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Ul Haq, Zia (2014) *Adiposity and subjective well-being*. PhD thesis.

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Adiposity and subjective well-being

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Thesis is submitted in fulfilment of the requirements for the degree of Doctor of Philosophy (PhD)

Public Health

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July 2014

Abstract

Since 1980, the global prevalence of obesity has more than doubled. According to the World Health Organization (WHO) more than one in ten of the world's adult population are now obese. The prevalence of obesity is high both in the developed and developing countries, leading to suggestions of an "obesity pandemic" or "globesity". In Scotland alone, 28% of adults are now obese, and a further 36% are overweight. Historically, the main focus of healthcare has been the avoidance of preventable mortality. As life-expectancy has increased, attention has focused on the need to improve health, as well as longevity. The WHO definition of health encompasses mental and social, as well as physical, well-being. It is widely accepted that obesity causes, or aggravates, a number of medical conditions, and is also associated with reduced life-expectancy. However, the research on adiposity and subjective well-being is still in its infancy and previous studies suggest that the relationship is complex.

This thesis starts by demonstrating the importance of subjective well-being in terms of its association with adverse outcomes: all-cause death, coronary heart disease (CHD), cancer incidence, and psychiatric hospitalisations. This is followed by six complementary studies that explore the relationship between adiposity and subjective well-being. Subjective well-being is explored using various approaches including self-reported health (SRH), health-related quality of life (overall, physical and mental/psychosocial), mental health and mood disorder, and adiposity is assessed using four measures: body mass index (BMI), waist circumference (WC), waist-to-hip ratio (WHR) and body fat percentage (BF%) across the whole range of adiposity (from underweight to class III obese).

The first study (chapter 2) examined the association between SRH and mental health (measured using the General Health Questionaire-12 [GHQ-12]), and long-term adverse outcomes over 17 years of follow-up among 19,625 Scottish adults. Poor SRH was a significant independent predictor of a range of adverse clinical outcomes, including incident cancer, CHD events, psychiatric hospitalisations and all-cause mortality. There was evidence of dose relationships and the associations remained significant after adjustment for mental health. The associations between poor mental health and non-psychiatric outcomes were

mediated by SRH, but poor mental health was an independent predictor of psychiatric hospitalisations.

The second study (chapter 3) examined whether health-related quality of life (HRQoL) was an independent predictor of the long-term adverse outcomes over 8 years of follow-up, among 5,272 Scottish adults recruited from the general population. Being in the lowest quintile of physical HRQoL (worst HRQoL) was a strong independent predictor of all-cause death, incident cancer, and CHD events, compared to the highest quintile. Mental HRQoL was not associated with incident cancer and CHD.

The third and fourth studies (chapter 4 and 5) collated the existing evidence. The third study (chapter 4) was a meta-analysis of the published literature on the separate relationships between adult obesity and mental and physical HRQoL. It comprised a total of 43,086 participants. Different patterns were observed for physical and mental HRQoL. In comparison with normal weight adults, mental HRQoL was reduced among class III obese adults and increased among overweight. In contrast, both overweight and obese adults had significantly reduced physical HRQoL with a clear dose relationship across all categories of adiposity.

The fourth study (chapter 5) was a meta-analysis of the published literature on the relationship between childhood and adolescent obesity and HRQoL. It comprised a total of 13,210 participants. Obese children and adolescents reported significantly reduced overall, physical and psychosocial HRQoL with a clear dose relationship across all categories of adiposity. Parents reported the same pattern but a larger effect size.

The fifth study (chapter 6) assessed the association between adiposity and overall HRQoL, and whether it varied by sex and comorbidity, among 5,608 Scottish adults. There were significant interactions of BMI with sex ($p<0.001$) and with metabolic comorbidity ($p=0.007$). Being overweight was associated with significantly higher utility scores (indicating the overall HRQoL of the individuals, ranges from 0 “death” to 1 “full health) in men only. In contrast, being underweight and obese was associated with significantly lower utility score in women only. Individuals with metabolic comorbidity had lower utility scores and

a steeper decline in utility with increasing BMI. However, increased BMI was associated with reduced HRQoL, even in the absence of metabolic comorbidity, casting doubt on the notion of "healthy obesity" (obesity in the absence of metabolic comorbidity).

The sixth study (chapter 7) investigated the relationship between BMI and self-reported mental health (assessed by the GHQ-12), and whether it varied by sex among 37,272 Scottish adults. Overall, overweight participants reported better mental health than the normal-weight group, and underweight, class II or class III obese individuals had poorer mental health. However, the adverse associations between adiposity and mental health were specific to women. In contrast, overweight men had better mental health than normal weight men.

The seventh study (chapter 8) investigated the associations between four different measurements of adiposity (BMI, WC, WHR and BF%) and probable major depression and whether they varied by sex, among 140,564 middle-aged UK Biobank participants. Overall, both overweight and obese individuals were significantly more likely to have probable major depression with evidence of dose relationship, irrespective of the measurement used. The relationship between adiposity and depression varied significantly by sex, such that the overall association was largely driven by women. In contrast, only men with class III obesity were at significantly increased risk of major depression

The eight study (chapter 9) explored the relationship between the same four measurements of adiposity (BMI, WC, WHR and BF%) and self-reported poor health and unhappiness among 163,066 middle-aged UK Biobank participants. Obesity was associated with both unhappiness and poor SRH, but the association with unhappiness was no longer statistically significant after adjustment for SRH, indicating this may be mediated by poor health. Compared with obese men, obese women were less likely to report poor health but more likely to feel unhappy.

In summary, poor subjective well-being was a significant independent predictor of a range of adverse outcomes, including mortality. There were overall associations between obesity and different measures of subjective well-being including: poor physical and mental HRQoL, poor SRH, unhappiness, and poor

mental health. However, there were significant differences between men and women. Compared with obese men, obese women were less likely to report poor physical health but more likely to report poor mental health and unhappiness. Furthermore, only severely obese men reported poorer well-being, whereas the adverse associations between adiposity and well-being were apparent in all groups of women with above normal weight. This thesis provides further evidences to support the injurious effects of obesity on all aspects of health, and supports the need to take action to reverse the higher prevalence of obesity. Subjective well-being should be considered by health care providers and policy makers in addition to objective measures of health risk, when devising strategies to improve individual and population health.

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Dedication

I dedicate this work to my beloved mother, Hidayat Bibi who died at the age of 58 years on October 1, 2012 during the middle of my PhD. Mom, I'm sorry for not being with you, especially during the last days of your life but I'm very hopeful that when we meet again on the day of judgment under the shade of ALMIGHTY ALLAH, you must be proud of your lonely son, Insha'ALLAH.

Acknowledgement

I was very lucky to have Prof Jill Pell as my primary research supervisor who is the Director of Institute of Health and Wellbeing (IHW) and Henry Mechan Professor of Public Health, University of Glasgow. Individually, she has great experience, skills and has extensively published in the field of Public Health and Epidemiology. ALLAH has gifted her with extraordinary managerial skills and a loving personality. She is an exceptional mentor and has provided me the vision, direction and motivation throughout the project. I am also very thankful to my co-supervisors, Dr. Daniel Mackay and Prof. Elizabeth Fenwick for guiding me through the process with patience and understanding. I am particularly indebted to Dr. Daniel Mackay whose support enabled me to learn the statistical methods needed to complete this thesis. Throughout the project I liaised closely with my supervisors and I found them very helpful all the time. I should acknowledge that without their help and guidance, it would have impossible for me to learn the research skills to publish eight studies during the three years period of my PhD project. I wish to express my sincere gratitude to them for their excellent support through the course of my study.

I would also like to acknowledge the help and assistance of Lorraine Waddell and Margaret Ashton (administration), my friends Liya, Uduak, Nasser and Clair (PhD students), Prof. Andrew Briggs and Dr. David Morrison (assessors), Dr. Jim Lewsey (advisor), all the faculty members of the Master in Public Health programme, David (janitor) and many others for their support during my stay in Glasgow. Thank you very much to Eleanor, Claire, and Breda Cullen for the proof reading. Apart from my research, I enjoyed my role as a post graduate student representative in the company of Camilla baba, Uduak and Prof Kate O' Donnel.

Dr Kashif Shafique who was my senior at the Department of Public Health, Glasgow and now one of my best friends, has tremendously helped me and I will remember him forever.

There are a number of colleagues within the department and outside whom I would like to acknowledge their input for this thesis:

Chapter 2 and 3 – I am particularly grateful to the ISD team from the NHS Scotland for providing me with the SMR linked data.

Chapter 4, 5 – Thanks to the authors of the studies included in the meta-analysis for providing me with further details where needed.

Chapter 6 – I would like to extend my gratitude to Brazier and colleagues at the University of Sheffield for providing me the SF-6D algorithm.

Chapter 8 and 9 - I am thankful to my co-authors from UK Biobank Mental Health Group for their contribution and feedback on manuscripts: Chair; Prof Jill Pell, members; Daniel Smith, Barbara Nicholl, Breda Cullen, Daniel Martin, Jason Gill, Jonathan Evans, and Daniel Mackay (University of Glasgow, UK), Beverly Roberts and Ian Deary (University of Edinburgh, UK), John Gallacher and Nick Craddock, (University of Cardiff, UK), and Matthew Hotopf (Kings College London, UK).

I am grateful to Khyber Medical University, Peshawar, Pakistan and Higher Education Commission of Pakistan for providing me with funding for my higher studies. I am particularly indebted to Prof. HafizUllah, Prof. Shad Muhammad, Dr. Ayaz Ayub, Col. Ihtesham, Mr. Arshad, Prof. Jawad and all KMU PhD Scholars.

I am also thankful to The Charles Wallace Pakistan Trust, University of Glasgow Hardship fund and my supervisor Prof Jill Pell for their financial support during the last period of my project. Closer to my heart, I thank my friends in Pakistan, UK and other parts of the world for providing me with great company and always tolerating me.

The encouragement, prayers and support of my father, Syed Matiullah and my sisters throughout my whole career have been invaluable. I would like to apologize to my wife, Dr Anjum Naz and my three lovely kids Huzaifa, Zaina and Zoha for not giving them the proper attention and love which they deserved. This really would not have been possible without their patience. Lastly, I am extremely thankful to my Creator and Sustainer, ALMIGHTY ALLAH, who is all alone in HIS powers (Surely we belong to ALLAH & to HIM shall we return) for HIS countless bounties on me and for sending HIS Prophets from ADAM (PBUH) to the last Prophet, MUHAMMAD (PBUH) who showed us how to live a successful life.

Author's Declaration

This thesis is submitted in fulfilment of the requirement for the degree of Doctor of Philosophy at the University of Glasgow. Unless stated otherwise, the work is that of the author. Parts of the research work included in this thesis has been published or submitted with co-authors. The following publications and presentations originated from this thesis.

List of Publications

Chapter 2

1. **Ul-Haq Z,** Mackay DF, Pell JP. Association between self-reported general and mental health and adverse outcomes; a retrospective cohort study of 19,625 Scottish adults. *PLoS One* 2014;9:e93857.

Chapter 3

2. **Ul-Haq Z,** Mackay DF, Pell JP. Association between physical and mental health-related quality of life and adverse outcomes; a retrospective cohort study of 5,272 Scottish adults. *BMC Public Health* 2014 (in press).

Chapter 4

3. **Ul-Haq Z,** Mackay DF, Fenwick E, Pell JP. Meta-analysis of the association between body mass index and health-related quality of life among adults, assessed by the SF-36. *Obesity* 2013;21(3):E322-7.

Chapter 5

4. **Ul-Haq Z,** Mackay DF, Fenwick E, Pell JP. Meta-analysis of the association between body mass index and health-related quality of life among children and adolescents assessed, using the pediatric quality of life inventory index. *J Pediatr* 2013;162:280-286.

Chapter 6

5. **Ul-Haq Z,** Mackay DF, Fenwick E, Pell JP. Impact of metabolic comorbidity on the association between body mass index and health-related quality of life: a Scotland-wide cross-sectional study of 5,608 participants. *BMC Public Health* 2012;12:143

Chapter 7

6. **Ul-Haq Z,** Mackay DF, Fenwick E, Pell JP. Association between body mass index and mental health among Scottish adult population: a cross-sectional study of 37,272 participants. *Psych Med 2014;*44,1-10.

Chapter 8

7. **Ul-Haq Z,** Smith D, Nicholl Barbara, *et al*. Gender differences in the association between adiposity and probable major depression: a cross-sectional study of 140,564 UK Biobank participants. *BMC Psychiatry* 2014;14:153.

Chapter 9

8. **Ul-Haq Z,** Mackay DF, Martin D, *et al*. Heaviness, Health and Happiness: A Cross-Sectional Study of 163,066 UK Biobank Participants. *J Epidemiol Community Health* 2014;68:340–348.

Abstracts and Presentations

Abstracts resulting from this thesis were accepted for presentation at the following conferences:

- Chapter 2, 3: Annual Health Research Conference, Khyber Medical University, Peshawar, Pakistan (Feb 2013, Feb 2014)
- Chapter 4, 5: 140th Annual Meeting, American Public Health Association's San Fransico, CA (Oct 2012)
- Chapter 6: Royal Statistical Society, London (July 2012)
- Chapter 7: Weight Stigma Conference, University of Birmingham (May 2013)
- Chapter 4, 7: 46th Annual Society for Epidemiologic research, Boston, Massachusetts (June 2013)

Abbreviations

ADP	air displacement plethysmography
BF%	body fat percentage
BMI	body mass index
CDC	Centre for Disease Control
CHD	coronary heart disease
CI	confidence interval
CT	computer tomography
CVD	cardiovascular disease
DEXA	dual-energy x-ray absorptiometry
F	female
FTO	fat mass and obesity associated gene
GH	self-reported general health
GHQ	General Health Questionnaire
HR	hazard ratio
HRQoL	health-related quality of life
ICD	International Classification of Diseases
IOTF	International Obesity Task Force
ISD	Information Services Division
M	male
MCS	mental summary component
METS	metabolic equivalents
MH	mental health
MVPA	moderate to vigorous physical activity
NHS	National Health Service
OECD	Organisation for Economic Co-operation and Development
OR	odds ratio
PCS	physical component summary
PedsQL	Pediatric Quality of Life Inventory
Qol	quality of life
RR	relative risk
SD	standard deviation
SF	short form
SHeS	Scottish Health Survey

SIMD	Scottish Index of Multiple Deprivation
SMR	Scottish Morbidity Record
SRH	self-reported health
UK	United Kingdom
USA	United States of America
WC	waist circumference
WHO	World Health Organization
WHR	waist-to-hip ratio
WMD	weighted mean difference

1 Chapter 1: General introduction

1.1 Chapter outline

In this chapter, a general introduction of the adiposity is presented along with a discussion on the development, measurements, and trends of adiposity. A short overview of subjective well-being and its association with adiposity is also discussed. Finally the aims and objectives of this thesis are discussed.

Section 1.2: Introduction and causes of adiposity

Section 1.3: Measurements of adiposity

Section 1.4: Trends of adiposity

Section 1.5: Impact of adiposity on physical health

Section 1.6: Adiposity and mortality

Section 1.7: Introduction of subjective well-being and its different measures

Section 1.8: Association between adiposity and subjective well-being

Section 1.9: Summary of the introduction

Section 1.10: Aims and objectives of this thesis

Introduction

"Overweight", "obesity" and "adiposity" are terms used to describe the accumulation of abnormal or excessive body fat that may impair individuals' health and well-being (World Health Organization 2013). The fundamental cause of adiposity (overweight and obesity) is imbalance between energy intake and output. When calorie intake exceeds calorie expenditure, the remainder energy is stored as "fat" throughout the body, in specialized cells called adipocytes. On average, the human body stores around 50,000 to 60,000 kilocalories of energy in adipocytes (Coyle 1995). A normal weight adult has about 130,000 kilocalories of energy stored in around 35 billion fats cells, while morbidly obese adult can have about 1 million kilocalories of energy stored in around 140 billion fats cells (Hall KD et al. 2012). This stored energy works as fuel for most body organs, including the liver, muscle and heart. The function of adipocytes was thought to be limited to the passive storage and release of fat but recently, they have been recognized as being a critical component of metabolic control and as endocrine organs that have both beneficial and harmful effects (Kershaw & Flier 2004). Obesity is associated with increases in both adipocyte number and size. It has been documented that when human body weight exceeds 170% of the healthy range, the size of fat cells doubles (Hirsch & Batchelor 1976).

1.2 Development of adiposity

The development of adiposity is a complex, multifactorial process that is influenced by lifestyle, genetic and environmental factors as described below.

1.2.1 Lifestyle factors

Lifestyle factors that are strongly associated with adiposity include high energy dietary intake, sedentary behavior and low levels of physical activity.

1.2.1.1 Diet

Easily available food which is high in fat and added sugar and low in fibre and starch predisposes to obesity. Caloric intake can be reduced by avoiding energy dense food and drinks and increasing the consumption of vegetables which have high fibre content. Reducing daily intake by 600 calories (20-25% of energy

intake) can achieve the recommended loss of 0.5 kg per week (McNeill & Cummings 2004). The intake of sugar-sweetened soft drinks is independently associated with a significant increase in body weight (Ludwig et al. 2001), and avoiding these alone can achieve significant reductions in weight (Ebbeling et al. 2006). In a large study, conducted across 25 different countries, Scottish children had the second highest intake of sweetened drinks, after Israel, with more than 40% of Scottish children consuming sweetened drinks on a daily basis, (Candace et al. 2004). In the same study, Scottish children were also ranked third in terms of the consumption of sweets, after Malta and Netherlands. In another study, Scottish children were found to obtain 17.4% of their food energy from non-milk extrinsic sugar which is higher than the UK recommendation of 11% (McNeill et al. 2010). The authors concluded that, changing this unhealthy dietary behaviour would require the support and involvement of family, schools, retailers, advertisers and food policy makers.

A recently published systematic review of systematic reviews advocated caution when reading the results of industry sponsored research on the association between sugar sweetened beverages and weight gain or adiposity (Bes-Rastrollo et al. 2013). Of the 12 (83.3%) reviews which had no stated conflict of interest, 10 found a significant association between the consumption of sugar-sweetened beverages and weight gain. In contrast, 83.2% (5/6) of the reviews which had some form of connection with the food industry report insufficient evidence of a positive association. The risk ratio for independent versus industry sponsored reviews was 5.0 (95% confidence interval [CI] 1.29, 19.3).

1.2.1.2 Sedentary behaviour and low physical activity

The second most important factor in the development of adiposity is sedentary behaviour which has been recently re-defined as “any waking behaviour characterized by an energy expenditure ≤1.5 metabolic equivalent (METS) while in a sitting or reclining posture” (Sedentary Behaviour 2012). In contrast, it was suggested that the term “inactive” should be used to describe those “who are performing insufficient amounts of moderate to vigorous-intensity physical activity (i.e., not meeting specified physical activity guideline”).

Sedentary behaviour and low levels of physical activity are consistently reported to be associated with adiposity and they often cluster in the same individuals (Tremblay et al. 2010). Furthermore, sedentary behaviour increases the consumption of high energy diets. In a large, multi-centre, longitudinal study, participants aged 9 or 10 years were followed for 18 or 19 years (Kimm et al. 2005). BMI and skin fold thickness were measured annually and physical activity was measured at baseline, 3, 5 and 7-10 years. A reduction in physical activity of 10 METS per week (equivalent to 30 minutes of brisk walking 2.5 times per week) was associated with a significant increase in BMI of 0.14 kg/m^2 and 0.09 kg/m^2 in African and caucasian girls, respectively. At the end of the study, there was a 3 kg/m^2 difference in BMI between active and non-active participants. Similar results were observed for skinfold thickness.

1.2.1.3 Other lifestyle factors

Other lifestyle factors such as not eating breakfast and increased alcohol consumption are also associated with adiposity (Croezen et al. 2009). Most studies demonstrate a negative association between smoking and adiposity but smokers have more metabolically adverse fat distributions and BMI increases with the amount smoked (Kim et al. 2012). Smoking cessation is also associated with increased BMI (Froom et al. 1998).

Even though current smokers have a lower BMI, advocating smoking as a means of reducing BMI would injurious to public health. A large prospective study, examined the combined effects of adiposity and smoking on mortality (Koster et al. 2008). Current smokers with a high BMI had a 6-8 times higher risk of all-cause mortality, compared to non-smokers with normal BMI. Similarly, smokers with a high WC were at more than 5 times higher risk of all-cause mortality than non-smokers with a normal WC.

