all items listed, even if you have not started taking Methotrexate.

	Strongly disagree	Disagree	Uncertain	Agree	Strongly agree
1. My health, at present, depends on my medication	❍	❍	❍	❍	❍
2. My life would be impossible without my medicines	❍	❍	❍	❍	❍
3. Without my medicines I would be very ill	❍	❍	❍	❍	❍
4. My health in the future will depend on my medicines	❍	❍	❍	❍	❍
5. My medicines protect me from becoming worse	❍	❍	❍	❍	❍
6. Having to take medicines worries me	❍	❍	❍	❍	❍
7. I sometimes worry about the long-term effects of my medicines	❍	❍	❍	❍	❍
8. My medicines are a mystery to me	❍	❍	❍	❍	❍
9. My medicines disrupt my life	❍	❍	❍	❍	❍
10. I sometimes worry about becoming too dependent on my medicines	❍	❍	❍	❍	❍
11. My medicines give me an unpleasant side effect	❍	❍	❍	❍	❍
12. Doctors use too many medicines	❍	❍	❍	❍	❍
13. People who take medicines should stop their Treatment for a while every now and then	❍	❍	❍	❍	❍
14. Most medicines are addictive	❍	❍	❍	❍	❍
15. Medicines do more harm than good	❍	❍	❍	❍	❍
16. All medicines are poisons	❍	❍	❍	❍	❍
17. Doctors place too much trust on medicines	❍	❍	❍	❍	❍
18. If doctors had more time with patients they would prescribe fewer medicines	❍	❍	❍	❍	❍

We would like to thank you for completing this booklet of questionnaires.

Your contribution is much appreciated.

If you have any questions or queries about this booklet, please contact:

Suzan Verstappen Tel: (0161) 275 5663

Please return this questionnaire in the pre-paid envelope to:

RAMS study

Arthritis Research UK Epidemiology Unit

University of Manchester

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9.6 Appendix F: Results for incident rheumatoid arthritis – Chapter 4

9.6.1 Description of the cohort

Of the people who had at least one nurse visit at waves 2, 4 or 6 (n=11,848), 917 people were excluded as they had RA at baseline; as a result, the final sample for the RA analyses included 10,931 participants. Of the final sample, 1,216 participants (11.1% of the sample) developed RA after a mean follow-up of 8.8 years. The baseline characteristics of the people who developed RA and those who did not are shown in Table S1. In comparison to individuals who did not develop RA, those who did were more likely to be women, older, have less education, and have higher baseline rates of both total and central obesity.

Table S1: Baseline characteristics of the sample, stratified by those who developed RA and those who did not