1.2.2 Genetic factors

Whilst lifestyle factors, such as high energy diets and physical inactivity, are the main contributors to obesity, genetic predisposition also plays a role (O'Rahilly & Farooqi 2006). Genetic variations have effects on metabolism, tolerance to physical activity and appetite which makes a strong argument for their role in the current conducive environment for adiposity (Frayling 2012). Genetic heritability is estimated to be as high as 70% for BMI and 80% for body fat (Andreasen 2009). A study of 37,000 twin pairs was conducted in eight European countries, including the United Kingdom (Schousboe et al. 2003). The correlation between self-reported BMI was significantly stronger for identical twins (range 0.65 to 0.83) than non-identical twins (ranges 0.31 to 0.58). Similarly a meta-analysis of twin and adoption studies was conducted to investigate the impact of both genetics and environment on the development of adiposity (Silventoinen et al. 2010). Data from nine twin and five adoption studies were extracted and analyzed. The analyses of data from twin studies revealed that genetic factors made a significant and consistent contribution to BMI at all ages. In contrast, common environmental factors were significant in childhood but became non-significant in adolescence. The analyses of data from adoptive studies demonstrated a significant correlation between the role of family environment in adoptees' children and their adoptive parents but it was much stronger between children and their biological parents, further supporting the role of genetics.

In the recent past, scientists have identified many genes that predispose to obesity (O'Rahilly & Farooqi 2006), the most important of which is "fat mass and obesity associated gene or FTO" discovered in 2007 and since analysed in many studies (Frayling et al. 2007). A meta-analysis was recently published focusing on the interaction between FTO and physical activity (Kilpelainen et al. 2011). Forty five studies conducted on a total of 218,166 adults were included. The analysis showed that physical activity attenuated the effect of FTO variation on BMI. The odds of adiposity, defined using BMI, were reduced by 30%. Interactions were also demonstrated for adiposity measured using WC and BF%. These findings demonstrate the importance of physical activity in adults who are genetically predisposed to obesity.

1.2.3 Environmental factors

There is consistent evidence that highlights the role of genetic predisposition in the development of adiposity, but emerging studies reflect that environmental factors have a vital contribution as well. The increases prevalence of adiposity has occurred predominantly over the past three decades across the globe. This rapid change cannot be explained by genetics alone (Stunkard et al. 1990; Wilding 2012). In contrast, marked changes occurred in the environment over that period that promote sedentary behaviour, increased consumption of energy dense food and low physical activity (Cohen 2008). In the last few decades, a remarkable change has occurred in food production which is often called the "green revolution". This has been made possible by new research such as advancement in molecular genetics and increased use of modern technology, including new irrigation projects, sophisticated cultivators, fertilizer, pesticides, herbicides and seed development. It is now possible to plant multiple cycles of crops in the same year. This increased production has made food more affordable. Moreover, the accessibility of food has risen enormously due to the increased number and type of food outlets. Energy dense food is now available in grocery stores, hardware stores, petrol stations, leisure facilities and workplaces, in addition of vending machines which are installed in many public places. Also by applying new marketing techniques and advertisements, individuals are encouraged to chose branded energy dense foods (Pieters et al. 2002).

In addition to increased food production and accessibility, low prices, and stimulation of individuals towards the use of energy dense food, the requirement of physical activity has been significantly reduced over the past few decades (Hill & Peters 1998). The increased use of cars and greater availability of other modes of transport has reduced the need to walk. There are now fewer physical demands both in domestic and work life due to modern technologies and conveniences. Sedentary time has also increased due an escalation in indoor activities such as playing computer games, chatting on online social network sites, watching increasing numbers of television channels. Fears relating to child safety have reduced the willingness of parents to allow their children to play outside (Helen & Shirley 2008). Current guidelines recommend at least 60 minutes of daily moderate-to-vigorous physical activity (MVPA) for children aged

5-18 years. For adults aged 19-64 years, guidelines recommend 30 minutes of MVPA on 5 or more days a week, or collectively 150 minutes over a week (NHS 2014). Children younger than 5 years of age should be encouraged to undertake physical activity and reduce the time spent watching television, playing video-games and travelling by car, bus or train. Based on self-report, about 62% of Scottish adults and 70% of children achieved the recommended level of MVPA (The Scottish Government 2014). However, self-reported levels of physical activity are likely to exceed direct measurements (Prince et al. 2008). For example, in 2005, a representative cross-sectional survey of US adults conducted by the Centers for Disease Control and Prevention (CDC) showed that, according to self-report, 49.1% of US adults met the recommended level of MVPA (Carlson et al. 2009). In contrast, less than 5% of US adults actually met the recommended MVPA when their physical activity was measured directly by using accelerometers (Troiano et al. 2008).

The “communicable” nature of adiposity has also been documented in different studies of social networks. In one particular study, a significant “person-to-person” spread of adiposity was observed in a social network of more than 12,000 individuals who were followed over the period of 32 years (Christakis & Fowler 2007).There were clusters of obese individuals and the likelihood of becoming obese increased by 57% if an individual’s friend became obese around the same time. The corresponding increased likelihood for siblings and spouses were 40% and 37% respectively. The association was more pronounced in people of the same sex. However, there was no spread among neighbours suggesting that adiposity spread mainly through peers.

In summary, the development of adiposity is a complex phenomenon and involves multiple factors: including the consumption of high caloric diets, sedentary behaviour, lack of physical activity, genetic predisposition, and an obesogenic environment. People influence the behaviours of others (Christakis 2004). It has been shown that smoking and alcohol cessation programmes which involved social networks were more successful than those targeting only individuals (Malchodi et al. 2003; Wechsler et al. 1995), and the same is true of weight management programmes (Wing & Jeffery 1999).Tackling the current obesity epidemic will require a multi-faceted approach including: both individual

and community level multi-sector and multi-disciplinary approaches, which are culturally relevant and easily adaptable.

1.3 Measures of adiposity

The most commonly used measures of adiposity are those that indirectly measured body fat mass including: BMI, WC, and WHR. The direct measures of adiposity, including skin fold thickness, bioelectrical impedance, underwater weighing, dual-energy x-ray absorptiometry (DXA) and isotope dilution, are used less commonly in population studies. These measures are briefly discussed below:

1.3.1 Body mass index

BMI is the most widely used measure of adiposity. It is derived by dividing an individual's weight, measured in kilograms (kg), by the square of their height, measured in metres (kg/m^2). Based on the strength of association between BMI and comorbidity, standardized cut-off points have been developed by the WHO that are also used by various national and international organizations (Table 1.1). The National Health Service (NHS), in the United Kingdom, recommends using the same cut-offs to identify those needing interventions, and they are used in their online BMI calculator (www.nhs.uk).

Table 1.1 Body mass index categories

Classification	BMI range (kg/m^2)
Underweight	<18.5
Normal-weight	18.5 to 24.9
Overweight	25 to 29.9
Obese	≥30
Class I	30 to 34.9
Class II	35 to 39.9
Class III	≥40

The relative risk (RR) of obesity-related comorbidity is higher in Asian population so additional intermediate cut-off points were suggested in this population group

as trigger points for public health action; 23.0 kg/m^2 and 27.5 kg/m^2 for "increased risk" and "higher risk" respectively (WHO Expert Consultation 2004).

The main advantage of BMI is that the same cut-off can be applied to all ages and both genders, only height and weight is required for calculation, and it is a relatively cheap and easy method for measuring clinically or in population studies. In calculating BMI, weight is standardized for height which enables people of different heights to be compared. In children and adolescents, BMI is calculated in the same way as for adults but age and sex specific percentiles are used to determine cut-offs. BMI has been used across the globe over the last few decades thus providing the opportunity to do comparisons over time and between different populations. A BMI value higher than 25 is significantly associated with adverse outcomes and mortality (Calle et al. 1999). Obese individuals are at higher risk of medical complications than overweight or normal-weight individuals. However, BMI is only a screening and not a diagnostic tool for diagnosis of obesity (Mei et al. 2002). BMI correlates reasonably well at population level with the direct measure of body fat but it has some limitations. A major criticism of BMI is that it categorizes individuals as overweight or obese on the basis of the total body weight (fat and muscle) which can be misleading, particularly in the case of athletes and body builders who have a high lean body mass. However, misclassified individuals are relatively uncommon at a population level (US Department of Health 1998). At a similar BMI, older people and women are likely to have more body fat than young adults and men respectively. In summary, BMI is a proxy measure of body fat and has some limitations, but remains a commonly used tool in population studies.

1.3.2 Waist Circumference

WC is the most widely used estimate of central adiposity and is strongly correlated with central or abdominal fat mass (Pouliot et al. 1994). It can be easily assessed with a normal inelastic measuring tape. It should be measured between the two bony landmarks; this is mid-way between the lower border of last palpable rib and the upper border of the iliac crest in standing position and at the end of a gentle expiration (World Health Organization 2008). The WHO has recommended sex-specific thresholds for interventions which are followed

by many national and international organizations for community and clinical settings (Table 1.2).

Table 1.2 Waist circumference categories

Classification	Men	Women
Normal-weight	<94 cm	<80 cm
Overweight	94 cm to 102 cm	80-88 cm
Obese	>102 cm	>88 cm

For South Asian and Chinese adults, lower thresholds of ≥90 cm and ≥80 cm are recommended for men and women respectively (International Diabetes Federation 2014). Several studies have shown that BMI may not be a reliable measure of adiposity across age, sex, and ethnic groups (Gallagher et al. 1996). For this reason, WC has gained a considerable attention as a complementary measure or alternative anthropometric measure to BMI (Janssen et al. 2004). Abdominal adiposity is reported to be more strongly associated with metabolic syndrome, diabetes, cardiovascular disease (CVD), and all-cause mortality when measured by WC than BMI (Pischon et al. 2008). The limitations of WC include the lack of recommended cut-offs for use in children. It can be more challenging to use in some population studies because of the need for physical contact and lifting up participants' shirts and some basic training is required to ensure accurate measurements. It is not used as commonly as BMI, particularly in population studies, and so is less useful for historical and international comparisons.

1.3.3 Waist-to-hip ratio

WHR is the second most widely used measure of central adiposity after WC, and is shown to be significantly correlated with abdominal fat (World Health Organization 2008). It requires two measurements; waist and hip circumference. Hip circumference should be measured at the widest part of the buttocks (at the level of the greater trochanter) using a stretch resistant measuring tape. Both measurements should be done in a relaxed standing position and at the end of gentle expiration with feet together. The measurement should be repeated twice and in the case of one centimetre difference, the mean should be calculated. As with WC, the WHO has recommended sex-specific thresholds of

WHR on the basis of its association with adverse outcomes and mortality (Table 1.3).

Table 1.3 Waist-to-hip-ratio categories

Classification	Men	Women
Normal-weight	<0.94	<0.80
Overweight	0.94 to 0.99	0.80-0.84
Obese	≥1	≥0.85

There are fewer studies from which to derive appropriate WHR cut-offs for South Asian and other non-White ethnic groups. A recent review concluded that the cut-offs for threshold of higher risk WHR for the South Asian ethnic groups; ≥0.90 and ≥0.80 for men and women, respectively (Lear et al. 2010). Some studies have reported that central obesity is a stronger predictor of adverse outcomes than BMI (Lee et al. 2008). Two recent studies showed that WHR was more strongly associated with CVD than BMI and WC (Chen et al. 2007; Dalton et al. 2003). WC is strongly associated with diabetes (Mamtani & Kulkarni 2005) but WHR is the strongest predictor of myocardial infarction (Yusuf et al. 2005). WHR is an indirect estimate of abdominal and hip fat mass. The limitations of WHR include: the need for two measurements thereby increasing the chance of measurement error, expression of the result as a ratio which may be more difficult to interpret, the need for physical contact and training; fewer studies from which to derive ethnic-specific cut-offs, less widespread use making comparisons more difficult and the absence of reference percentiles for use in children.

1.3.4 Other measures of adiposity

A number of other measures exist for measuring fat mass. A special caliper can be used to measure subcutaneous fat. Skin fold thickness is measured by pinching the skin at a number of predefined points on the body, such as upper arm, trunk, and thighs (Deurenberg & Deurenberg-Yap 2002). The readings are then compared with age-sex-specific charts. Bioelectrical impedance can be measured by passing a low electrical current through the body and measuring the difference of flow in body fat, water and lean body mass (Jebb et al. 2000). Underwater weighing is the gold standard method of directly measuring body

fat. Participants are weighed in air and then submerged in a specialized tank in a laboratory setting. Individuals with high fat mass weigh less inside the water compared to those with a high lean body mass. However, Air displacement plethysmography (ADP) has replaced underwater weighing as the best two-compartment method for measuring adiposity (Fields 2002). ADP has the same principle as underwater weighing but it is based on air displacement. It has the advantage of being rapid, non-invasive, automated and safe process. It is suitable for children, older, morbidly obese and disabled individuals. Dual-energy x-ray absorptiometry (DEXA), uses low dose x-ray to accurately record the fat distribution in the body. Isotope dilution is another method where participants drink isotope-labelled water and are then analyzed for isotope levels to calculate body fat mass. Computerized tomography (CT) and magnetic resonance imaging (MRI) can also be used for directly measuring body fat mass in different parts of the body. The advantage of these direct measures of body fat is their accuracy. However, they are expensive, time consuming, and unsuitable for serial measurements making them impractical for use in large population studies. They are mostly used in clinical settings or for validating other measures such as BMI, WC and WHR. No agreed cut-offs are available but generally BF% is classified among men as; normal weight (<18%), overweight (18-25%) and obese (>25%). The equivalent cut-off values for women are <25%, 25-32% and >32%, respectively (The American Council on Exercise 2013).

In summary, BMI is the anthropometric measure of choice for most large population studies, and is likely to remain so for the near future. However, it is only a surrogate measure of body fat since it actually measures total body weight in relation to height. Therefore, BMI might give misleading results in some scenarios, such as increasing age (Deurenberg et al. 1991), different ethnic groups (Deurenberg et al. 1998), sportsmen and women (Katch & Katch 1984), and weight loss with enhancing physical activity (Whatley et al. 1994). It is evident that using both BMI and WC or WHR produces more informative results (Pischon et al.2008). It is now argued that this is the time that adiposity researchers should shift toward direct measurements of body fat mass rather than relying only on proxy measures (Prentice & Jebb 2001). Recently UK Biobank, which is one of the world's largest population studies with more than 500,000 UK participants, included a series of anthropometric measures such as

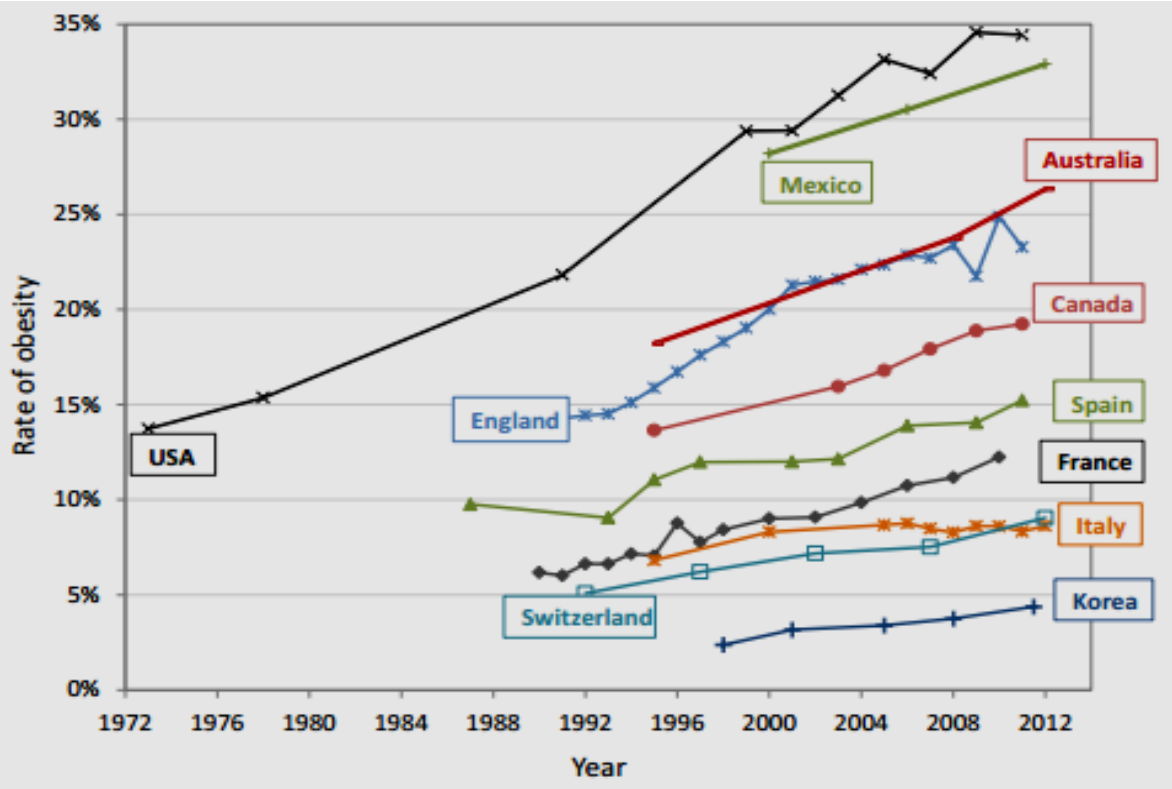
WC, WHR and bio-impedance, as well as BMI, and therefore will be interesting to explore (Allena et al. 2012).

1.4 Trends in adiposity

Adiposity is a global health problem and according to the WHO, if immediate action is not taken, many will suffer from a range of serious health problems. In 2008, more than 1.4 billion adults, worldwide, were overweight and more than 0.5 billion were obese (World Health Organization 2013). The prevalence of adiposity has nearly doubled from 1995 to 2008 (Finucane et al. 2011). Historically, the adiposity epidemic was thought to be restricted to developed countries but the prevalence is now high dramatically in both low and middle-income countries. One large study used data from 243 national health surveys across 199 countries to estimate the trends in the global prevalence of overweight and obesity between 1980 and 2008 (Stevens et al. 2012). The age-standardized global prevalence of adults (aged 20 years or above) classified as overweight increased from 24.6% (95% CI 22.7%, 26.7%) in 1980 to 34.4% (95% CI 33.2%, 35.5%) in 2008. The corresponding global prevalence of obesity increased from 6.4% (95% CI 5.7%, 7.2%) in 1980 to 12.0% (95% CI 11.5%, 12.5%) in 2008.

Among the OECD countries, 18% of the adult population are obese (OECD 2014). Since 1990, the prevalence of obesity has increased at a faster rate in England, USA and Australia than other OECD country (Figure 1.1). However, since 2008 the adiposity rates have almost stabilized in most of the countries and slightly increased in others. This could be attributed to the adaptation of “obesity tackling policies” in many of the OECD countries.

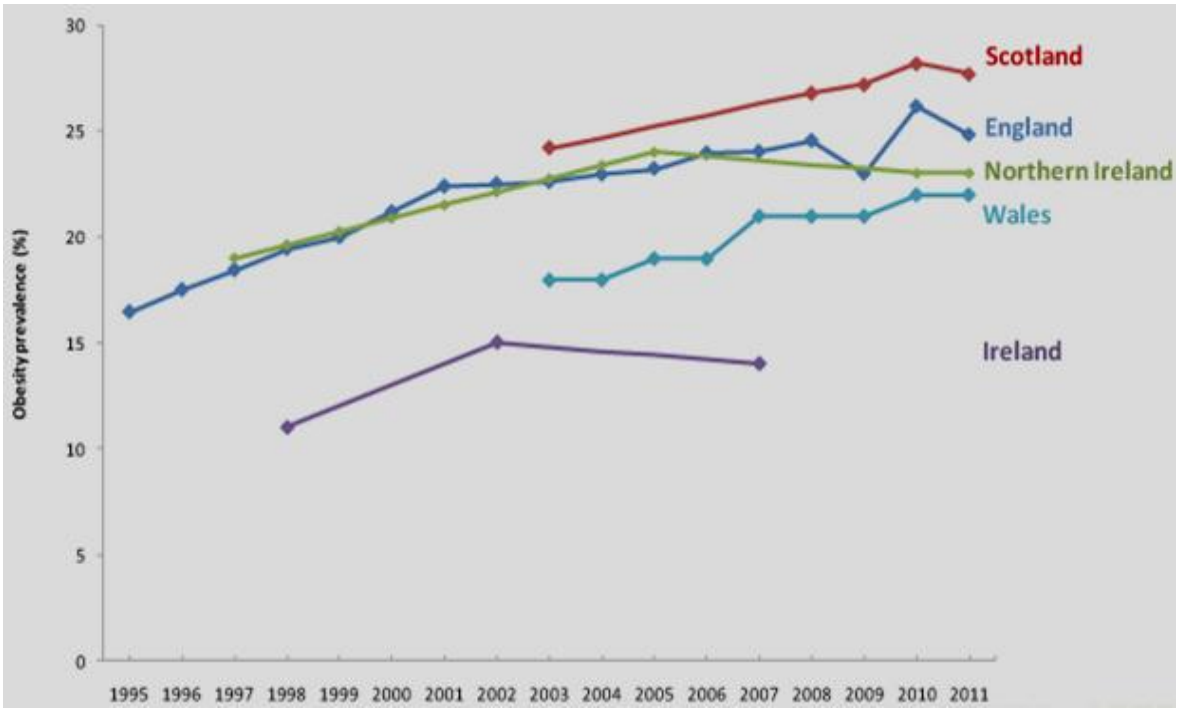
Figure 1.1 Obesity rates (age and gender adjusted) in the OECD countries



Source: from OECD obesity update 2014
http://www.oecd.org/els/health-systems/Obesity-Update-2014.pdf

Among the European countries, the UK has the second highest prevalence of obesity after Hungry, where 2 out of 3 men are overweight and 1 in 4 individuals are obese (OECD 2014). In 2011, among adults in England, 65% of men and 58% of women had a BMI above 25 kg/m^2 (overweight and obese). This had increased from 58% and 49%, respectively in 1993 (NHS 2013). The prevalence of obesity (BMI ≥30 kg/m^2) in 2011 was 24% in men and 26% in women and had increased from 13% and 16% respectively in 1993. Among all the countries in the UK, Scotland continues to have the highest prevalence of obesity (Figure 1-2). The prevalence of obesity in the UK is predicted to reach 60% in men, 50% in women and 25% in children by 2050 (Foresight 2007), but more recent data shows that the adiposity rates have almost stabilized or slightly decreased in all of the UK countries (Figure 1.2). The Department of Health, UK aimed to achieve the downward trend of excess body weight among adult and the sustained decline in childhood obesity by 2020 (Department of Health 2013).

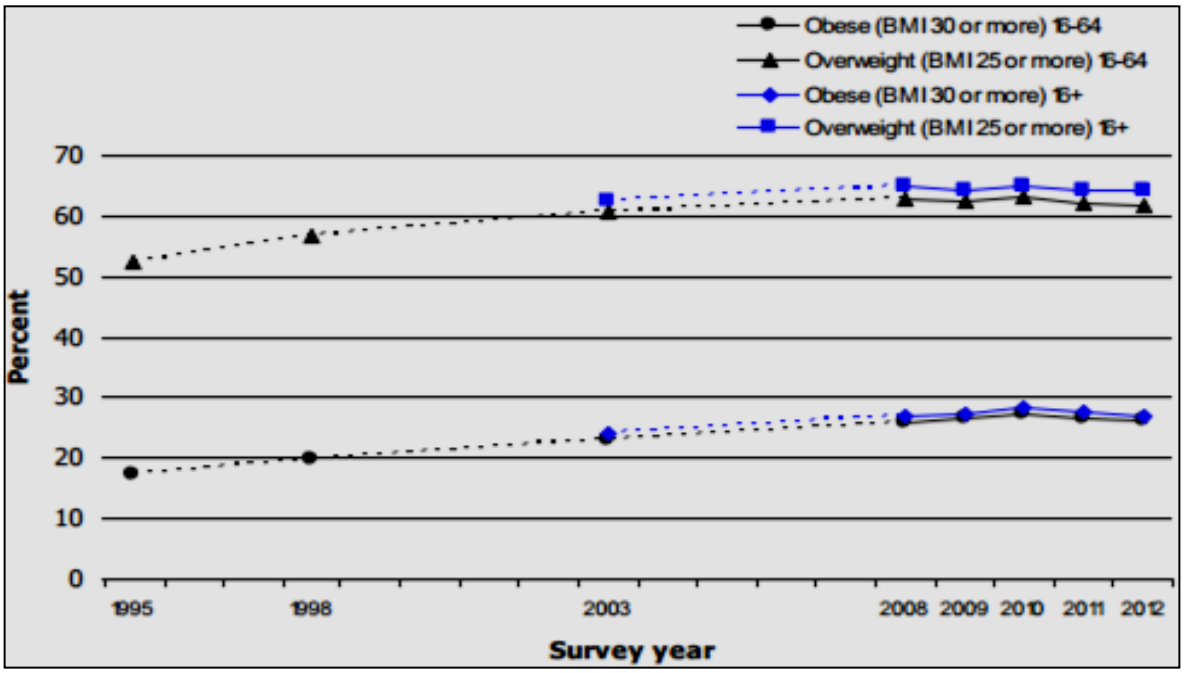
Figure 1.2 Trends in adult (≥16 years) prevalence of obesity in the UK and Ireland



Source: from Public Health, England
http://www.noo.org.uk/NOO_about_obesity/adult_obesity/international

In Scotland, the percentage of overweight or obesity in adults rose from 52.4% in 1995 to 61.9% in 2012, and that of obesity from 17.2% to 26.1%, respectively (Keenan et al. 2011). However, the prevalence of both obesity and overweight has been levelling off since 2008 (Figure 1.3). In 2010, the Scottish Government showed its commitment by producing a comprehensive Route Map "Preventing overweight and obesity in Scotland. A route map towards health weight" (The Scottish Government 2010). The ultimate goal of which is to reduce the prevalence of obesity in Scotland.

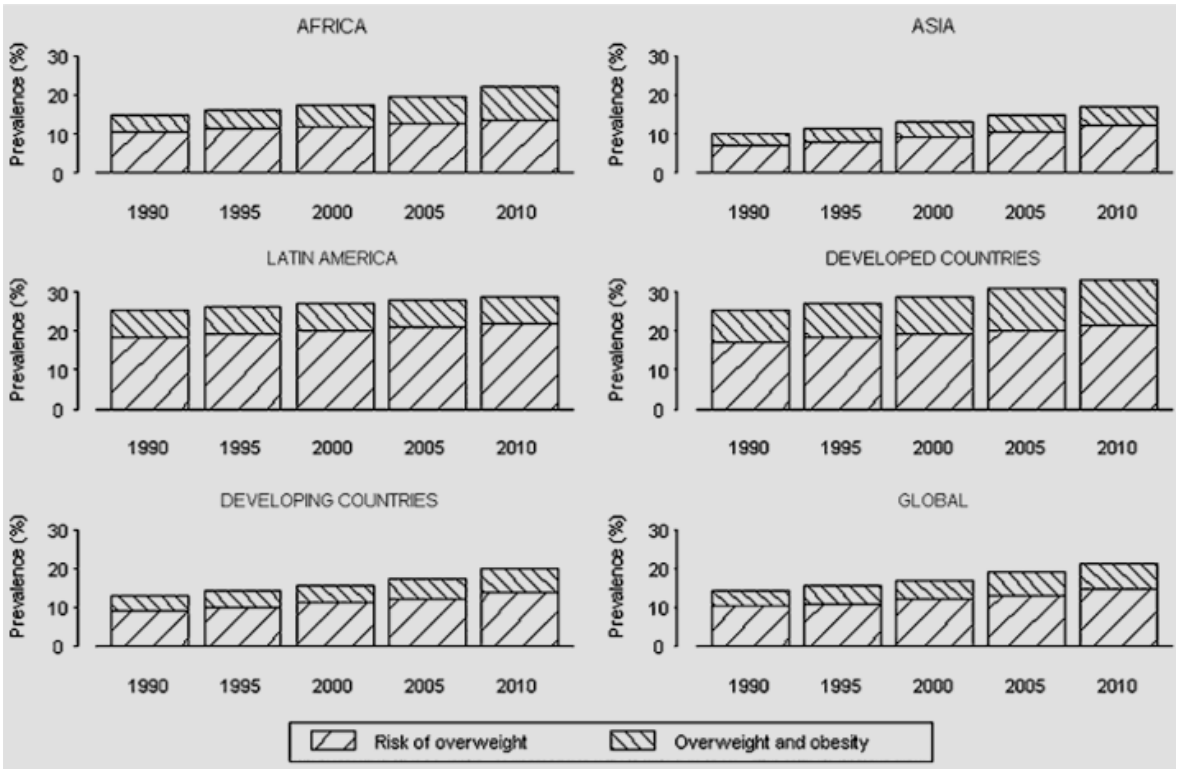
Figure 1.3 Prevalence of overweight and obesity in Scottish adults 1995 to 2010 (aged 16 to 64 years), 2003 to 2012 (age 16 years and above)



Source: from the Scottish Health Survey 2012 report
http://www.scotland.gov.uk/Resource/0043/00434580.pdf

Similarly, childhood adiposity is highly prevalent in both developed and developing countries. A larger study collated data on 43 million children from 450 nationally cross-sectional surveys conducted in 144 countries (de OM et al. 2010). In 2010, the global prevalence of childhood overweight and obesity was 6.7% (95% CI 5.6%, 7.7%). This was dramatically higher than, in 1990, when the global prevalence was estimated to be 4.2% (95% CI 3.2%, 5.2%) (Figure 1.4). Furthermore, the global prevalence is expected to rise further and reach 9.1% (95% CI 7.3%, 10.9%) by 2020 (de OM et al. 2010, Foresight 2007).

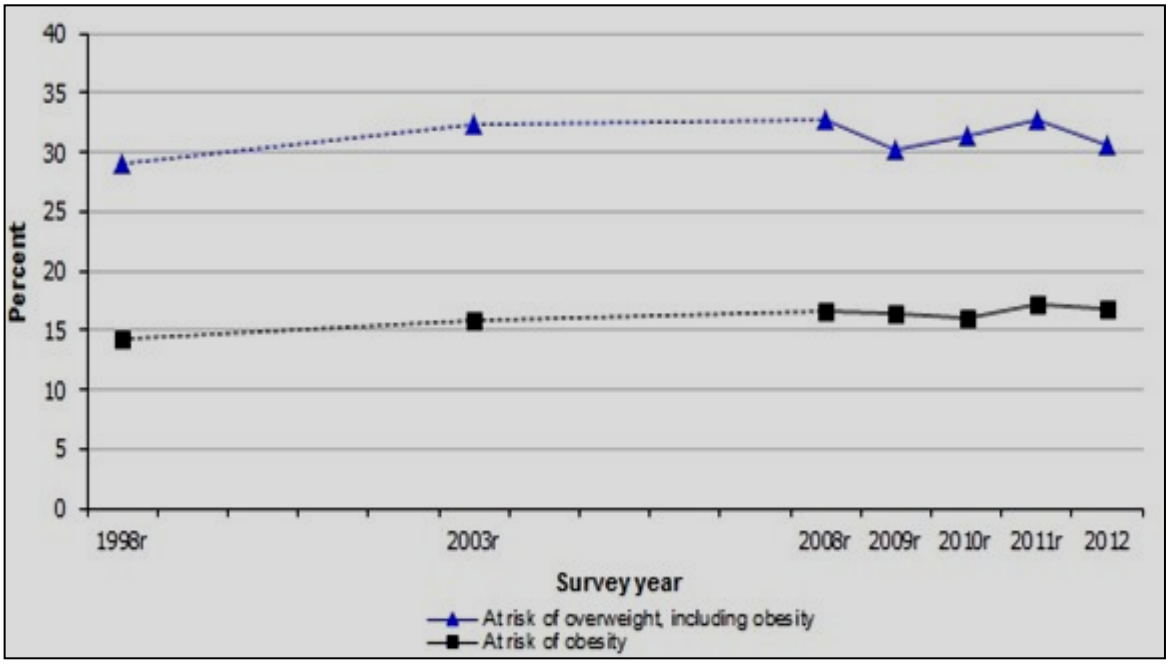
Figure 1.4 Global, prevalence and trends of overweight and obesity in preschool children



Source: from Onis de et al. Global prevalence and trends of overweight and obesity among preschool children. Am J Clin Nutr 2010;92:1257-64.

However, in line with the trend of adult obesity, the latest data shows that the rate of childhood obesity is not only stabilizing but is on the decline in most of the OECD countries (OECD 2014). From 2003-2004 through 2011-2012 in USA alone, the prevalence of obesity among 2 to 5 years old children significantly decreases by 43% (from 13.9% to 8.4%) (Ogden et al. 2014). Similarly, in Scotland since 2008, the prevalence of overweight and obesity is not only stabilized but is on decline (Figure 1.5). In 2012, 30.6% of children (aged 2 to 15 years) were at risk of overweight or obese in Scotland, 16.8% of which were at risk of obese only. The Scottish Government is working on the national indicator for children to “reduce the rate of increase in the proportion of children with their body mass index outwith a healthy range by 2018” (The Scottish Government 2010).

Figure 1.5 Prevalence of children at risk of overweight and obesity, 2003 to 2012 (aged 2 to 15 years)



Source: from the Scottish Health Survey 2012 report
http://www.scotland.gov.uk/Resource/0043/00434580.pdf

In summary, the prevalence of adiposity has dramatically increased over the past three decades across the globe, to such an extent that being overweight has become the norm in most countries (Finucane et al. 2011). If effective strategies are not adopted then more than 50% of the population might become obese in the next few decades (Foresight 2007). However, since 2008 there is no significant change in the trend of obesity prevalence among adults, and there is even evidence of decline in children. This could be attributed to the reduction of soft drink sales, improvement in the intake of healthy diet, increase in leisure activities and decline in the time spent in front of TV in the recent past (http://www.scotland.gov.uk/Publications/2013/11/4898).

1.5 Impact of adiposity on physical health

There is a plethora of evidence that adiposity has an adverse impact on physical health and mortality. These are discussed below.

1.5.1 Cardiovascular diseases

During the 14 year follow-up of the 5,881 Framingham Heart Study participants, a 5% increase in the RR of heart failure for men, and 7% for women, was demonstrated for each one unit increment in BMI (Kenchaiah et al. 2002). Overall, obese individuals had a 2-fold higher risk of heart failure than normal-weight individuals (adjusted hazard ratio (HR) 2.04 (95% CI 1.59, 2.63, p<0.001).For women, the adjusted HR was 2.12 (95% CI 1.51, 2.97, p-value <0.001), and for men it was 1.90 (95% CI 1.30, 2.79, p-value <0.001). The overall HR for overweight was 1.34 (95% CI 1.08, 1.67, p-value 0.007); HR 1.50 (95% CI 1.12, 2.02, p-value 0.007) for women and HR 1.20 (95% CI 0.87, 1.64, p-value 0.27) for men. Furthermore, 11% of total heart failure cases in men, and 14% in women, were attributable to obesity. A prospective cohort study conducted in the United States measured BMI in 1,132 white men, and followed up over a much longer period (median 46 years) (Shibab et al. 2012). In comparison to normal weight men, both overweight (adjusted HR 1.65, 95% CI 1.29, 2.09) and obese (adjusted HR 4.83, 95% CI 2.47, 9.44) men were more likely to develop incident hypertension. In another study,379 middle-aged normotensive men from Finland were followed for 11 years, a 5 cm increase in WC was significantly associated with development of hypertension (adjusted OR 1.31, 95% CI 1.04, 1.66) (Niskanen et al. 2004). The 21,414 participants of the US physician's health study were followed-up for more than 12 years (Kurth et al. 2002). In comparison with normal weight, obesity was found to be an independent predictor of total stroke (adjusted HR 2.00, 95% CI 1.48, 2.71), ischemic stroke (adjusted HR 1.95, 95% CI 1.39, 2.72) and haemorrhagic stroke (adjusted HR 2.25, 95% CI 1.01, 5.01). Similarly, each unit increase in BMI, was associated with a 6% (95% CI 4%, 8%) increase in the risk of stroke.

1.5.2 Type 2 Diabetes

Adiposity is a major modifiable risk factor for developing type 2 diabetes. In the Nurses' Health Study of 114,281 registered female nurses, even modest baseline adiposity was found to be an independent predictor of type 2 diabetes (Colditz et al. 1995). Over 14 years follow-up, 5, 40 and 93 fold higher risk of type 2 diabetes was recorded in women with a BMI 24.0-24.9 kg/m^2, 31.0-32.9 kg/m^2, and≥35.0 kg/m^2 respectively, compared to women of BMI less than 22 kg/m^2. In another study, similar associations were reported among 6,916 men over 12 years of follow-up (Wannamethee and Shaper 1999); for BMI 25.0-27.9 kg/m^2 the adjusted RR was 2.25 (95% CI 1.45, 3.47), for BMI 28.0 -29.9 kg/m^2 it was 4.74 (95% CI 2.99, 7.51), and for BMI ≥30.0 kg/m^2 it was 8.04 (95% CI 5.06, 12.74), compared to normal-weight men. In a clinical trial 3,234, participants were randomly assigned to one of three interventions groups; placebo, metformin or intensive lifestyle intervention (Knowler et al. 2002). The target for participants assigned to the intensive lifestyle modification arm was to achieve and maintain a weight reduction of at least 7% of their baseline body weight. After a mean follow-up of 2.8 years the incidence of diabetes was reduced by 58% (95% CI 48%, 66%) in the lifestyle modification arm and 31% (95% CI 17%, 43%) in the metformin arm, compared to the placebo group, suggesting weight reduction was more effective than the use of metformin.

1.5.3 Cancer

The WHO International Agency for Research on Cancer (IARC) concluded that there is now adequate evidence for the association between adiposity and cancer, particularly with oesophageal adenocarcinoma, post-menopausal breast cancer, colorectal cancer, endometrial cancer and renal cell cancer (International Agency for Research on Cancer 2002). Overweight and inactivity were responsible for one quarter to a third of these cancers. A meta-analysis was conducted, in 2008, to quantify the association between a 5 kg/m^2 increase in BMI and the risk of 20 common and less common cancers (Renehan et al. 2008). A total of 28,2137 incident cases were included from 141 longitudinal studies: 28 conducted in North America,35 in Europe and Australia and 11 in Asia-Pacific. Among women, there were positive significant associations with endometrial cancer (RR 1.59, 95% CI 1.50 to 1.68, $p<0.001$), gallbladder cancer

(RR 1.59, 95% CI 1.02 to 2.47, p=0.04), oesophageal adenocarcinoma (RR 1.59, 95% CI 1.31 to 1.74, p-value <0.001), and kidney cancer (RR 1.34, 95% CI 1.25 to 1.43, p<0.001). There were also significant associations with leukaemia, thyroid cancer, postmenopausal breast cancer, pancreatic cancer, multiple myeloma and colon cancer. Among men, there were significant associations with oesophageal adenocarcinoma (RR 1.52, 95% CI 1.33 to 1.74, p<0.001), thyroid cancer (RR 1.33, 95% CI 1.04, 1.70, p=0.020), colon cancer (RR 1.24, 95% CI 1.20, 1.28, p<0.001), and renal cancer (RR 1.24, 95% CI 1.15, 1.34, p<0.001). There were also significant associations with malignant melanoma, multiple myeloma, rectal cancer and leukaemia. This evidence suggests that adiposity is important modifiable risk factors for cancer.

1.5.4 Respiratory diseases

Adiposity imposes extra load on the respiratory system to fulfil the increased metabolic demand. It alters normal respiratory physiology due to reduced chest wall compliance because of the extra fat accumulated in the thorax and abdomen, reduction of lung volumes, rate of total oxygen consumption and carbon dioxide production, pattern of breathing, and respiratory drive. About half of sleep apnoea patients are obese (Young et al. 1993). The sleep apnoea has several complications, such as cardiac arrhythmias, pulmonary and systemic hypertension, CVD and daytime somnolence. Adiposity is a significant risk factor for the development of other respiratory diseases, including bronchial asthma, pneumonia, deep vein thrombosis, pulmonary embolism, pulmonary hypertension and chronic obstructive pulmonary disease (Murugan & Sharma 2008).

1.5.5 Other physical health conditions

Adiposity is associated with a number of other physical conditions. About six percent of primary infertility is linked with adiposity due to hormonal imbalance which causes disruption in normal female reproductive function and impotency in men (Esposito et al. 2004; Green et al. 1988). Adiposity predisposes to a number of musculoskeletal disorders, including back pain, osteoarthritis, rheumatoid arthritis and gout (Grotle et al. 2008). Obese individuals have a 42% higher risk of Alzheimer's disease compared to normal-weight individuals (Beydoun et al. 2008). Class III obese women and men have a seven-fold and

two-fold higher risk of developing gallstones than normal-weight women and men respectively (Stampfer et al. 1992; Tsai et al. 2004). Adiposity is also an independent predictor of kidney disease, and non-alcoholic fatty liver disease (Fox et al. 2004).