	Total cohort (N=9,281)	
	Non-RA cases (N=9,715), N (%)	RA cases* (N=1,216), N (%)
Gender (female, %)	5,177 (53.3%)	733 (60.3%)
Age (mean (SD))	63.8 (9.7)	65.6 (9.3)
Ethnic group		
- White	9,457 (97.4%)	1,174 (96.7%)
- Non-white	254 (2.6%)	40 (3.3%)
- Missing	4 (0.0%)	0 (0.0%)
Education		
- Degree/NVQ4/5	1,584 (16.3%)	115 (9.5%)
- Higher education/below degree	1,267 (13.1%)	160 (13.2%)
- A level/NVQ3	781 (8.1%)	83 (6.8%)
- O level/NVQ2/GCE	1,830 (18.9%)	203 (16.7%)
- CSE/NVQ1	423 (4.4%)	56 (4.6%)
- Other	826 (8.5%)	112 (9.2%)
- No qualification	2,993 (30.8%)	485 (39.9%)
- Missing	11 (0.1%)	2 (0.1%)
Occupation (NS-SEC5) (current or most recent occupation if retired)		
- Managerial/professional	3,354 (35.4%)	333 (27.4%)
- Intermediate	1,315 (13.9%)	159 (13.1%)
- Small employers	1,049 (11.1%)	137 (11.3%)
- Lower supervisory/technical	952 (10.0%)	130 (10.7%)
- Semi-routine	2,813 (29.7%)	432 (35.5%)
- Missing	232 (2.4%)	25 (2.1%)
Smoking status		
- Never smoked	3,769 (38.9%)	432 (35.5%)
- Ex-smoker	4,453 (45.9%)	596 (49.0%)
- Current smoker	1,474 (15.2%)	186 (15.3%)
- Missing	19 (0.2%)	2 (0.1%)
Alcohol consumption		
- Less than monthly	2,140 (24.8%)	326 (26.8%)
- 1x/month–4x/week	4,464 (51.7%)	518 (42.6%)
- (Almost) every day	2,023 (23.5%)	243 (20.0%)
- Missing	1,088 (11.2%)	129 (10.6%)
BMI (mean (SD)) [kg/m^2]	27.9 (5.0)	29.2 (5.3)
- Missing	423 (4.4%)	58 (4.8%)
WHO BMI categories†		
- Underweight	93 (0.9%)	4 (0.3%)
- Normal weight	2,614 (26.9%)	234 (19.2%)
- Overweight	3,946 (40.6%)	462 (38.0%)
- Obesity	2,639 (28.4%)	458 (37.7%)
WC (mean (SD)) [cm]	95.5 (13.4)	98.0 (13.3)
Missing	254 (2.6%)	32 (2.6%)
Central obesity‡	4,715 (49.8%)	728 (59.9%)

BMI, body mass index; cm, centimetres; NS-SEC, National Statistics Socio-economic classification; NVQ, National Vocational Qualification; RA, rheumatoid arthritis; SD, standard deviation; WC, waist circumference. *Characteristics defined at baseline, when participants are recruited (not at RA onset) †WHO categories defined as: underweight (BMI <18.5 kg/m2), normal weight (BMI 18.5–24.9 kg/m2), overweight (BMI 25.0–29.9 kg/m2), obese (BMI >30.0 kg/m2). ‡Central obesity defined as: WC ≥102 cm for men or ≥88 cm for women.

9.6.2 Associations between socioeconomic position and incident rheumatoid arthritis

Participants with lower SEP had a greater risk of developing RA than participants with higher SEP (Table S2). Formal tests of interaction were statistically significant for obesity and occupation (p=0.051) and obesity and income (p=0.013). Stratified analyses (Table S3) showed that the relationships between occupation/income and RA are weaker in obese people (lowest vs highest occupation hazard ratio (HR) 1.37 (95% confidence interval (CI) 1.05, 1.80) and income HR 1.54 (95% CI 1.08, 2.20)) compared with non-obese people (lowest vs highest occupation HR 1.96 (95% CI 1.56, 2.47) and income HR 2.31 (95% CI 1.73, 3.09)).

Table S2: Weighted* Cox proportional hazards regression for the associations between different SEP indicators and RA incidence