In summary, adiposity is a significant risk factor for the development of many chronic non-communicable diseases, including CVD (hypertension, CHD, varicose vein, deep venous thrombosis), respiratory diseases (sleep apnoea, asthma, chronic-obstructive pulmonary disease), metabolic disorders (hypercholesterolemia, type 2 diabetes, menstrual irregularity), gastrointestinal diseases (fatty liver, gallstones) and cancer (post-menopausal breast, oesophageal, colorectal, endometrial, kidney). Recent studies have shown that adiposity is associated with more physical health conditions than smoking, alcohol and socio-economic deprivation (Sturm & Wells 2001). Adiposity is a modifiable risk factor and its prevention could lead to significant improvements in health, reduced morbidity and annual savings of billions of pounds in direct and indirect health care costs (Vlad 2003).

1.6 Adiposity and mortality

Adiposity predisposes to many chronic conditions, which themselves are associated with mortality. However, there is a growing literature that suggests that whilst obesity is associated with higher mortality, being overweight is not and may, in fact, be protective for all-cause death. In a recent meta-analysis including 97 studies with 2.88 million participants and more than 270,000 deaths, classes II and III obesity were significantly associated with higher all-cause mortality than normal-weight participants (Flegal et al. 2013). In contrast, overweight individuals were 6% less likely to die over follow-up (HR 0.94, 95% CI 0.91, 0.96) (Flegal et al. 2013). In a meta-analysis of 26 published studies with 388,622 participants and 60,374 deaths, obesity was associated with higher all-cause death, among both men (RR 1.28, 95% CI 1.18,1.37) and women (RR 1.20, 95% CI 1.12, 1.29) but being overweight was protective for all-cause death among both men (RR 0.97, 95% CI 0.93, 0.99) and women (RR 0.97, 95% CI 0.92, 1.0) (McGee 2005).

In a recent Scottish study, the birth records of 37,709 adult offspring (of 28,540 mothers) aged 34 to 61 years were linked to their death records from 1950 to 2011 inclusive (Reynolds et al. 2013). All cause mortality was significantly increased among the adult offspring of overweight (adjusted HR 1.11 (overweight and obesity), 95% CI 1.03, 1.19), and obese (adjusted HR 1.35, 95% CI 1.17, 1.55) mothers, compared with the offspring of normal-weight mothers. In another Scottish study, 3,613 women who had never smoked were followed up for 28 years (Hart et al. 2011). Obese (class II and III) women had higher risk of all-cause mortality (adjusted RR 1.56, 95% CI 1.29, 1.89) compared to the normal-weight women, but the association did not reach statistical significance in overweight women (adjusted RR 1.02, 95% CI 0.92, 1.14),. There is no consensus as to why being overweight may be protective against all-cause mortality. Some of the potential reasons proposed include a cardio-protective role of higher body fat in overweight patients, an advantage conferred by increased metabolic reserves, earlier presentation, and increased chance of screening and optimal health care (Flegal et al.2013).

Although, being overweight may not increase the risk of death, there is substantial published evidence that all-cause mortality increases in a dose-response fashion with increasing obesity. Therefore, the current obesity epidemic threatens to halt and possibly reverse the steady increase that has occurred in life expectancy (Lavie et al. 2009).

1.7 Subjective well-being

Subjective well-being has been defined in several ways. The Organisation for Economic Co-operation and Development (OECD) defined it as “all of various evaluations, positive and negative, that people make of their lives and the affective reactions of people to their experiences”. It has also been described as “the personal perception and experience of positive and negative emotional response and global and specific cognitive evaluations of satisfaction with life… Simply, subjective well-being is the individual’s evaluation of quality of life” (European framework for measuring progress 2012).

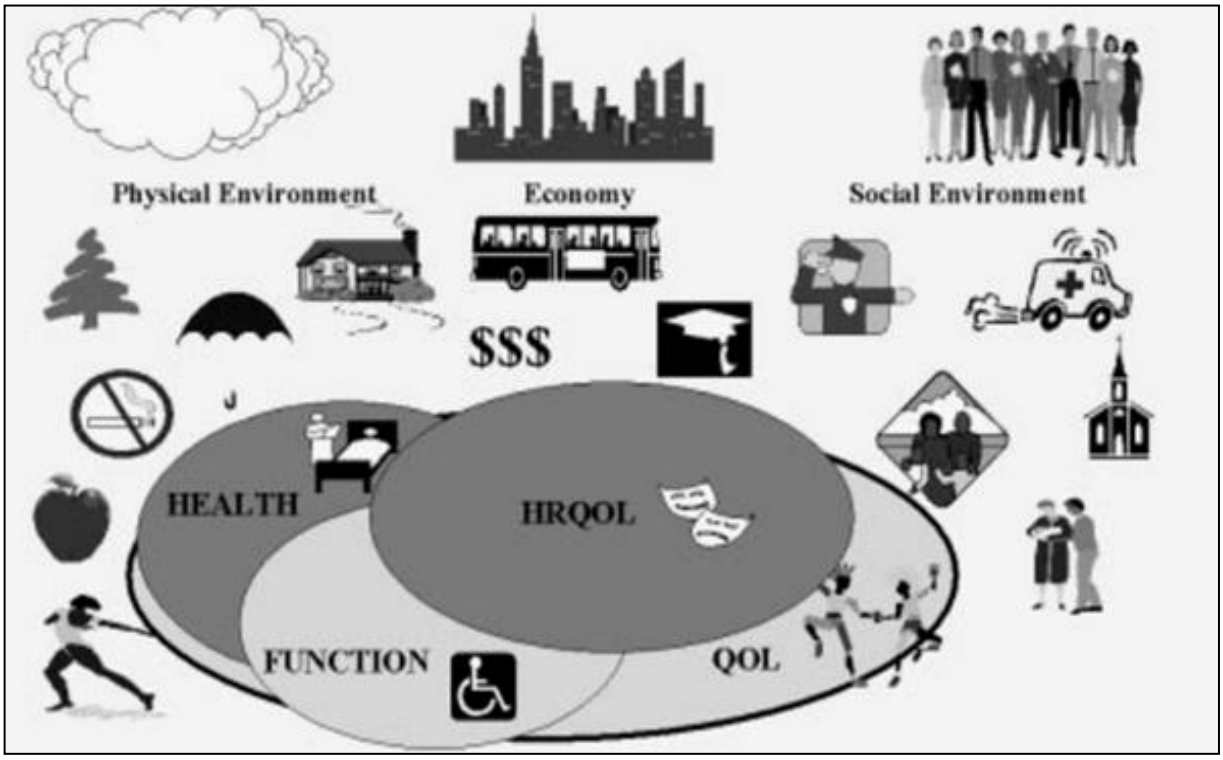
More recently, subjective well-being has been redefined as “An umbrella term for the different valuations people make regarding their lives, the events

happening to them, their bodies and minds, and the circumstances in which they live" (Diener 2006). This later definition of subjective well-being is very close to that of quality of life; "An individual's perception of their position in life, in the context of the culture and value systems in which they live, and in relation to their goals, expectations, standards, and concerns". It is a broad ranging concept, affected in a complex way by the person's physical health, psychological state, level of independence, social relationships, and their relationship to salient features of their environment" (WHOQOL Group 1995). The terms life satisfaction, happiness, and subjective well-being are often used interchangeably as synonyms. Similarly, health status, well-being, life-satisfaction and happiness are sometimes used interchangeably with quality of life. On closer scrutiny of the current definitions of subjective well-being, and quality of life, researchers have reported that both these terms are virtually synonymous (Camfield & Skevington 2008). Subjective well-being, or quality of life, is therefore the scientific term relating to how individuals evaluate their lives.

1.7.1 Health-related quality of life

Health extends beyond the absence of disease, to encompass physical, mental and social well-being. An ideal health assessment would include all these aspects of health. But conventionally, health is measured narrowly using symptoms, physical signs and objective measurements, such as laboratory tests, to indicate the presence or absence of disease. Although health makes an important contributor to overall "quality of life", the latter is also influenced by many other aspects of life, such as education, housing, employment, leisure time, neighbourhood and social belonging. So the concept of HRQoL was developed to encompass those aspects of overall quality of life that can are clearly related to health, either physical or mental (Figure 1.6). HRQoL is defined as "the impact of general medical conditions or symptoms on functional health and well-being and includes physical, mental, emotional, and social aspects of health (Turner-Bowker et al. 2003). In simple terms, HRQoL is "an individual's or group's perceived physical and mental health over time" (Centers for Disease Control and Prevention 2000). In the recent past, HRQoL has gained increasing acceptance as a useful measure and has been incorporated into an increasing number of population studies.

Figure 1.6 Health, function, health-related quality of life, quality of life and related factors



Source: from Centers for Disease Control and Prevention. Measuring healthy days: Population assessment of health-related quality of life. CDC, Atlanta, Georgia 2000.

Worldwide, the life expectancy at birth has considerably increased, due to which the concept of "well-being" has gained popularity. How individuals consider their own health is an important indicator of health status. A subjective measure of overall health is now an important part of measuring health outcomes (Bowling 2014), and is normally determined through national health interview surveys on a regular basis in many countries. Self-perceived health is multidimensional and includes at a minimum, the dimensions of general and mental health, physical, social and role functioning (Hennessy et al. 1994). In contrast the traditional dominant model is the biomedical one, which relies on the medical history, physical examination, laboratory investigation, and treatment and ultimately the outcome is measured on the basis of clinical improvement (Asadi-Lari et al. 2004). This narrow concept of health could lead to the "paternalism" in doctor-patient relationship (McKinstry 1992). In which the doctor considers himself superior than the sick person on the basis of his technical knowledge in taking important decisions for the patient. It is argued that if a mentally sound sick person is capable of taking important decision in his

personal life then it should also be extended to the treatment choice (Gillan 1985).

Therefore, self-perceived health is gradually becoming a part of the clinical practice to help in the diagnosis of otherwise unobserved physical and mental health conditions, monitoring the health and treatment response and assessing the delivery of health care (Detmar et al. 2002). The inclusion of self-perceived health assessment to the daily clinical consultation is reported to be acceptable to both doctors and patient and is feasible in terms of financial and human resources investment (Wagner et al. 1997; Detmar & Aaronson 1998). This also encourages the doctors to inquire about the detailed aspects of patient's health and well-being. A prospective randomized controlled trial of 10 doctor and 214 palliative chemotherapy patients revealed that the doctors in the intervention group (inclusion of HRQoL questionnaire and education session to both doctors and patient before the consultation) identified significantly greater proportion of moderate to severe medical conditions, compared to the control group (Detmar et al. 2002). Moreover, all of the doctors and majority of the patients noted improvement in the communications and were happy for its further use in the OPD.

However, there are studies which reported no improvements after addition of self-assessment of health to the clinical consultations. A systematic review of breast cancer patients were published in 2003, which showed that the introduction of self-assessment of health to the clinical trials did not make a considerable contribution to the clinical decision making (Goodwin et al. 2003). This contribution was too little in comparison to the introduction of increased burden, in terms of time consumption and expenses and addition of complexity to the trails. However, an updated systematic review was published in 2011, which demonstrated that with growing experience the standard of HRQoL studies has improved over the last decade, due to more robust techniques than those used in earlier studies (Osoba 2011). The self-assessment of health provides additional useful information and is now a more accurate predictor of survival than many clinical parameters. It is likely that the self-assessment of health will become the standard part of routine clinical assessment in near future but there is still a need for a universal standard of "clinically minimum important

difference" which is possible with the completion of more individual studies (Osoba 2011).

Studies have reported that self-perceived health is a reliable measure of overall/disease-specific mortality (Benjamins et al. 2004; Idler & Benyamini 1997). It provides additional information by covering those aspects of health which are difficult to capture by objective measurements such as subclinical disease, help-seeking behaviour and health system use (Nielsen et al. 2008). The exact mechanism by which self-perceived health may impact on health and life-expectancy is not known. Self-perceived health is more inclusive and may identify accurate health status by incorporating both objectively measured and subjective assumptions of health risk factors, the full array of medical condition and possibly may detect very early symptoms of underlying disease even at subclinical or prodromal stages (Idler et al. 2000). Better perceived health may reflect an individual's attitude towards improving health, and thus adopting preventive measures. In contrast, the poor perception of own health may result in neglecting of the primary or secondary prevention such as balance diet, physical activity, screening and taking medication for existing medical conditions which may eventually result in early death or disease incidence (Idler & Benyamini 1997). Some have suggested that personality traits, such as optimism, may inflate self-assessment of health (Benyamini et al. 2000). Self-perceived health may reflect changes in health status (improvement or decline) rather than only relying on the current or static health status. It may be influenced by the existing knowledge about familial risk factors and longevity. Others have related better perception of health with better immune responses (Lekander et al. 2004). However, these are all speculations and further qualitative and quantitative research is needed to explore these mechanisms.

Self-perceived health is a relative measure and studies have reported that individuals' perceive their health according to their situation, culture and expectation, and their peers (Idler & Benyamini 1997). Therefore, caution is required when comparing the self-perceived health status among different populations due to socio-cultural diversity and the variation in survey questions and answer categories (OECD 2011).

In summary, self-perceived health is an important indicator of both health and health risk and its routine use may enhance individuals and community health. However, our knowledge about the self-perception of health is still in its early phase and more scientific research is needed.

1.7.2 Measure of subjective well-being

The **Short Form 36** (SF-36) is one of the most commonly used instruments of functional health and well-being. It has been translated into many languages and validated in more than 50 countries across the globe (http://www.sf-36.org/tools/sf36.shtml). SF-36 is a generic measure and consists of 36 questions, covering eight physical and mental health domains. Summary scores can be derived for physical and mental health HRQoL, called the physical component summary (PCS) and mental component summary (MCS) respectively (Ware Jr. 2000). Higher PCS and MCS scores indicate better physical and mental health status, respectively.

The strength of SF-36 or any generic instrument is that they could be used across a wider scope of health conditions. The limitation of generic instruments is that they are less sensitive to clinically important change and the broader applicability may compromise the detailed information, compared to disease-specific measures (Chen 2005; Brazier et al. 1999). The wider and generic use of SF-36 provides the opportunity of comparing the results across the studies and different population. It is a shorter, simple to administer and reproducible measure of general population and different subgroups. However, there is evidence that the survey mode; telephone or postal questionnaire influence the rating of SF-36 (Jörngården et al. 2006). Both men and women are more likely to score higher (better HRQoL) in the telephonic mode than the postal questionnaire. This may be due to the difference in the anonymity between the two modes of questionnaire administration. There is no clearly defined standardized clinically important difference among the SF-36 score. But a between-groups difference of 5 points in individual SF-36 domains, or 2-3 points in the PCS and MCS is generally considered clinically significant (Samsa et al. 1999; Kosinski et al. 2000; Ware 1994). The time to complete the SF-36 questionnaire is 10-12 minutes, compared to 2 minutes for the SF-12 questionnaire (Pickard et al. 1999). Other limitations include a higher rate of

missing data among older participants due to expressing concerns over the relevance of some of the SF-36 questions (Brazier et al. 1996; Hayes et al. 1995). There is loss of information when calculating the two summary scores of PCS or MCS (Hobart et al. 2002). SF-36 is originally designed for self-reporting and may not produce accurate results in proxy reporting for impaired patients (Dikmen et al. 2001).

The **Short Form 12** (SF-12) is a shorter version of SF-36 and is also a validated and a widely used tool for measuring generic HRQoL (Ware Jr, et al. 1996). The advantage of the SF-12 is that it only takes one third of the time needed to complete the SF-36 and is therefore used in many large surveys. The 12 questions of the SF-12 can also be combined to form summary scores for physical and mental health. These summary scores are reported to be closely correlated with that of SF-36 (Wee et al. 2008). Overall SF-12 scores can also be converted to utility scores, via an algorithm developed by Brazier and colleagues at the University of Sheffield (http://www.shef.ac.uk/scharr/sections/heds/mvh/sf-6d/revisions.html). Utilities are values that correspond to people preferences for various health outcomes (Drummond et al. 2005). In health economics, the utilities are used to generate quality-adjusted life years (QALYs). It can be calculated directly such as standard gamble, time trade-off or visual analogue scale or indirectly by applying the utility algorithm to the disease specific or generic HRQoL questionnaire such EQ5D or SF-6D, and HUI (Szende et al. 2006). The indirect method of applying the SF-6D algorithm to the SF-12 questionnaire produce a single digit utility score, indicating the overall HRQoL of the individuals ranges from 0 “death” to 1 “full health”.

The strength of SF-12 includes the reduced burden on the respondents, in terms of less number of questions and the required time for completion. SF-12 produces precise estimates when the summary scores are used, particularly in larger studies (Ware et al. 1996). The limitations include the 10% loss in ability to differentiate between various disease groups and the generation of less precise results in the individual domains in smaller studies, compared to the SF-36 (Ware et al. 1999). When the sample size is less than 500, it is generally recommended to use the SF-36 for accurate results (Ware et al. 1996). Compared t o SF-36, there is inability of SF-12 to produce PCS and MCS when a single item is left unanswered (Pickard et al. 1999). Moreover, the SF-12 may

have less sensitivity and specificity when used as a screening tool, compared to SF-36 (Pickard et al. 1999).

The **Pediatric Quality of Life Inventory** (PedsQL) is a generic HRQoL index developed for self-reporting by children and adolescents aged 5-18 years, as well as parent-proxy reporting for participants aged 2-18 years (Varni et al. 2003). It comprises of 23 items that encompass physical, emotional, social and school functioning. It produces standardized scores for overall, physical and psychosocial HRQoL, ranging from 0 to 100, with higher scores indicating better HRQoL.

The strength of PedsQL is that it comprises of child-self reports and corresponding parents-proxy reports forms. Child self-reports is believed to be the standard for assessing the child's own health, but it is reported that the parent assessment of child's perceived health plays decisive role in utilizing the health care (Campo 2002; Varni et al. 1999; Sawyer et al. 2005). However, there is generally a poor agreement between child self-report and parent-proxy reports ($r < 0.30$), particularly for social and emotional domains (Eiser & Morse 2001). It is reported that parent reports usually explain only 10-25% of variance in child perception of their own health (Varni et al. 2007). The PedsQL is used frequently in both clinical settings and general population as it is multi-dimensional, requires only 5 minutes to complete, and is a straightforward scoring method. The 4.4 points change in the total score for child self-report is considered as minimal clinical importance difference (Varni 2003). The corresponding difference for parents is 4.5. PedsQL can be administered over the telephone from the child as young as eight years, which results in less burdensome and also reduce the possibility of missing outcome data (Dunaway et al. 2010).

Self-reported health (SRH) is a simple but reliable measure of overall, subjective well-being (World Health Organization 2014). Several studies have demonstrated that it is a significant predictor of all-cause mortality. The participants are usually asked "In general how would you rate your overall health?: excellent, good, fair or poor". In most studies, SRH is recoded into good (excellent or good) or poor (fair or poor) for analysis.

There is an ongoing debate that if a single question such as, SRH is available and is consistently reported to be a reliable measure then why to use a lengthy and multiple item questionnaires such as SF-36. The SRH has clear advantage of reducing burden on respondents, particularly when the researchers are only interested for a broader view of overall health rather than a detail assessment. Nonetheless, SRH is a simple and reliable measure but it is at the cost of a detailed assessment on the individual domains of subjective well-being (Bowling 2005). A multi-item measure, such as SF-36 and SF-12 offer more precise and complete multi-dimensional information of the individual's perception of their own health. Health is a central element of SRH; but it is not the only determinant. SRH may differ in different age-groups, men and women, socio-economic status, comorbidity, employment, education, geographic location, psychological sense of community, and mental health status (Ross 2002; Idler & Benyamini 1997; Benyamini et al. 2000).

Individuals give more importance to physical well-being than psychological well-being when self-reporting their health (Smith et al. 1999). Compared to men, women are reported to consider a wider range of both health and non-health-related factors in the course of reporting their self-assessed health (Idler & Benyamini 1997). SRH is influenced by the ongoing changes in the health status over time; improvement or decline rather than the current health status (Idler & Benyamini 1997). SRH is measured regularly in the OECD countries through national health surveys. Although the life expectancy in the OECD countries has considerably increased but there is a relative stability in the trend of SRH. This indicates that people in OECD countries have a longer life but may not be healthier (OECD 2011). There is also variation in the response categories in some countries. Most of the countries used 2 positive responses i.e, very good, good, fair, poor, very poor. In contrast, some countries like USA, Australia, New Zeland and Canada use 3 positive responses i.e, excellent, very good, good, fair, poor. The later may produce more positive results compared to the earlier one (OECD 2011).