Predictors	Unadjusted HR (95% CI)	Age and gender adjusted HR (95% CI)
Education		
No qualification	2.77 (2.17, 3.54)	2.23 (1.74, 2.86)
Other	2.01 (1.50, 2.77)	1.72 (1.27, 2.35)
NVQ1/CSE	2.15 (1.48, 3.12)	1.89 (1.30, 2.75)
O level/NVQ2/GCE	1.59 (1.22, 2.08)	1.49 (1.14, 1.96)
A level/NVQ3	1.58 (1.13, 2.20)	1.56 (1.12, 2.17)
Higher education/below degree	1.68 (1.27, 2.23)	1.59 (1.20, 2.11)
Degree/NVQ4/5	ref	ref
Occupation (NS-SEC5)		
Semi-routine	1.97 (1.67, 2.33)	1.79 (1.50, 2.13)
Lower supervisory/technical	1.53 (1.20, 1.95)	1.45 (1.13, 1.86)
Small employers	1.51 (1.20, 1.91)	1.47 (1.17, 1.86)
Intermediate	1.29 (1.03, 1.62)	1.15 (0.91, 1.46)
Managerial/ professional	ref	ref
Wealth (1=lowest wealth, 5=highest wealth)		
Quintile 1	2.60 (2.09, 3.24)	2.31 (1.84, 2.89)
Quintile 2	2.02 (1.63, 2.50)	1.93 (1.56, 2.40)
Quintile 3	1.68 (1.36, 2.09)	1.61 (1.30, 2.00)
Quintile 4	1.49 (1.20, 1.85)	1.45 (1.17, 1.80)
Quintile 5	ref	ref
Income (1=lowest income, 5=highest income)		
Quintile 1	2.52 (2.03, 3.13)	2.08 (1.67, 2.60)
Quintile 2	2.38 (1.92, 2.96)	1.96 (1.56, 2.45)
Quintile 3	1.90 (1.52, 2.37)	1.67 (1.34, 2.08)
Quintile 4	1.38 (1.10, 1.72)	1.29 (1.03, 1.61)
Quintile 5	ref	ref
Index of Multiple Deprivation (1= most deprived, 5= least deprived)		
Quintile 1	2.21 (1.77, 2.76)	2.18 (1.75, 2.73)
Quintile 2	1.70 (1.38, 2.08)	1.67 (1.36, 2.04)
Quintile 3	1.35 (1.09, 1.66)	1.32 (1.07, 1.63)
Quintile 4	1.21 (0.98, 1.47)	1.16 (0.95, 1.42)
Quintile 5	ref	ref

CI, confidence interval; HR, hazard ratio; NS-SEC, national statistic socio-economic classification; NVQ, National Vocational Qualification; RA, rheumatoid arthritis; ref, reference category. *Longitudinal survey weights were used to correct for historical non-response. Formal tests of interaction between SEP and gender/obesity were run but in all cases $0.08<p<0.89$ except for obesity*occupation ($p=0.051$), obesity*income ($p=0.013$). Stratified analyses for this can be found in Table S3.

Table S3: Stratified analyses of the interaction terms that were statistically significant for the association between SEP and incident RA

Interaction terms	**HR (95% CI)**	**HR (95% CI)**
	Obesity	*No obesity*
*Obesity*occupation†*		
Semi-routine	1.37 (1.05, 1.80)	1.96 (1.56, 2.47)
Lower supervisory/technical	1.45 (1.00, 2.09)	1.31 (0.95, 1.82)
Small employers	1.38 (0.94, 2.05)	1.49 (1.12, 2.00)
Intermediate	1.08 (0.74, 1.56)	1.18 (0.87, 1.60)
Managerial/ professional	ref	ref
*Obesity*income†*		
Quintile 1 (=lowest)	1.54 (1.08, 2.20)	2.31 (1.73, 3.09)
Quintile 2	1.36 (0.94, 1.97)	2.26 (1.69, 3.01)
Quintile 3	1.53 (1.09, 2.15)	1.62 (1.22, 2.16)
Quintile 4	1.16 (0.81, 1.67)	1.31 (0.98, 1.75)
Quintile 5 (=highest)	ref	ref

†P-values interaction terms: obesity*occupation in RA (p=0.051) and obesity*income in RA (p=0.013). CI, confidence interval; HR, hazard ratio; IMD, index of multiple deprivation; RA, rheumatoid arthritis.

9.6.3 Associations between obesity and incident rheumatoid arthritis

Total and central obesity were both associated with incident RA, independent from SEP (Table S4). Risk of developing RA increased by 4% for each 1 kg/m^2 increase in BMI and increased by 7% for each 5 cm increase in WC. There was no evidence of gender or SEP differences in the associations between total obesity and incident RA (p-values from tests of interaction 0.08<p<0.97), except for occupation and obesity and income and obesity (Table S3).