The **General Health Questionnaire-12** (GHQ-12) is a validated and widely-used measure of psychological well-being, and is suitable for use in the general population (Goldberg et al. 1997). The 12 questions ask about relevant experiences over the previous few weeks (including sleep disturbance, feelings

of tension, anxiety, stress, depression, lack of confidence and inability to cope). The responses to each question are summed producing an overall score ranging from 0 to 12. Higher GHQ scores (usually defined as ≥4) indicate poor psychological well-being.

GHQ-12 is as robust as the GHQ-28, but it is very quick as can be administered only in two minutes (Goldberg et al. 1997). It is suggested that the longer GHQ should only be chosen if the investigators are interested in scaled score rather than the total score. GHQ-12 is widely used, which makes it possible to do comparisons between groups and monitor trends over time. However, it assesses the current mental health status and is not suitable for screening the long-term individual attributes. The GHQ can be used in adolescents but it is not recommended to be used for the screening of children psycho-social health. It is only a screening tool and an aid to diagnosis but it is not a detailed assessment of mental health (Goldberg et al. 1998). Many studies have found it as a valid and reliable measure of detecting the minor psychological distress (Quek 2001; Tait 2003), but some studies have revealed that GHQ-12 has lower positive predictive value in screening, and using it alone may misclassify people with psychiatric disorder (Gilbody 2001). Others have questioned its reliability as a screening tool for psychiatric morbidity (Hankins 2008; Hahn et al. 2006). It is not designed to detect specific mental disorder such as depression, anxiety or others but as a general indicator of mental health status.

There is no single standardized **happiness** questionnaire, but overall happiness is usually self-reported and based on the response to the question “In general, how happy are you?; extremely happy, very happy, moderately happy, moderately unhappy, very unhappy or extremely unhappy”.

1.8 Adiposity and subjective well-being

There is a strong association between adiposity and a number of physical health conditions. In contrast, the research on adiposity and subjective well-being is still in its infancy. However, in the recent past, some studies have started to address this issue. Most have been based on the association between BMI and HRQoL. There is a need to review the existing literature on the association between BMI and HRQoL and to see if these results are corroborated by other

measures of subjective well-being, including self-rated health, happiness, GHQ-12, and mood disorder. Further work is needed to explore whether the association between BMI and subjective well-being is robust to other measures of adiposity (BMI, WC, WHR and BF%), and whether it varies by sex and comorbidity, and to investigate the long-term outcomes of these different measures of subjective well-being.

1.9 Summary of the introduction

Adiposity is the accumulation of excessive body fat, mainly caused by the imbalance between energy intake and output. There are multiple factors involved in the development of adiposity, but the most important is the presence of an obesogenic environment. Adiposity can be spread through social networks. There are many measures of adiposity, but BMI has been the most commonly used measure, particularly in population studies. However, researchers are increasingly using additional measures such as WC, WHR and BF%. Therefore, many population studies are now recording multiple measures of adiposity on the same individuals.

Over the past three decades, the prevalence of adiposity has nearly doubled. Traditionally, the adiposity epidemic was thought to be limited to developed countries but it is now known to be equally prevalent in developing countries. Worldwide, about one and a half billion adults are overweight and more than half a billion are obese. In Scotland alone, 53% of the adult population are either overweight or obese, and about 27% are obese (Figure 1.2). The prevalence of adiposity is expected to further rise.

Adiposity is a significant predictor of many diseases, including CVD, respiratory disease, metabolic disorder, gastrointestinal diseases, and many malignancies. The impact of adiposity on morbidity and disease incidence is thought to be even greater than that of smoking, alcoholism and poverty. Being overweight is not significantly associated with mortality in many larger studies. However, obesity is thought to be a serious threat to the improvements in life-expectancy achieved over the last few decades.

As adiposity has reached epidemic levels in both developed and developing countries, the impact of this modifiable risk factor on the community is of greater concern, not only in terms of physical health and life-expectancy but possibly also in terms of subjective well-being. Previous studies have been limited in number and scope and suggest a complex relationship between adiposity and subjective well-being. This in an ideal time to collate and build on the existing evidence.

1.10 Aims and objectives

The aims of this thesis were to use large samples from the United Kingdom adult general population, firstly, to investigate the long-term outcomes associated with different measures of subjective well-being. Secondly, to determine overall relationships between different measures of adiposity (measured by BMI, WC, WHR, BF%) and different measures of subjective well-being (HRQoL, happiness, SRH, GHQ-12 and mood disorder) across the whole range of adiposity (from underweight to class III obese) and, thirdly, to determine whether any associations varied by sex, and comorbidity.

The thesis comprises eight complementary studies that address the following specific objectives:

1. To determine whether SRH and mental health (measured using the GHQ-12) were independent predictors of incident cancer, psychiatric hospitalisations, incident CHD and all-cause deaths, and whether it varied by sex.

2. To determine whether physical and mental HRQoL (measured using the SF-12) were independent predictors of incident cancer, incident CHD and all-cause deaths, and whether it varied by sex.

3. To undertake a systematic review and meta-analysis of published studies to determine the relationships between adult BMI and mental and physical HRQoL.

4. To undertake a systematic review and meta-analysis of published studies to determine the relationships between childhood/adolescent BMI and overall, physical and psychosocial HRQoL.

5. To investigate the relationship between “healthy obesity” (obesity without metabolic comorbidity) and overall HRQoL, and whether it varied by sex.

6. To investigate the relationship between adiposity (measured by BMI) and mental health (measured using the GHQ-12), and whether it varies by sex.

7. To investigate the relationship between adiposity (measured by BMI, WC, WHR and BF%) and probable major depression, and whether it varied by sex.

8. To investigate the relationship between adiposity (measured by BMI, WC, WHR and BF%) and SRH, and whether it varied by sex.

2 Chapter 2: Self-reported health and adverse outcomes

Published in;

Ul-Haq Z, Mackay DF, Pell JP (2014) Association between self-reported general and mental health and adverse outcomes; a retrospective cohort study of 19,625 Scottish adults. *PLoS One* **9**:e93857.

2.1 Chapter summary

Self-reported general health (GH) and mental health (MH) are independent predictors of all-cause mortality. This study examines whether they are also independent predictors of incident cancer, CHD and psychiatric hospitalisation.

I conducted a retrospective, population cohort study by linking the 19,625 Scottish adults who participated in the Scottish Health Surveys (SHeS) 1995-2003, to hospital admissions, cancer registrations and death certificate records. I conducted Cox proportional hazard models adjusting for potential confounders including age, sex, socioeconomic status, alcohol, smoking status, BMI, hypertension and diabetes.

Poor GH was reported by 1,215 (6.2%) participants and was associated with cancer registrations (adjusted HR 1.30, 95% CI 1.10, 1.55), CHD events (adjusted HR 2.30, 95% CI 1.86, 2.84) and psychiatric hospitalisations (adjusted HR 2.42, 95% CI 1.65, 3.56). There was evidence of dose relationships and the associations remained significant after adjustment for MH. 3,172 (16%) participants had poor MH (GHQ ≥4). After adjustment for GH, the associations between poor MH and CHD events (adjusted HR 1.36, 95% CI 1.13, 1.63) and all-cause death (adjusted HR 1.38, 95% CI 1.23, 1.55) became non-significant, but MH remained associated with psychiatric hospitalisations (fully adjusted HR 2.02, 95% CI 1.48, 2.75).

GH is a significant predictor of a range of clinical outcomes independent of MH. The association between MH and non-psychiatric outcomes is mediated by GH but it is an independent predictor of psychiatric outcome. Individuals with poor GH or MH warrant close attention.

2.2 Introduction

GH is a simple but reliable measure of overall, subjective well-being (Martikainen et al. 1999; World Health Organization 1996). Several studies have demonstrated that it is a significant predictor of all-cause mortality (Benjamins et al. 2004; Idler & Benyamini 1997; Nielsen et al. 2008). There is a relative paucity of studies on the association between GH and specific diseases, especially in relation to non-fatal outcomes such as hospitalisation. Also, it is not clear to what extent the association is independent of lifestyle factors (Salomon et al. 2004; Sen 2002). Studies suggest that GH is influenced more by physical health than mental health (Mavaddat et al. 2011; Smith & Assmann 1999). Therefore, it is unclear whether GH predicts psychiatric hospitalisations as well as physical disease.

The GHQ-12 is a validated measure of MH and has been widely used in population studies (Goldberg et al. 1997). GHQ score is predictive of both all-cause mortality (Lazzarino et al. 2013; Robinson et al. 2004; Russ et al. 2012) and CVD (Brotman et al. 2007; Nicholson et al. 2006). It is not clear whether the association is independent of GH. Higher GHQ scores, indicative of poor MH, have also been observed among patients with other chronic diseases such as cancer in cross-sectional studies (Gao et al. 2010), but the association has rarely been studied longitudinally. Relatively few studies have formally tested for interactions but those that have suggest that the association between poor GH and all-cause death is greater in men than women, whilst the association between poor MH and all-cause death is stronger in women than men (Kivimaki et al. 2003; Tiainen et al. 2013).

I hypothesized that GH may be an independent predictor of other forms of morbidity and that any association between MH and physical morbidity will be explained by GH. Some other recent studies have made similar hypotheses but they have rarely been tested, particularly in longitudinal studies (van der Linde et al. 2013). It is possible that they have a direct causal effect. Perceived health (general or mental) may impact on lifestyle and therefore incident disease and survival. It is also possible that subjective well-being is a marker of sub-clinical morbidity or that the incident diseases and subjective well-being share common risk factors. The aim of this study was to determine whether GH and MH were

independent predictors of incident cancer, psychiatric and CHD as well as all-cause deaths, and whether the associations varied by sex.

2.3 Material and methods

2.3.1 Data sources

The SHeS collects information on health and health-related risk factors in the Scottish general population (http://www.scotland.gov.uk/Topics/Statistics/Browse/Health/scottish-healthsurvey). The first SHeS was undertaken in 1995. It was repeated in 1998 and 2003 and, since 2008, has been undertaken annually. Different households have been targeted in each survey and the recruitment rates have exceeded 60%. The members of participating households are interviewed by trained data collectors who use computer assisted personal interviewing (CAPI) to collect information on demographics (including age, sex, postcode of residence and social class), lifestyle (including smoking status and alcohol consumption) and SRH. During a subsequent visit, a nurse uses standard operating procedures and calibrated tools to record height, weight and blood pressure. More than 90% of SHeS participants have consented to passive follow up via record linkage to routine administrative data. The SHeS records have been linked, at an individual level, to several Scotland-wide databases including: death certificates (collated by the General Registrar Office), admissions to acute hospitals (Scottish Morbidity Record SMR01), psychiatric hospitalisation (Scottish Morbidity Record SMR04) and cancer registrations (Scottish Morbidity Record SMR06) (Gray et al. 2010). Cancer was defined by the International Classification of Diseases-10 (ICD-10) codes C00-C97. Psychiatric hospitalisation was defined as first hospitalisation with an ICD-10 code F00-F99 in principal position. CHD event was defined as death or hospitalisation due to CHD. The latter was defined as first hospitalisation with an ICD-10 code I20-I25 in the principal position. The SMR data are reported to be 94% accurate and 99% complete (NHS Scotland 2010). The extract of linked data provided follow-up to a censor date of 31 December 2011.

2.3.2 Inclusion criteria and definitions

For this study, I combined the first three SHeS surveys (1995, 1998 and 2003) and restricted my analyses to participants aged ≥16 years. I excluded participants with established cancer, CHD or psychiatric disease at recruitment. Age was categorised into 16-29, 30-44, 45-59 and ≥60 years. BMI was categorised into underweight (<18.5 kg/m^2), normal weight (18.5-24.9 kg/m^2), overweight (25.0-29.9 kg/m^2), class I (30.0-34.9 kg/m^2), class II (35.0-39.9 kg/m^2) and class III obese (≥40 kg/m^2). The occupation of the household's main income earner was used to derive social class: I (professional), II (managerial), III NM (skilled non manual), III M (skilled manual), IV (semi-skilled manual) and V (unskilled manual) (General Register Office), and area-based deprivation was derived from the postcode of residence using general population quintiles of the Scottish Index of Multiple deprivation (SIMD) (http://www.scotland.gov.uk/Topics/Statistics/SIMD). Smoking status and alcohol consumption were both self-reported and were categorised as never, previous and current, and never, previous, within limit and excessive respectively. Prevalent hypertension (blood pressure ≥140/90 mmHg or use of anti-hypertensive medication) and diabetes were based on self-report of a physician diagnosis. GH was self-reported and based on responses to the question; "In general, how would you rate your overall health." Possible responses were: very good, good, fair, bad and very bad. In this study, the five responses were collapsed into three categories: good (very good or good), fair and bad (bad or very bad). MH was based on participants' responses to the GHQ-12 questionnaire. GHQ-12 scores range from 0 to 12, with 12 indicating the poorest mental health. In this study, the scores were collapsed into three categories: 0, 1-3 and ≥4.

2.3.3 Statistical analyses

Differences in the characteristics of participants by GH and MH were analysed using chi-square tests for categorical data, and chi-square tests for trend for ordinal data. Separate Cox proportional hazard models were used to examine the association between GH and four separate outcomes: all-cause deaths, cancer registrations, CHD events (admissions or death) and psychiatric admissions. The model was run in three stages: adjusted for age only (model 1);

adjusted for age, sex, social class, SIMD quintile, BMI, alcohol consumption, smoking status, hypertension, diabetes and survey year (model 2); and adjusted for these covariates plus MH (model 2a). I tested for statistical interactions between GH and the covariates, including sex. The same Cox proportional hazard models were then repeated for MH, adjusting for GH in the final model. Global test was used to check the proportional-hazards assumption of the survival models (StataCorp 2011). All statistical analyses were performed using Stata version 12.1 (StataCorp, College Station, Texas). Statistical significance was defined as $p<0.05$.

2.4 Results

Of the 21,252 survey participants, 1,627 were excluded because of prevalent disease: 559 had cancer, 629 CHD and 439 psychiatric disease. Therefore, 19,625 were eligible for inclusion. Of these, 8,858 (45.1%) were men, 6,494 (33.1%) were current smokers, 4,228 (21.5%) consumed excessive amounts of alcohol and 3,919 (20.0%) had either hypertension, diabetes or both (Table 2.1). Their mean age at recruitment was 45 years (SD 16 years), and their mean BMI was 26.7 kg/m^2 (SD 5.0 kg/m^2). Participants were followed-up for up to 17 years (median 13 years), providing a total of 237,463 person years of follow-up. Incident events included 2,077 all-cause deaths, 1,777 cancer registrations, 829 CHD hospitalisations or deaths and 287 hospitalisations for psychiatric disease.

Overall, 3,669 (18.7%) participants classified themselves as being in fair GH and 1215 (6.2%) in bad GH. There was no significant difference between men and women. Compared to those with good GH, those with bad GH were more likely to be old, socioeconomically deprived, obese, smoke and have hypertension or diabetes, but were less likely to consume excessive amounts of alcohol (Table 2.1). Overall, 3,172 (16.2%) participants had poor MH (GHQ-12 score ≥4). Compared to those with good MH (GHQ-12 score 0), they were more likely to be women, young, socioeconomically deprived, smoke, and have diabetes or hypertension, but were not significantly different in terms of alcohol consumption and BMI (Table 2.1). Of the 1,215 participants with bad GH, 202 (16.6%) had good MH (GHQ-12 score 0), and of the 3,172 participants who had poor MH (GHQ-12 score ≥4), 1526 (48.1%) reported good GH.

Table 2.1 Baseline characteristics of study population in relation to self-reported general health and mental health (measured by GHQ-12)

	Self-reported General Health				GHQ-12 score			
	Good	**Fair**	**Bad**		**0**	**1-3**	**≥4**	
	N=14 741 N (%)	N=3669 N (%)	N=1215 N (%)	*P*	N=11 720 N (%)	N=4733 N (%)	N=3172 N (%)	*P*
Sex								
Male	6630 (45.0)	1644 (44.8)	584 (48.1)	0.104	5574 (47.6)	2087 (44.1)	1197 (37.7)	<0.001
Female	8111 (55.0)	2025 (55.2)	631 (51.9)		6146 (52.4)	2646 (55.9)	1975 (62.3)	
Age (years)								
16-29	2990 (20.3)	504 (13.7)	59 (4.9)	<0.001	2062 (17.6)	966 (20.4)	525 (16.6)	0.001
30-44	5294 (35.9)	904 (24.6)	257 (21.2)		3845 (32.8)	1506 (31.8)	1104 (34.8)	
45-59	3947 (26.8)	1131 (30.8)	458 (37.7)		3253 (27.8)	1294 (27.3)	989 (31.2)	
≥60	2510 (17.0)	1130 (30.8)	441 (36.3)		2560 (21.8)	967 (20.4)	554 (17.5)	
Body Mass Index								
Underweight	179 (1.2)	73 (2.0)	31 (2.6)	<0.001	142 (1.2)	66 (1.4)	75 (2.4)	0.152
Normal-weight	6079 (41.2)	1185 (32.3)	360 (29.6)		4437 (37.9)	1913(40.4)	1274 (40.2)	
Overweight	5738 (38.9)	1308 (35.7)	411 (33.8)		4684 (40.0)	1704 (36.0)	1069 (33.7)	
Class I obese	2071 (14.1)	738 (20.1)	238 (19.6)		1803 (15.4)	761 (16.1)	483 (15.2)	
Class II obese	493 (3.3)	256 (7.0)	108 (8.9)		461 (3.9)	208 (4.4)	188 (5.9)	
Class III obese	181 (1.2)	109 (3.0)	67 (5.5)		193 (1.7)	81 (1.7)	83 (2.6)	
SIMD								
1	2582 (17.5)	1083 (29.5)	488 (40.2)	<0.001	2157 (18.4)	1073 (22.7)	923 (29.1)	<0.001
2	2969 (20.1)	911 (24.8)	331 (27.2)		2418 (20.6)	1023 (21.6)	770 (24.3)	
3	3150 (21.4)	736 (20.1)	184 (15.1)		2516 (21.5)	1000 (21.1)	554 (17.5)	
4	3075 (20.9)	574 (15.7)	136 (11.2)		2458 (21.0)	841 (17.8)	486 (15.3)	
5	2965 (20.1)	365 (10.1)	76 (6.3)		2171 (18.5)	796 (16.8)	439 (13.8)	
Social Class								
I & II	5111 (34.7)	807 (22.0)	201 (16.5)	<0.001	3713 (31.7)	1558 (32.9)	848 (26.7)	<0.001
III NM	2223 (15.1)	466 (12.7)	129 (10.6)		1654 (14.1)	664 (14.0)	500 (15.8)	
III M	4452 (30.2)	1297 (35.4)	472 (38.9)		3826 (32.7)	1413 (29.9)	982 (31.0)	
IV/V	2955 (20.1)	1099 (30.0)	413 (34.0)		2527 (21.6)	1098 (23.2)	842 (26.5)	
Smoking status								
Never	6994 (47.5)	1195 (32.6)	244 (20.1)	<0.001	5330 (45.5)	2021 (42.7)	1082 (34.1)	<0.001
Previous	3445 (23.4)	911 (24.8)	342 (28.2)		2904 (24.8)	1140 (24.1)	654 (20.6)	
Current	4302 (29.2)	1563 (42.6)	629 (51.8)		3486 (29.7)	1572 (33.2)	1436 (45.3)	
Alcohol consumption								
Never	650 (4.4)	218 (5.9)	101 (8.3)	<0.001	581 (5.0)	233 (4.9)	155 (4.9)	0.244
Previous	401 (2.7)	248 (6.8)	152 (12.5)		380 (3.2)	198 (4.2)	223 (7.0)	
Within limits	10421 (70.7)	2436 (66.4)	770 (63.4)		8291 (70.7)	3255 (68.8)	2081 (65.6)	
Excessive	3269 (22.2)	767 (20.9)	192 (15.8)		2468 (21.1)	1047 (22.1)	713 (22.5)	
Medical comorbidity								
No	12591 (85.4)	2467 (67.3)	648 (53.3)	<0.001	9637 (82.2)	3736 (78.9)	2333 (73.6)	<0.001
Yes	2150 (14.6)	1202 (32.8)	567 (46.7)		2083 (17.8)	997 (21.1)	839 (26.5)	

GHQ-12 score							
0	9930 (67.4)	1588 (43.3)	202 (16.6)	<0.001	-	-	-
1-3	3285 (22.3)	1114 (30.4)	334 (27.5)		-	-	-
≥4	1526 (10.4)	967 (26.4)	679 (55.9)		-	-	-
Self-reported general health							
Good	-	-	-		9930 (84.7)	3285 (69.4)	1526 (48.1)	<0.001
Fair	-	-	-		1588 (13.6)	1114 (23.5)	967 (30.5)	
Bad	-	-	-		202 (1.7)	334 (7.1)	679 (21.4)	

P values were determined by χ2 test.GHQ General Health Questionnaire; N number; SIMD Scottish Index of Multiple Deprivation 1 most deprived, 1 least deprived; NM non- manual; M manual

There were positive dose relationships between baseline GH and all-cause deaths, cancer registrations, CHD events, and psychiatric hospitalisations (Figure 2.1). Compared with those with good GH, participants with bad GH were significantly more likely to experience all of the adverse outcomes when adjusted for age only (Table 2.2). Further adjustment, for all potential confounders (model 2), attenuated the associations slightly but they all remained statistically significant (Table 2.2). Studies have reported that the baseline MH may also influence the GH (Han 2002; DeSalvo et al. 2006). To explore this, the model 2 was adjusted for MH, but it did not bring any significant change (model 2a, Table 2.2). There was a significant interaction with age ($p<0.001$), but not with sex ($p=0.443$).

There were positive dose relationships between MH and all-cause death, CHD events and psychiatric hospitalisations, but not with cancer registrations (Figure 2.1). In the Cox proportional hazard model, poor MH was associated with a significantly increased risk of all-cause death and cardiovascular events (Table 2.3). After adjustment for potential confounders, the HR were attenuated but remained statistically significant. When also adjusted for GH, the associations became statistically non-significant. There was no significant association between MH and cancer registrations. MH was a significant, independent predictor of psychiatric admissions, and remained so after adjustment for GH (Table 2.3). There was no significant interaction with sex ($p=0.163$).

Table 2.2 Cox proportional hazard models of the association between self-reported general health and adverse outcomes of Scottish adults (n=19,625)

	Model 1		Model 2		Model 2a	
	HR (95% CI)	**P value**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**
All-cause death						
Good	1.00		1.00		1.00	
Fair	2.10 (1.90, 2.31)	<0.001	1.67 (1.51, 1.86)	<0.001	1.66 (1.50, 1.85)	<0.001
Bad	3.74 (3.32,4.20)	<0.001	2.50 (2.20, 2.83)	<0.001	2.48 (2.16, 2.85)	<0.001
Cancer registration						
Good	1.00		1.00		1.00	
Fair	1.13 (1.01, 1.27)	0.032	1.08 (0.96, 1.22)	0.195	1.08 (0.96, 1.22)	0.189
Bad	1.41 (1.20, 1.66)	<0.001	1.30 (1.10, 1.55)	0.003	1.32 (1.09, 1.58)	0.003
Coronary heart disease hospitalisation/death						
Good	1.00		1.00		1.00	
Fair	1.75 (1.49, 2.06)	<0.001	1.39 (1.18, 1.64)	<0.001	1.37 (1.16, 1.63)	<0.001
Bad	3.34 (2.75, 4.06)	<0.001	2.30 (1.86, 2.84)	<0.001	2.26 (1.79, 2.84)	<0.001
Psychiatric hospitalisation						
Good	1.00		1.00		1.00	
Fair	2.37 (1.82, 3.09)	<0.001	1.88 (1.43, 2.47)	<0.001	1.60 (1.21, 2.13)	0.001
Bad	3.80 (2.65, 5.46)	<0.001	2.42 (1.65, 3.56)	<0.001	1.73 (1.15, 2.62)	0.009

HR, hazard ratio; CI, confidence interval

Model 1 adjusted for age; Model 2 adjusted for age, sex, social class, SIMD quintile, body mass index, alcohol consumption, smoking status, hypertension, diabetes and survey year; Model 2a adjusted for same covariates as Model 2 plus self-rated mental health (GHQ-12 score)

Table 2.3 Cox proportional hazard models of the association between self-reported mental health (GHQ-12 score) and adverse outcomes of Scottish adults (n=19,625)

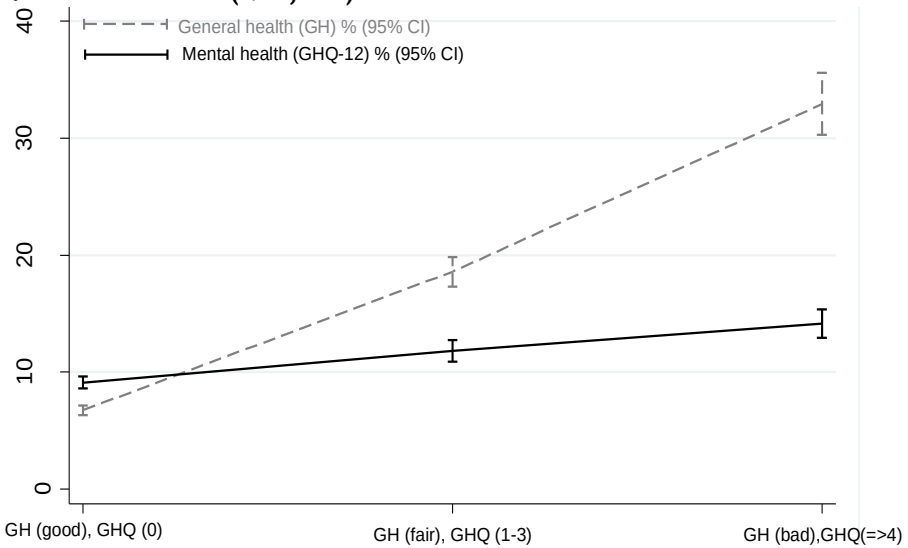
	Model 1		Model 2		Model 2a	
	HR (95% CI)	**P value**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**
All-cause death						
0	1.00		1.00		1.00	
1-3	1.33 (1.20, 1.47)	<0.001	1.25 (1.13, 1.39)	<0.001	1.06 (0.95, 1.18)	0.273
≥4	1.75 (1.57, 1.96)	<0.001	1.38 (1.23, 1.55)	<0.001	1.00 (0.88, 1.13)	0.968
Cancer registration						
0	1.00		1.00		1.00	
1-3	1.04 (0.93, 1.16)	0.515	1.04 (0.93, 1.16)	0.509	1.01 (0.90, 1.13)	0.883
≥4	1.09 (0.95, 1.24)	0.210	1.05 (0.92, 1.20)	0.468	0.97 (0.84, 1.13)	0.724
Coronary heart disease hospitalisation/death						
0	1.00		1.00		1.00	
1-3	1.20 (1.02, 1.42)	0.027	1.18 (1.00, 1.39)	0.055	1.05 (0.89, 1.24)	0.571
≥4	1.57 (1.32, 1.88)	<0.001	1.36 (1.13, 1.63)	0.001	1.04 (0.85, 1.27)	0.732
Psychiatric hospitalisation						
0	1.00		1.00		1.00	
1-3	1.88 (1.42, 2.49)	<0.001	1.76 (1.33, 2.33)	<0.001	1.61 (1.21, 2.14)	0.001
≥4	3.02 (2.28, 4.00)	<0.001	2.41 (1.81, 3.21)	<0.001	2.02 (1.48, 2.75)	<0.001

HR, hazard ratio; CI, confidence interval

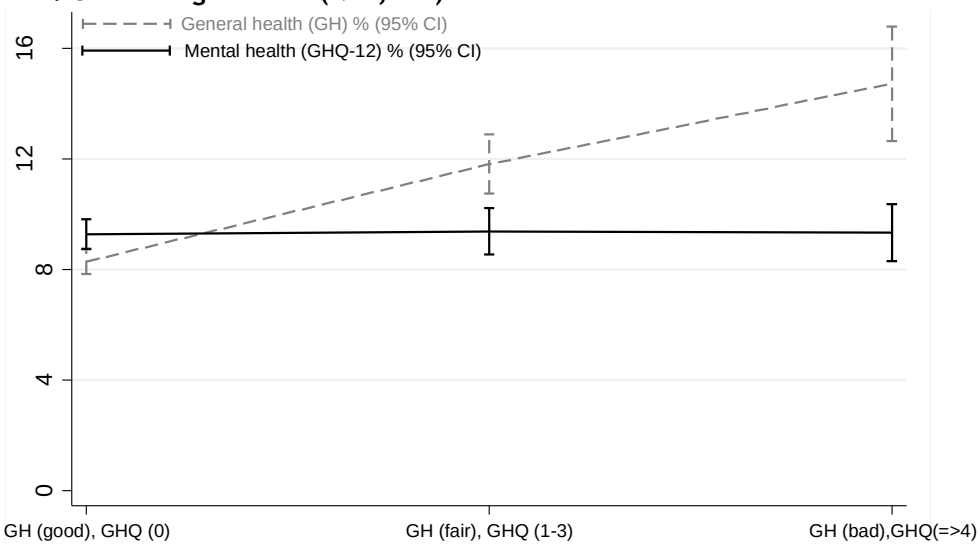
Model 1 adjusted for age; Model 2 adjusted for age, sex, social class, SIMD quintile, body mass index, alcohol consumption, smoking status, hypertension, diabetes and survey year; Model 2a adjusted for same covariates as Model 2 plus self-rated general health

Figure 2.1 Frequency (%) of adverse outcomes by self-reported general health (GH) and mental Health [GHQ-12 score].

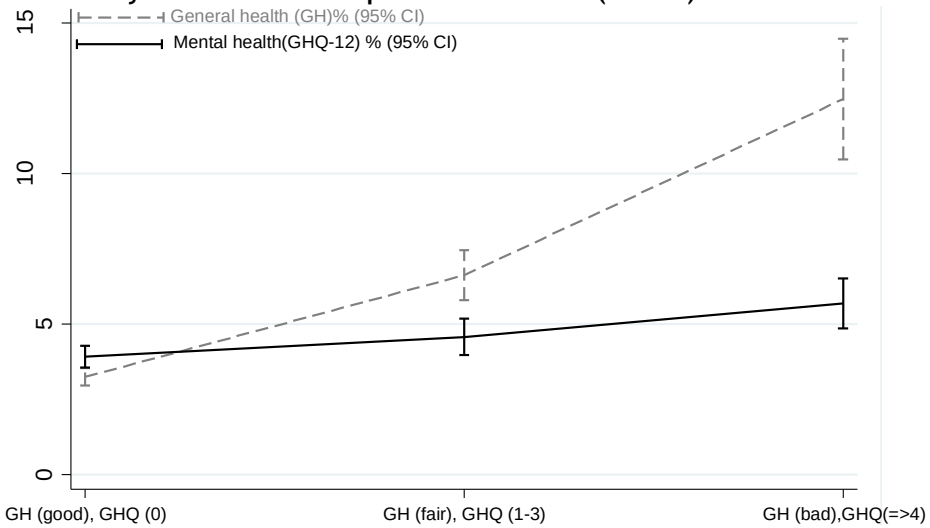
a. All-cause death (N=2,077)



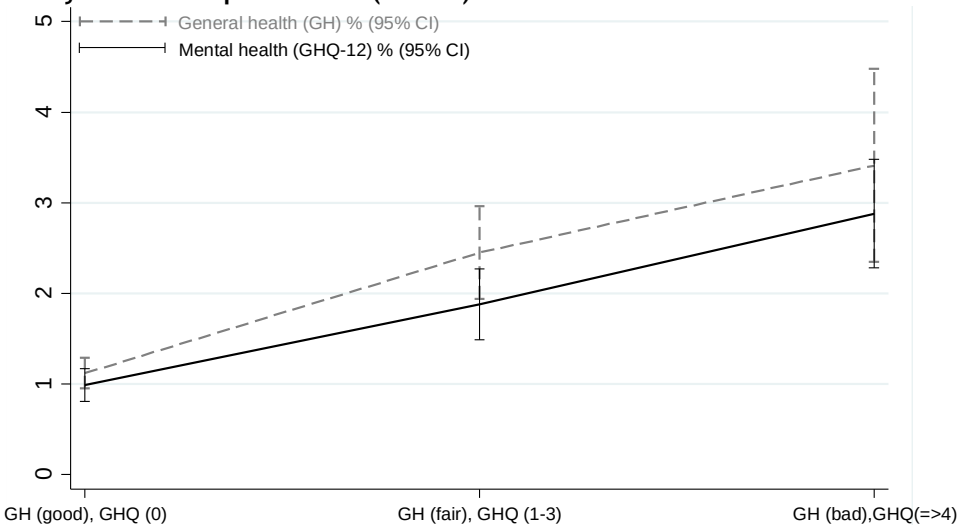
b. Cancer registration (N=1,777)



c. Coronary heart disease hospitalisation/death (N=829)



d. Psychiatric hospitalisation (N=287)



2.5 Discussion

GH was a significant predictor of incident cancer, psychiatric hospitalisations and CHD events as well as all-cause mortality. The associations were independent of potential confounders and MH, and there was evidence of a dose relationship. In contrast, MH was not associated with cancer and the association with CHD and all-cause death was lost when adjusted for GH. However, it was a significant independent predictor of psychiatric hospitalisations. There were no statistically significant differences in the associations between men and women.

The United Kingdom "Annual Population Survey 2011/12" revealed that GH was the most important determinant of personal well-being; followed by employment and relationship status (Oguz et al. 2013). Those with poor GH were, on average, less satisfied, more unhappy and more likely to be depressed.

Poor GH has been widely studied as a predictor of all-cause mortality. The latest meta-analysis collated data from 14 studies published up to 2003, and reported a pooled RR of 1.92 (95% CI 1.64, 2.25) (DeSalvo et al. 2006). Five of the 14 studies adjusted for baseline depression, reducing the pooled RR to 1.87 (95% CI 1.31, 2.67). None of the studies used the GHQ to measure MH. This study corroborates the previous studies in demonstrating an association between poor GH and all-cause mortality (adjusted HR 2.50, 95% CI 2.20, 2.83, $p<0.001$) but adjustment for MH made very little difference to the magnitude of the association; the HR changing from 2.50 to 2.48. Most of the studies included in the meta-analysis were conducted in the USA. Only one of the studies was conducted in the United Kingdom; it did not adjust for mental health and included only participants aged 65 years and above (Bath PA 2003). Overall, the number of participants ranged from 630 to 6,523, with a total of 31,350 participants. The maximum number of deaths in any study was 1,919, with a total of 8,437 deaths. Among the studies that adjusted for depression, the maximum number of participants in any study was 3,971 and the maximum number of deaths was 854. This study of almost 20,000 adults followed-up for up to 17 years provided information on more than 2,000 deaths.

In contrast to all-cause mortality, GH has not been extensively studied as a predictor of other health outcomes. In a cohort study of 4,770 US adults aged

51-61 years, Latham and Peek demonstrated associations between GH and a number of self-reported incident conditions including arthritis, diabetes, lung disease, stroke (Latham & Peek 2013). Compared with participants who had poor GH, those with excellent GH were significantly less likely to report subsequent CHD (adjusted HR 0.80). In contrast, GH was not associated with cancer. Van der Linde and colleagues conducted a prospective cohort study of 20,041 residents of Norfolk, England, aged 39-74 years. Over an average follow-up period of 11 years (range 0-14 years), they recorded 2,176 CVD events, and they reported a HR of 3.3 (95% CI 2.4, 4.4) for the association between poor GH and CVD (van der Linde et al. 2013). In my study, poor GH was associated with both CHD and cancer but the association with CHD (HR 2.30, 95% CI 1.86, 2.84, p<0.001) was stronger than with cancer (HR 1.30, 95% CI 1.10, 1.55, p=0.003) and only the former demonstrated a dose-relationship. Very few studies have explored the relationship between GH and subsequent depression. Kosloski et al. showed a small but significant effect of GH on depressive symptoms over time in an autoregressive, cross-lagged panel study of 7,475 US participants (Kosloski et al. 2005). Badawi G et al analyzed repeated cross-sectional surveys of 1,265 Canadian adults with type II diabetes (Badawi et al. 2013). When re-assessed after three years, those with poor GH at baseline had a two-fold increased risk of self-reported depression even after controlling for potential confounders (adjusted odds ratio [OR] 2.05, 95% CI 1.20, 3.48). In a prospective cohort study of 1,468 Canadians aged 65 years or older, St John and Montgomery reported that GH was associated with future dementia among participants who were cognitively intact at baseline (St John & Montgomery 2013). Similar findings were reported in a French prospective cohort study (Montlahuc et al. 2011). Both studies reported HR of around 2.5.

Some studies have reported that GH was a stronger predictor of health outcomes in men than women (Hirve et al. 2012), whilst others have reported the reverse (Nery Guimaraes et al. 2012), and some have reported no difference (Bath PA 2003; van der Linde et al. 2013). Most studies have not reported interaction tests and many were underpowered to do so. I formally tested for an interaction with sex but no significant difference was found.

Fewer studies have been conducted on MH than GH. A recent large study using multiple English Health Surveys reported a HR for all-cause death of 1.37 (95% CI 1.23, 1.51) for GHQ scores of 4-6, and a HR of 1.67 (95% CI 1.41, 2.00) for GHQ scores ≥7 (Russ et al. 2012). In contrast, other studies have reported no significant associations in either men or women (Kivimaki et al. 2003). This study demonstrated a dose relationship between MH and all-cause mortality with significantly higher risk even among participants with GHQ-12 scores between 1 and 3 (adjusted HR 1.25, 95% CI 1.13, 1.39, p<0.001). Nicholson et al followed-up 5,449 men aged 35-55 years who were living in London, over a mean of 6.8 years. They reported a significant association between poor MH and CHD events, which was highest among those with recent onset distress (HR 1.77, 95% CI 1.13, 2.78) (Nicholson et al. 2006). Another study reported an OR of 1.83 (95% CI 1.5, 2.3) for the association between psychological distress at baseline and self-reported CHD among 2,383 middle-aged participants working in London (Stansfeld et al. 2002). My finding of no association between MH and cancer is consistent with previous studies. A prospective cohort study of Scottish adults with 30 years follow-up reported a significant association between moderate stress (GHQ 4-5) and both breast cancer (HR 2.16, 95% CI 1.00, 4.71) and prostate cancer (HR 1.65, 95% CI 1.20, 2.27), but no significant association with more severe stress (≥6) (Russ et al. 2012). A Scottish retrospective cohort study of 15,453 participants who were followed up for an average of 7 years, demonstrated a significant association with cancer mortality among the 295 participants who had a history of cancer at baseline (HR 1.97, 95% CI 1.05, 3.71), but not in cancer-free individuals (Hamer et al. 2009).

The study included in this Chapter did not explore the underlying mechanism by which subjective well-being may impact on health and life-expectancy. It has been suggested that subjective well-being provides additional information by incorporating both subjective assumptions and objectively measured health (Idler et al. 2000). Previous studies have suggested that personality traits, such as optimism, may inflate self-assessment of health (Benyamini et al. 2000). Others have related good GH with better immune responses (Lekander et al. 2004). GH may detect very early symptoms of underlying disease at subclinical stage. Finally, subjective well-being may reflect an individual's attitude towards improving health, and thus adopting preventive measures (Idler & Benyamini

1997). MH was not associated with risk of all-cause mortality when adjusted for GH. This possibly reflects the fact that GH is a measure of perceived overall health and includes perceived MH, whereas MH is only one component.

2.6 Strengths and limitations

Use of the SHeS provided me with a large, representative sample of Scottish adults recruited from the general population, and enabled me to adjust for a series of potential confounders and test for interactions. Many previous studies have used GH and MH as binary variables. By using ordinal data I was able to examine whether there were evidence of a dose relationship. The GHQ-12 is validated measure of MH and has been widely used in epidemiological studies. The WHO recommended that GH should be a standard component of health surveys and is, thus, worldwide, the most frequently used measure of health in surveys (World Health Organization 1996). Use of a cohort, rather than cross-sectional, design enabled me to demonstrate a temporal relationship between baseline GH and MH and incident disease, and avoid reverse causation. The Scottish Morbidity Record system has Scotland wide coverage and is subjected to regular quality assurance checks. Linkage to SMR records and death certificates enabled me to study both all-cause mortality and disease-specific outcomes in the same cohort.

2.7 Implications of this research

GH is a strong predictor of all-cause death, cancer, CHD events and psychiatric hospitalisations. The association is independent of potential confounders and MH. Further research is required to understand the underlying mechanism. Individuals with poor GH are a higher risk group who may merit closer surveillance and earlier intervention. Subjective well-being is as important as objective measures of health risk, and should be considered in identifying how best to target public health and health care interventions.