Table S4: Weighted* Cox proportional hazards regression for the associations between different definitions of obesity and RA

Predictors	**Unadjusted HR (95% CI)**	**Fully adjusted HR (95% CI)**
Total obesity (BMI≥30kg/m^2)		
Obesity	1.63 (1.42, 1.87)	1.48 (1.29, 1.72)†
No obesity	ref	ref
Central obesity (WC≥102 cm for men and ≥88 cm for women)		
Central obesity	1.54 (1.34, 1.77)	1.40 (1.21, 1.61)
No central obesity	ref	ref
Continuous		
BMI per 1 kg/m^2 increment	1.05 (1.03, 1.06)	1.04 (1.03, 1.05)
WC per 5 cm increment	1.06 (1.04, 1.09)	1.07 (1.05, 1.10)

CI, confidence interval; HR, hazard ratio; NS-SEC, national statistic socio-economic classification; ref, reference category; WC, waist circumference. Fully adjusted model for obesity/central obesity: adjusted for gender, age, alcohol, smoking, physical activity, education, occupation, wealth, income and IMD. *Longitudinal survey weights were used to correct for historical non-response. Formal tests of interaction between obesity and gender/SEP were run but in all cases 0.08<p<0.97, except for obesity*occupation in RA (p=0.051) and obesity*income in RA (p=0.013). †As interactions between occupation/income and obesity were statistically significant, this estimate is not adjusted for occupation and income, instead stratified analyses are shown in Table S3.

9.6.4 The mediating effect of body mass index on the relationship between socioeconomic position and incident rheumatoid arthritis

Results from the confirmatory factor analysis showed a good fit for the definition of the latent variable SEP, using education, NS-SEC5, wealth quintiles and income quintiles (CFI 0.998, RMSEA 0.039, SRMR 0.007). Tables S5 and S6 and Figure S6 present the findings of the mediating effect of BMI and WC on the relationship between lower SEP and the development of RA in the total population and stratified by gender. Both the indirect effect (0.002 (95% CI 0.002, 0.003)) and the direct effect (0.014 (95% CI 0.009, 0.018)) were statistically significant, indicating that the relationship between a lower SEP and incident RA can partly be explained by BMI. The proportion mediated was slightly higher for women than men (16.8% and 10.0%, respectively). Causal mediation analyses showed similar results for the separate indicators for SEP (Table S7).

Table S5: The total, direct and indirect effect via BMI of SEP on incident RA adjusted for age and gender

	Total		Direct		Indirect		Proportion mediated (95% CI)*
	Regression estimate (95% CI)	p-value	Regression estimate (95% CI)	p-value	Regression estimate (95% CI)	p-value	
Combined	0.016 (0.012, 0.028)	p<0.001	0.014 (0.009, 0.018)	p<0.001	0.002 (0.002, 0.003)	p<0.001	14.9% (9.8%, 23.1%)
Women	0.020 (0.013, 0.026)	p<0.001	0.017 (0.010, 0.023)	p<0.001	0.003 (0.002, 0.005)	p<0.001	16.8% (10.1%, 29.0%)
Men	0.013 (0.006, 0.019)	p<0.001	0.011 (0.005, 0.017)	p<0.001	0.001 (0.001, 0.002)	p<0.001	10.0% (4.6%, 22.2%)

CI, confidence interval; RA, rheumatoid arthritis. *Calculated by indirect effect/total effect*100%. 95% CI estimated with bootstrapping.

Table S6: The total, direct and indirect effect via WC of SEP on incident RA adjusted for age and gender

	Total		Direct		Indirect		Proportion mediated (95% CI)*
	Regression estimate (95% CI)	p-value	Regression estimate (95% CI)	p-value	Regression estimate (95% CI)	p-value	
Combined	0.016 (0.012, 0.021)	p<0.001	0.014 (0.009, 0.018)	p<0.001	0.002 (0.002, 0.003)	p<0.001	13.8% (8.9%, 21.4%)
Women	0.021 (0.014, 0.027)	p<0.001	0.017 (0.011, 0.024)	p<0.001	0.003 (0.002, 0.004)	p<0.001	15.2% (8.4%, 26.2%)
Men	0.012 (0.005, 0.018)	p<0.001	0.010 (0.004, 0.016)	p<0.001	0.001 (0.001, 0.002)	p<0.001	10.8% (4.8%, 25.4%)

CI, confidence interval; RA, rheumatoid arthritis. *Calculated by indirect effect/total effect*100%. 95% CI estimated with bootstrapping.