This chapter suggests that SRH is a strong independent predictor of fatal and non fatal adverse outcomes in the Scottish adult population but SRH is only one aspect of subjective well-being. Therefore, in the next chapter (Chapter 3), I will explore whether the same associations exist for another measure of subjective well-being: HRQoL.

3 Chapter 3: Health-related quality of life and adverse outcomes

Published in;

Ul-Haq Z, Mackay DF, Pell JP (2014). Association between physical and mental health-related quality of life and adverse outcomes; a retrospective cohort study of 5,272 Scottish adults. *BMC Public Health* (in press).

3.1 Chapter summary

HRQoL is associated with adverse outcomes in disease-specific populations. This study examines whether it is also an independent predictor of incident cancer, CHD and mortality in the general population.

The records of adult participants in the SHeS 2003 were linked with hospital admissions, cancer registrations and death certificates. Cox proportional hazard models were used to explore the associations between quintiles of physical and mental component summary scores (PCS and MCS respectively) of the SF-12 and adverse outcomes. Higher quintiles of both PCS and MCS indicate better health status.

Among the 5,272 study participants, the mean PCS score was 49 (standard deviation (SD) 10.3). Participants were followed-up for a mean of 7.6 years. On survival analysis the lowest quintile of PCS was a strong predictor of all-cause death HR 2.81, 95% CI 1.76, 4.49), incident cancer (HR 1.63, 95% CI 1.10, 2.42), and CHD events (HR 1.99, 95% CI 1.00, 3.96), compared to the highest quintile. This association was independent of potential confounders. The mean MCS score was 52 (SD 8.8). MCS quintile was not associated with incident cancer, CHD and all-cause death.

Physical HRQoL is a significant predictor of a range of adverse outcomes, even after adjustment for potential confounders. This study highlights the importance of subjective well-being in the general population.

3.2 Introduction

Studies have shown that overall HRQoL is associated with adverse outcomes, such as hospitalisation and death, in several disease-specific populations including: patients receiving haemodialysis (Kalantar-Zadeh et al. 2001) and patients with diabetes (Li CL et al. 2013), pulmonary diseases (Nishiyama et al. 2012), CHD (Zuluaga et al. 2010), stroke (Grool et al. 2012), cancer (Sehlen et al. 2012), arthritis (Michaud et al. 2012), and liver disease (Kanwal et al. 2009). However, results have conflicted in relation to the associations with the physical and mental components of HRQoL. Some studies have shown that physical HRQoL is significantly associated with adverse outcomes (Li Chang et al. 2013), but others have reported no association (Nishiyama et al. 2012). Similar contradictory findings have been reported for mental HRQoL (Hayashino et al. 2009; Osthus et al. 2012). There is a general paucity of studies that have examined the associations between overall, physical or mental HRQoL and adverse outcomes in the general population (Haring et al. 2011).

SF-12 is a validated and widely used tool for measuring generic HRQoL (Ware Jr. et al. 1996). It is a shorter version of SF-36, takes only one-third of the time to complete and is, therefore, used in many large surveys (Burstrom & Fredlund 2001). The 12 questions of SF-12 are combined to form summary scores for physical and mental HRQoL, called PCS and MCS. These summary scores are closely correlated with those produced using the SF-36 (Wee et al. 2008).

In Chapter 2, I conducted a retrospective cohort study of 20,000 Scottish adults with 17 years follow-up. I found that poor SRH at baseline was an independent predictor of all-cause death, incident cancer, psychiatric hospitalisations and CHD events (Chapter 2, Ul-Haq et al. 2014a). In contrast, there was no independent association between poor mental health (measured by GHQ-12) and these adverse outcomes.

In this study I investigate whether physical and mental HRQoL (derived from the SF-12) were independent predictors of incident cancer, CHD events, and all-cause deaths, and whether the associations varied by sex among a large representative sample from the Scotland adult population, after adjusting for

potential confounding factors including: demographic and life-style factors, socio-economic status and medical comorbidity.

3.3 Material and methods

3.3.1 Data sources

I used an extract of data from the SHeS 2003. (http://www.scotland.gov.uk/Topics/Statistics/Browse/Health/scottish-health-survey). Unlike, the earlier two SHeS's, which were conducted in 1995 and 1998, the SHeS 2003 had no age limitation and it is the only SHeS which included the SF-12 questionnaire to measure the physical and mental HRQoL. The details of the SHeS have been described previously in Chapter 2. In brief, participants were interviewed face to face by trained staff who collected information on demographics (including age and sex), socio-economic status (including area of residence and level of education) and lifestyle behaviours (including smoking habits and alcohol consumption) as well as completing the SF-12 questionnaire. The data collectors also measured the weight and height of study participants. In a follow-up visit, a qualified nurse measured blood pressure and collected saliva and urine samples. The overall response rate was around 60%. Furthermore, over 90% of SHeS participants consented to passive follow-up via record linkage to the Scotland-wide routine administrative databases held by the Information Services Division including: admissions to acute hospital (Scottish Morbidity Record SMR01), cancer registrations (Scottish Morbidity Record SMR06) and death certificates (Gray et al. 2010). The SMR data undergo regular quality assurance checks and have been shown to be 99% complete and 94% accurate (NHS Scotland 2010). The linkage provided follow-up data up to a censor date of 31 December 2011.

3.3.2 Inclusion criteria and definitions

SF-12 questionnaires were completed by SHeS participants aged ≥20 years. Therefore analysis was restricted to this age-group. Participants with a history of cancer or CHD at the time of the baseline interview were excluded from the study. Study participants were categorized into 20-44, 45-64 and ≥65 years of age. BMI was categorized, using WHO standardized cut-off points, into underweight (<18.5 kg/m^2), normal weight (18.5-24.9 kg/m^2), overweight (25.0-

29.9 kg/m^2), and obese (≥30 kg/m^2). Obese was further categorized into class I (30.0-34.9 kg/m^2), class II (35.0-39.9 kg/m^2) and class III obese (≥40 kg/m^2). The level of education was treated as four categories from level 1 (less than O level grade C) to level 4 (degree level or above). SIMD was used as the measure of socio-economic status. SIMD is a validated and widely used area-based measure of multiple deprivations and is derived from participants' postcodes of residence. SIMD is calculated using 31 indicators across 6 domains: income, employment, housing, health, education, skills and training, and area based access to the services (http://www.scotland.gov.uk/Topics/Statistics/SIMD). Self-reported smoking status was categorized into never, previous or current, and alcohol consumption was categorized as never, previous, within limits and excessive. Hypertension was defined as ≥140/90 mmHg or use of anti-hypertensive medication. Presence of diabetes was based on self-report of a physician diagnosis. PCS and MCS were calculated from the 12 responses to the SF-12 questionnaire. Higher scores indicate better physical and mental health status respectively. PCS and MCS score quintiles were used in the analyses. Cancer was defined using ICD-10 codes C00-C97. CHD event was defined as death or hospitalisation due to CHD. The latter was defined as first hospitalisation using ICD-10 code I20-I25 in the primary position of diagnosis.

3.3.3 Statistical analyses

The characteristics of participants by quintile of PCS and MCS were analysed using chi-square tests or chi-square tests for trend for binary and ordinal data respectively. Separate Cox proportional hazard models were used to examine the associations between PCS and MCS quintile and three outcomes: all-cause deaths, cancer registrations, and CHD events (hospitalisations or death). The highest quintile (best HRQoL) was used as the referent category. The models were first adjusted for age only (model 1), followed by further adjustment for sex, SIMD, education level, smoking status, BMI, alcohol consumption and medical comorbidity (hypertension and diabetes) (model 2). Global test was used to check the proportional-hazards assumption of the survival models (StataCorp 2011). I tested for statistical interactions between HRQoL summary scores and sex. All statistical analyses were performed using Stata version 12.1 (StataCorp, College Station, Texas). Statistical significance was defined as $p<0.05$.

3.4 Results

Of the 5,272 participants, 2,889 (54.8%) were women, 1,392 (26.4%) were current smokers, 1,096 (20.8%) consumed excessive amounts of alcohol and 1,316 (25%) had either hypertension, diabetes or both. Their mean age at recruitment was 50 years (SD 16 years). The mean BMI was 27.5 kg/m^2 (SD 5.1 kg/m^2); 59 (1.1%) were underweight, 1,689 (32%) normal-weight, 2,152 (40.8%) overweight, and 1,372 (26%) obese. Of the obese, 940 (17.8%) were class I, 297 (5.6%) were class II, and 135 (2.6%) were class III obese (Table 3.1). Participants were followed-up for a maximum of 8 years (median 7.8 years), providing a total of 40,067.2 person years of follow-up. Incident events included 391 (7.4%) all-cause deaths, 368 (7.0%) cancer registrations, and 134 (2.5%) CHD hospitalisations or deaths. I found no evidence that my specification violates the proportional-hazards assumption (p=0.246).

Overall, the mean PCS score was 49 (SD 10.3). The lowest quintile equated to < 42 and the highest to >56. Compared to the participants who were in the highest quintile of PCS (better physical HRQoL), those in the lowest quintile were older and more likely to be obese, male, socio-economically deprived, smoke and have hypertension or diabetes, but were less likely to consume excessive amounts of alcohol or have a higher degree (Table 3.1). Overall, the mean MCS score was 52 (SD 8.8). The lowest quintile equated to <47 and the highest quintile to >58. Compared to the participants who were in the highest quintile of MCS (better mental HRQoL), those in the lowest quintile were younger and more likely to be morbidly obese, female, well educated, smoke and consume excessive amounts of alcohol, but were less likely to have hypertension or diabetes or be socio-economically deprived (Table 3.1).

Table 3.1 Characteristics of the participants by physical and mental component summary score quintiles of the SF-12

	Physical component quintile (score)						Mental component quintile (score)					
	1 (<42)	**2 (42 - <51)**	**3 (51 - <55)**	**4 (55 - <56)**	**5 (≥56)**		**1 (<47)**	**2 (47 - <53)**	**3 (53 - <56)**	**4 (56 - <58)**	**5 (≥58)**	
	N=1,055 N (%)	N=1,054 N (%)	N=1,057 N (%)	N=1,068 N (%)	N=1,038 N (%)	P value	N=1,055 N (%)	N=1,054 N (%)	N=1,057 N (%)	N=1,068 N (%)	N=1,038 N (%)	P value
Body Mass Index												
Underweight	24 (2.3)	4 (0.38)	9 (0.85)	11 (1.0)	11 (1.1)	<0.001	21 (2.0)	4 (0.4)	15 (1.4)	11 (1.0)	8 (0.8)	0.045
Normal-weight	251 (23.8)	287 (27.2)	330 (31.2)	358 (33.5)	463 (44.6)		338 (31.7)	365 (34.0)	379 (36.0)	358 (32.6)	249 (25.4)	
Overweight	369 (35.0)	416 (39.5)	445 (42.1)	496 (46.4)	426 (41.0)		391 (36.7)	435 (40.5)	441 (41.9)	484 (44.0)	401 (40.9)	
Obese	411 (39.0)	347 (32.9)	273 (25.8)	203 (19.0)	138 (13.3)		315 (29.6)	271 (25.2)	217 (20.6)	247 (22.5)	322 (32.9)	
Class I	261 (24.7)	222 (21.1)	202 (19.1)	148 (13.9)	107 (10.3)		184 (17.3)	190 (17.7)	162 (15.4)	171 (15.6)	233 (23.8)	
Class II	95 (9.0)	95 (9.0)	48 (4.5)	34 (3.2)	25 (2.4)		81 (7.6)	54 (5.0)	39 (3.7)	56 (5.1)	67 (6.8)	
Class III	55 (5.2)	30 (2.9)	23 (2.2)	21 (2.0)	6 (0.6)		50 (4.7)	27 (2.5)	16 (1.5)	20 (1.8)	22 (2.2)	
Sex												
Men	463 (43.9)	476 (45.2)	508 (48.1)	508 (47.6)	428 (41.2)	<0.001	419 (39.3)	448 (41.7)	488 (46.4)	532 (48.4)	496 (50.6)	<0.001
Women	592 (56.1)	578 (54.8)	549 (51.9)	560 (52.4)	610 (58.8)		646 (60.7)	627 (58.3)	564 (53.6)	568 (51.6)	484 (49.4)	
Age (years)												
20-44	201 (19.1)	404 (38.3)	507 (48.0)	527 (49.3)	573 (55.2)	<0.001	473 (44.4)	508 (47.3)	518 (49.2)	484 (44.0)	229 (23.4)	<0.001
45-64	419 (39.7)	400 (38.0)	395 (37.4)	403 (37.7)	389 (37.5)		409 (38.4)	422 (39.3)	386 (36.7)	416 (37.8)	373 (38.1)	
≥65	435 (41.2)	250 (23.7)	155 (14.7)	138 (12.9)	76 (7.3)		183 (17.2)	145 (13.5)	148 (14.1)	200 (18.2)	378 (38.6)	
SIMD												
1 (most deprived)	267 (25.3)	197 (18.7)	153 (14.5)	157 (14.5)	105 (10.1)	<0.001	246 (23.1)	182 (16.9)	154 (14.6)	145 (13.2)	152 (15.5)	<0.001
2	247 (23.4)	197 (18.7)	204 (19.3)	179 (16.8)	168 (16.8)		233 (21.9)	187 (17.4)	182 (17.3)	196 (17.8)	197 (20.1)	
3	238 (22.6)	254 (24.1)	257 (24.3)	220 (20.6)	253 (24.4)		253 (23.8)	235 (21.7)	234 (22.2)	253 (23.0)	247 (25.2)	
4	189 (17.9)	209 (19.8)	230 (21.8)	248 (23.2)	252 (24.3)		198 (18.6)	240 (22.3)	234 (22.2)	223 (20.3)	233 (23.8)	

5 (least deprived)	114 (10.8)	197 (18.7)	213 (20.2)	264 (24.7)	260 (25.1)		135 (12.7)	231 (21.5)	248 (23.6)	283 (25.7)	151 (15.4)	
Education[a]												
Level 1	139 (13.2)	168 (15.9)	170 (16.1)	187 (17.5)	169 (16.3)	<0.001	170 (15.7)	185 (17.2)	175 (16.6)	166 (15.1)	137 (14.0)	0.015
Level 2	143 (13.6)	163 (15.5)	193 (18.3)	198 (18.5)	200 (19.3)		167 (15.7)	175 (16.3)	211 (20.1)	209 (19.0)	135 (13. 8)	
Level 2	32 (3.0)	77 (7.31)	78 (7.4)	92 (8.6)	93 (9.0)		167 (7.8)	175 (6.1)	211 (7.5)	209 (8.3)	135 (5.5)	
Level 4	151 (14.3)	210 (19.9)	290 (27.4)	314 (29.4)	400 (38.5)		224 (21.0)	321 (29.9)	326 (31.0)	289 (26.3)	205 (20.9)	
None of these	590 (55.9)	436 (41.4)	326 (30.8)	277 (25.9)	176 (17.0)		421 (39.5)	329 (30.6)	261 (24.8)	345 (31.4)	449 (45.8)	
Smoking status												
Never	361 (34.2)	441 (41.9)	447 (42.3)	526 (49.3)	541 (52.1)	<0.001	390 (36.6)	465 (43.3)	490 (46.6)	536 (48.7)	435 (44.4)	<0.001
Previous	387 (36.7)	317 (30.1)	296 (28.0)	306 (28.7)	258 (24.9)		268 (25.2)	311 (28.9)	318 (30.2)	319 (29.0)	348 (35.5)	
Current	307 (29.1)	296 (28.1)	314 (29.7)	236 (22.1)	239 (23.0)		407 (38.2)	299 (27.8)	244 (23.2)	245 (22.3)	197 (20.1)	
Alcohol consumption												
Never	92 (8.7)	53 (5.03)	36 (3.4)	39 (3.7)	32 (3.1)	<0.001	53 (5.0)	41 (3.8)	34 (3.2)	42 (3.8)	82 (8.4)	0.016
Previous	99 (9.4)	39 (3.7)	36 (3.4)	26 (2.4)	25 (2.4)		75 (7.0)	39 (3.6)	35 (3.3)	37 (3.4)	39 (4.0)	
Within limit	704 (66.7)	739 (70.1)	733 (69.4)	802 (75.1)	721 (69.5)		687 (64.5)	774 (72.0)	748 (71.1)	812 (73.8)	678 (69.2)	
Excessive	160 (15.2)	223 (21.2)	252 (23.8)	201 (18.8)	260 (25.1)		250 (23.5)	221 (20.6)	235 (22.3)	209 (19.0)	181 (18.5)	
Medical comorbidity												
No	576 (54.6)	725 (68.8)	829 (78.4)	886 (83.0)	940 (90.6)	<0.001	734 (68.9)	836 (77.8)	859 (81.7)	879 (79.9)	648 (66.1)	<0.001
Yes	479 (45.4)	329 (31.2)	228 (21.6)	182 (17.0)	98 (9.4)		331 (31.1)	239 (22.2)	193 (18.4)	221 (20.1)	332 (33.9)	

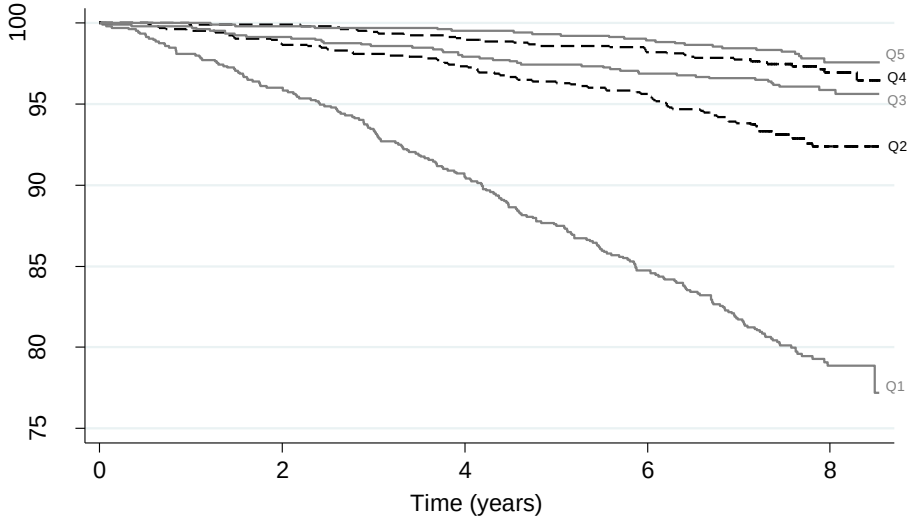
P values were determined by χ2 test; SIMD, Scottish index of multiple deprivations; [a]1 (Lower than O level Grade C), 2 (O level or equivalent), 3 (A level/other below degree), 4 (Degree level or above)

The Cox-proportional hazard models revealed that there were inverse dose-response relationships between baseline PCS and all-cause deaths, cancer registrations, and CHD events (Figure 3.1). Compared to those in the highest quintile (better physical HRQoL), participants in bottom two quintiles were significantly more likely to experience all-cause death, cancer registration and CHD events when adjusted for age only (Table 3.2). Further adjustment for sex, socioeconomic status, education level, smoking status, BMI alcohol consumption, hypertension and diabetes attenuated the associations but the participants in the lowest quintile of PCS remained at significantly higher risk of all-cause death (HR 2.81, 95% CI 1.76, 4.49), incident cancer (HR 1.63, 95% CI 1.10, 2.42), and CHD events (HR 1.99, 95% CI 1.00, 3.96), compared to the participants in the highest PCS quintile (PCS score > 56) (Table 3.2). There was no significant interaction between PCS quintile and either sex (p=0.968) relation to any of the adverse outcomes.