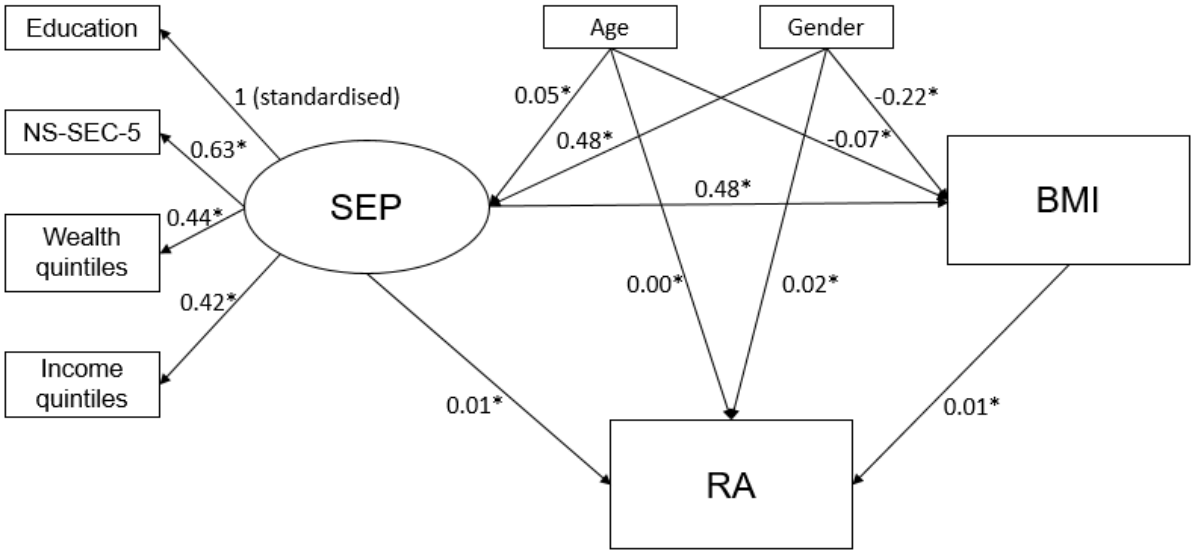

Figure S6: The structural equation models for the relationships between SEP, BMI and incident RA adjusted for age and gender

*statistically significant (p<0.05). BMI, body mass index; NS-SEC, national statistics socioeconomic classification; RA, rheumatoid arthritis; SEP, socioeconomic position.

Table S7: Causal mediation analysis for the total, direct and indirect effect via BMI of different SEP indicators on RA incidence adjusted for age and gender, as a sensitivity analysis

	Total		Direct		Indirect		Proportion mediated (95% CI)*
	Regression estimate (95% CI)	p-value	Regression estimate (95% CI)	p-value	Regression estimate (95% CI)	p-value	
Education	0.006 (0.004, 0.010)	<0.001	0.005 (0.003, 0.010)	<0.001	0.001 (0.001, 0.002)	<0.001	17% (11%, 28%) p<0.001
Occupation	0.008 (0.005, 0.010)	<0.001	0.007 (0.004, 0.010)	<0.001	0.001 (0.001, 0.002)	<0.001	14% (8%, 23%) p<0.001
Wealth	0.009 (0.007, 0.010)	<0.001	0.008 (0.004, 0.010)	<0.001	0.002 (0.002, 0.002)	<0.001	21% (14%, 35%) p<0.001
Income	0.010 (0.007, 0.010)	<0.001	0.009 (0.006, 0.010)	<0.001	0.001 (0.000, 0.002)	<0.001	8% (4%, 13%) p<0.001

CI, confidence interval; RA, rheumatoid arthritis. *Calculated by indirect effect/total effect*100%. 95% CI estimated with bootstrapping.