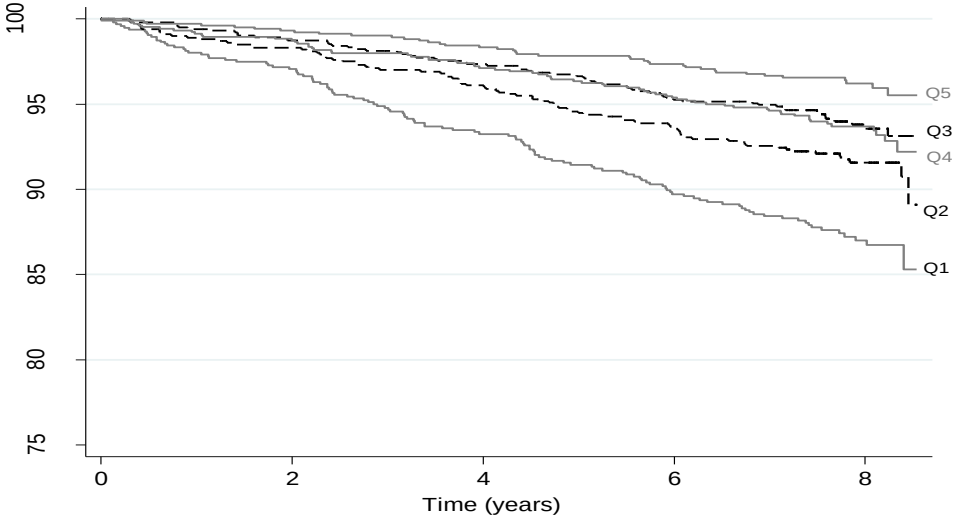
There were inverse dose response relationships between the two lowest quintiles of MCS and all-cause death, but not with CHD events or cancer registration. Being in the lowest quintile of MCS was a significant predictor of all-cause death after adjustment for age (Table 3.3). When further adjusted for sex, socioeconomic status, education level, smoking status, BMI, alcohol consumption, hypertension and diabetes the HR became statistically non significant (HR 1.25, 95% CI 0.95, 1.65). There was no significant interaction between MCS and sex (p=0.062) in relation to any of the adverse outcomes.

Figure 3.1 Kaplan-Meier plot of the association between Physical component summary quintile of the SF-12 and adverse outcome

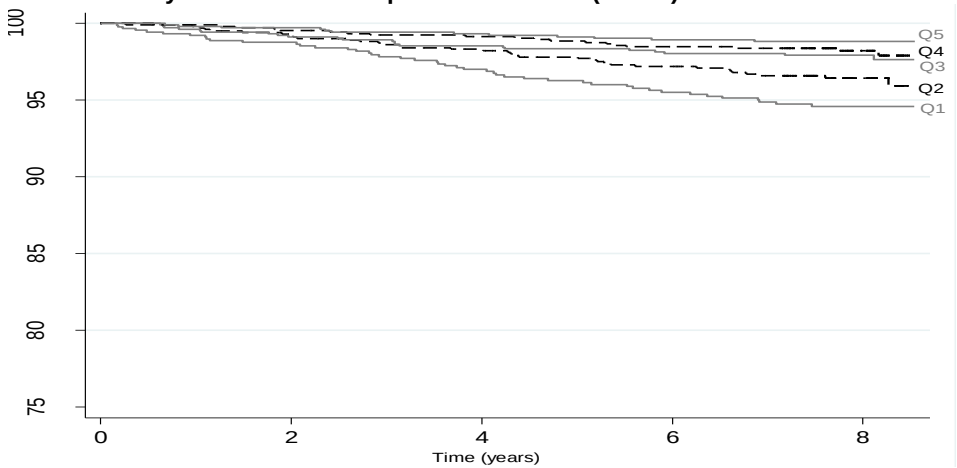
a. All-cause death (N=391)



b. Cancer registration (N=368)



c. Coronary heart disease hospitalisation/death (N=134)



Higher quintile indicate better perceived physical health; Q1 (worst), quintile 1 (PCS score <42); Q2, quintile 2 (PCS score 42 to 51); Q3, quintile 3 (PCS score 51 to 55); Q4 quintile 4 (PCS score 55 to 56); Q5 (best) quintile 5 (PCS score >56)

Table 3.2 Cox regression models of the association between quintiles of physical component summary score (PCS) of the SF-12 and adverse outcomes

	Model 1		Model 2	
	HR (95% CI)	**P value**	**HR (95% CI)**	**P value**
All-cause death				
PCS quintile				
1(worst)	4.23 (2.70, 6.63)	<0.001	2.81 (1.76, 4.49)	<0.001
2	1.97 (1.22, 3.19)	0.005	1.55 (0.95, 2.54)	0.078
3	1.45 (0.86, 2.42)	0.160	1.15 (0.68, 1.94)	0.599
4	1.06 (0.61, 1.84)	0.826	0.95 (0.55, 1.66)	0.869
5 (best)	1.00	-	1.00	-
Cancer registration				
PCS quintile				
1(worst)	1.87 (1.29, 2.71)	0.001	1.63 (1.10, 2.42)	0.015
2	1.58 (1.07, 2.31)	0.020	1.47 (0.99, 2.19)	0.056
3	1.39 (0.93, 2.07)	0.110	1.30 (0.86, 1.95)	0.212
4	1.50 (1.01, 2.23)	0.043	1.45 (0.98, 2.17)	0.066
5 (best)	1.00	-	1.00	-
Coronary heart disease hospitalisation/death				
PCS quintile				
1(worst)	2.57 (1.35, 4.93)	0.004	1.99 (1.00, 3.96)	0.049
2	2.23 (1.15, 4.30)	0.017	1.81 (0.92, 3.58)	0.087
3	1.61 (0.79, 3.25)	0.187	1.36 (0.66, 2.78)	0.402
4	1.36 (0.66, 2.80)	0.405	1.19 (0.57, 2.48)	0.640
5 (best)	1.00	-	1.00	-

Higher quintile indicate better physical health status; PCS, physical component summary quintile (score): 1 (<42), 2 (42 to 51), 3 (51 to 55), 4 (55 to 56), 5 (>56); HR, hazard ratio; CI, Confidence interval; Model 1 adjusted for age; Model 2 adjusted for age, sex, SIMD, education level, BMI, smoking status, alcohol consumption, hypertension and diabetes

Table 3.3 Cox regression models of the association between quintiles of mental component summary score (MCS) of the SF-12 and adverse outcomes

	Model 1		Model 2	
	HR (95% CI)	**P value**	**HR (95% CI)**	**P value**
All-cause death				
MCS quintile				
1(worst)	1.61 (1.24, 2.10)	<0.001	1.25 (0.95, 1.65)	0.117
2	1.04 (0.76, 1.41)	0.824	1.00 (0.73, 1.37)	0.998
3	0.83 (0.59, 1.15)	0.259	0.88 (0.63, 1.23)	0.463
4	0.66 (0.47, 0.91)	0.012	0.76 (0.55, 1.06)	0.104
5 (best)	1.00	-	1.00	-
Cancer registration				
MCS quintile				
1(worst)	0.81 (0.59, 1.10)	0.171	0.75 (0.55, 1.03)	0.079
2	0.75 (0.55, 1.03)	0.077	0.74 (0.54, 1.03)	0.071
3	0.70 (0.51, 0.97)	0.033	0.72 (0.52, 1.01)	0.054
4	0.78 (0.58, 1.06)	0.111	0.82 (0.61, 1.11)	0.206
5 (best)	1.00	-	1.00	-
Coronary heart disease hospitalisation/death				
MCS quintile				
1(worst)	0.91 (0.56, 1.48)	0.715	0.84 (0.51, 1.38)	0.499
2	0.60 (0.35, 1.05)	0.072	0.61 (0.35, 1.06)	0.082
3	0.55 (0.31, 0.97)	0.039	0.59 (0.33, 1.05)	0.073
4	0.75 (0.46, 1.22)	0.252	0.80 (0.49, 1.30)	0.363
5 (best)	1.00	-	1.00	-

Higher quintile indicate better mental health status; MCS, mental component summary quintile (score): 1 (<47), 2 (47 to 53), 3 (53 to 56), 4 (56 to 58), 5 (>58); HR, hazard ratio; CI, Confidence interval; Model 1 adjusted for age; Model 2 adjusted for age, sex, SIMD, education level, BMI, smoking status, alcohol consumption, hypertension and diabetes

3.5 Discussion

Physical HRQoL was found to be a strong predictor of incident cancer, CHD events and all-cause mortality on follow-up. The associations were independent of potential confounders, and there was evidence of inverse dose-response relationships. In contrast, poor mental HRQoL was not a significant predictor of any of the adverse outcomes. There were no statistically significant differences in the associations between men and women.

The majority of previous studies have focused on the association between HRQoL and mortality in diseases-specific populations and they have produced conflicting results. For example, in patients undergoing haemodialysis some studies have reported that both PCS and MCS were strong predictors of mortality (Kalantar-Zadeh et al. 2001). Some reported that MCS was a significant predictor of mortality, but not PCS (Osthus et al. 2012). Others reported the reverse findings with PCS being a significant predictor of mortality, but not MCS (Hayashino et al. 2009). In patients with pulmonary fibrosis, HRQoL did not predict death (Nishiyama et al. 2012). PCS was associated with higher mortality in diabetic patients, but not MCS (Li Chang et al. 2013). In a study of patients with heart failure, MCS predicted mortality, but PCS did not (Zuluaga et al. 2010). Others have reported that both MCS and PCS were associated with higher mortality in atherosclerotic patients (Grool et al. 2012). Similarly, only PCS was strongly associated with mortality in patients with rheumatoid arthritis (Michaud et al. 2012), but both PCS and MCS were in patients with liver cirrhosis (Kanwal et al. 2009). One recent study reported that HRQoL was the only psychosocial predictor of survival in cancer patients (Sehlen et al. 2012).

Very few studies have explored the association between HRQoL and adverse outcomes in the general population. In a recent German study, 4,259 participants, aged 20-79 years, completed the SF-12 at baseline and suffered 456 deaths over a mean of 9.7 years follow-up (Haring et al. 2011). The Cox-proportional hazard models revealed that the lowest quartile of PCS was an independent predictor of mortality (fully adjusted HR 1.64, 95% CI 1.19, 2.27), compared to the highest quartile. In contrast, MCS was not a significant predictor of mortality (HR 0.97, 95% CI 0.74, 1.28). Other studies conducted in general population have been few in number and have focused mainly on people

aged 60 years or more. A longitudinal study was conducted in Taiwan, in which 4,424 individuals, aged 65 years and older were followed over three years and 221 deaths recorded (Tsai et al. 2007). A 10-point decrease in both PCS and MCS scores was associated with higher mortality; RR 1.60, 95% CI 1.39, 1.83, and RR 1.16, 95% CI 1.01, 1.34, respectively. In a US study 2,166 participants, aged 65 years or older, completed SF-12 questionnaires at baseline and were passively followed-up over 28 months using data from their insurance records (Dorr et al. 2006). Participants in the lowest quartile of PCS had a higher risk of both all-cause deaths (HR 5.99, 95% CI 1.90, 18.95) and hospitalisation (HR 2.64, $p<0.001$) than those in the highest quartile. Those in the lowest quartile for MCS were also at higher risk of death (HR 2.30, 95% CI 1.64, 3.22) and hospitalisation (HR 1.40, $p<0.001$). A Spanish study followed 2,343 participants, aged 60 years and above for six years and recorded 212 deaths (Otero-Rodriguez et al. 2010). A five-point decrease in baseline PCS score was found to be a significant predictor of mortality (HR 1.28, 95% CI 1.17, 1.40) but this was not true for MCS (HR 1.05, 95% CI 0.97, 1.13). My model 2 results are consistent with these previous studies.

In Chapter 2, I demonstrated that after full adjustment, poor baseline SRH was an independent predictor of all-cause death (HR 2.48 95% CI 2.16, 2.85), incident cancer (HR 1.32, 95% CI 1.09, 1.58), and CHD events (HR 2.26, 95% CI 1.79, 2.84) (Chapter 2;Ul-Haq, Z 2014a). In contrast, after full adjustment, mental health (measured by GHQ-12) was not a significant predictor of these adverse outcomes. Similarly, in this study I showed independent associations between lowest quintile of baseline PCS (poor physical HRQoL) and all-cause death (HR 2.81, 95% CI 1.76, 4.49), incident cancer (HR 1.63, 95% CI 1.10, 2.42), and CHD events (HR 1.99, 95% CI 1.00, 3.96). In contrast, MCS was not associated with these adverse outcomes after adjustment for potential confounders.

Commonly, population health is measured in terms of morbidity and mortality. My results further strengthen the growing evidence that subjective well-being provides additional information and is predictive of future morbidity and mortality. It should be considered when undertaking both individual and community health assessments. It has been suggested that subjective well-being may be a stronger predictor of adverse outcomes than many objective measures of health (Idler & Benyamini 1997).

3.6 Strengths and limitations

I used data from a large representative sample of Scottish general population, and adjusted my analyses for a series of potential confounders. The "representativeness" of a health survey is generally determined by the higher number of responses which is based on the updated and correct sampling frame, study design and non-responses (Gray et al. 2013). The estimates from a representative sample which has strong external validity in association with the population of interest can be generalized in confidence to that particular population. The SHeS has rigorous methodology and maintains the overall higher response rate of 60% or above from the eligible households (http://www.scotland.gov.uk/Topics/Statistics/Browse/Health/scottish-health-survey). The age and sex proportion of the SHeS adult respondents is externally validated with the General Registrar Office for Scotland mid-year population estimates. The SHeS used weighting to take account of the underrepresentation of the large households responses and non-response biases. SHeS is also considered to be representative of the Scottish population in terms of the SIMD quintiles (Lawder et al. 2010; Gray et al. 2010). BMI and blood pressure were measured by trained individuals using standard operating procedures. The presence of diabetes was self-reported but based on physician diagnoses. The SF-12 is a very widely used measure of HRQoL in the general population (Ware Jr. et al. 1996). The Scottish Morbidity Record (SMR) has pan-Scotland coverage undergoes regular quality assurance checks (NHS Scotland 2010). Use of a cohort design enabled me to demonstrate a temporal relationship between baseline PCS and MCS and incident disease, and all-cause mortality and thereby avoid reverse causation. By treating PCS and MCS as ordinal data I was able to examine whether there were evidence of a dose relationship.

3.7 Implications of this research

Poor physical HRQoL is a strong predictor of all-cause death, cancer incidence and CHD events. The association is independent of potential confounders. This study adds to the growing evidence that subjective well-being is an important predictor of health risk, independent of comorbidity and other confounders, and should be considered when assessing the health of individuals and communities.

Chapters 2 and 3 have demonstrated the importance of subjective well-being. Three measures of subjective well-being were studied and all were associated with adverse fatal and non-fatal outcomes. Adiposity is preventable and higher in prevalence. Therefore, its relationship with subjective well-being is of immense public health importance. Previous studies have been limited in number and scope and suggest a complex relationship between adiposity and subjective well-being. In the subsequent Chapters (4 to 9, inclusive), I will investigate the relationship between adiposity and subjective well-being using various measures of both. In chapter 4, I will start by examining the relationship between adiposity and HRQoL among adults.

4 Chapter 4: Adiposity and health-related quality of life among adults

Published in;

Ul-Haq Z, Mackay DF, Fenwick E, Pell JP (2013) Meta-analysis of the association between body mass index and health-related quality of life among adults, assessed by the SF-36. *Obesity* **21**(3):E322-7.

4.1 Chapter summary

Obesity is associated with impaired overall HRQoL but individual studies suggest the relationship may differ between mental and physical quality of life. A systematic review was conducted using Medline, Embase, PsycINFO and ISI Web of Knowledge, and random effects meta-analyses performed.

Studies were included in the meta-analysis if they were conducted on adults (defined as age >16 years), reported physical and/or mental component scores using SF-36. Heterogeneity was assessed using I^2 statistics and publication and small study biases using funnel plots. Eight eligible studies, conducted on a total of 43,086 study participants, provided 42 estimates of effect size. Adults with higher than normal BMI had significantly reduced physical HRQoL with a clear dose-response relationship across all categories. Among class III obese adults, the score was reduced by 9.72 points (95% CI 7.24, 12.20, p<0.001). Mental HRQoL was also significantly reduced among class III obese (-1.75, 95% CI -3.33, -0.16, p=0.031), but was not significantly different among classes I and II obese individuals, and was significantly increased among overweight adults (0.42, 95% CI 0.17, 0.67, p=0.001), compared to normal weight individuals. Heterogeneity was high in some categories, but there was no significant publication or small study bias.

Different patterns were observed for physical and mental HRQoL, but both were impaired in obese individuals. This meta-analysis provides further evidence on the relationship between adiposity and both aspects of HRQoL.

4.2 Introduction

Since 1980, obesity has more than doubled worldwide and, in 2008, 1.5 billion adults aged ≥20 years were overweight (World Health Organization 2011). The higher prevalence of overweight and obese adults in most parts of the world is of public health concern (Gulliford et al. 1992; James et al. 2001). It is widely accepted that obesity causes, or aggravates, a number of medical conditions, such as cardiovascular and musculoskeletal diseases (Colditz 1992; Must et al. 1999). Obesity is also associated with reduced life-expectancy (Flegal et al. 2005; Olshansky et al. 2005; Orpana et al. 2010). Previous studies suggest a complex relationship between BMI and HRQoL (Fontaine & Barofsky 2001; Friedman & Brownell 1995). Overall HRQoL of life is reduced among obese individuals, but increased among those who are overweight (Bentley et al. 2011; Lopez-Garcia et al. 2003). HRQoL is comprised of different components, such as mental and physical HRQoL. A number of studies have examined the relationship between BMI and these separate components. Some studies suggest that the relationship may be different for physical and mental HRQoL but the published results are inconsistent, especially in relation to the latter. Several studies reported significant negative associations between increased BMI and reduced mental HRQoL (Scott et al. 2008), but others found no association (De wit et al. 2009). Two systematic reviews of published studies were published in 1995 (Friedman & Brownell 1995) and 2001 (Fontaine & Barofsky 2001) but, as yet, no meta-analysis has been conducted. The systematic reviews suggested that obesity is associated with reduced physical HRQoL but were inconclusive in relation to an association with mental HRQoL. The systematic reviews were updated and a meta-analysis of the published literature was conducted to determine the separate relationships between BMI and mental and physical HRQoL.

4.3 Materials and methods

4.3.1 Systematic review

A systematic review of published studies was conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines (http://www.prisma-statement.org/), which consists of 27-items checklist, aimed to improve the reporting of systematic reviews and meta-analysis (Moher et al. 2009). I adhered to most of the PRISMA checklist but not to item number 5 which is more relevant to clinical trials, and to item number 27 which is related to the statement of funding and was irrelevant to my study. I also could not adhere to PRISMA checklist items number 16 and 23; additional analyses; as these were not feasible due to the small number of underlying studies (Appendix 1). The following search terms were applied to the Medline, Embase, PsycINFO and ISI Web of Knowledge databases: (obes* OR overweight OR BMI OR body mass index) AND (quality of life OR QoL OR HRQoL). The search was limited to studies conducted on humans and published in, or translated into, English. The last search was undertaken on 31 July 2011. The resultant manuscripts were reviewed manually, and their reference lists checked for additional relevant studies. Studies were included in the meta-analysis if they were conducted on adults (defined as age >16 years). SF-36 was the most commonly used index of quality of life. Therefore, inclusion was restricted to studies that used SF-36, and reported the overall physical component score, overall mental component score or both (Figure 4.1). Information was extracted on the study design, size and country, year of publication, representativeness, populations, age and sex of participants, as well as the mean SF-36 scores by BMI category and their SD. Overweight was defined as a BMI of 25.0-29.9 kg/m^2, obese as 30.0-39.9 kg/m^2 and class III obese as ≥40 kg/m^2. Obese was further sub-divided into class I, defined as 30.0-34.9 kg/m^2 and class II, defined as 35.0-39.9 kg/m^2.

Risk of bias assessment was conducted for each study that was included in the systematic review using a generic validated checklist “QualSyst” for the quantitative studies. The QualSyst is designed; “to inform our systematic review meet a minimum quality standard” (Kmet et al. 2004), and is widely used in previously published systematic reviews and meta-analysis (Wu et al. 2008, Wu

et al. 2009). The assessment includes 14 checklists for the quantitative studies, which is supported by the recommendations of consensus statement of meta-analysis reporting of observation studies in epidemiology (Stroup D et al. 2000) and NHS Centres for reviews and Dissemination (NHS 2001). The checklist is a generic assessment of selected studies, including the clearly defined research purpose, appropriate study design, method of participant selection, sufficient base-line information, well defined outcome, appropriate sample size, reporting of analytic methods, estimate of variance, control of potential confounders, detailed description of result, and data supported conclusion.

4.3.2 Meta-analysis

A random effects meta-analysis was conducted, of the weighted mean difference (WMD) in SF-36 scores for each BMI category referent to the normal weight category. The aim of conducting this study or any meta-analysis is to statistically combine and critically review the findings from two or more individual studies on a particular research question. Meta-analyses are very useful as they provide a precise cumulative estimate due to higher power, particularly in the current climate where clinicians, public health practitioners and general public are bombarded with new research findings. However, if not conducted properly, there is a potential danger of providing misleading pooled estimates due to the presence of publication and/or individual study biases (Deeks et al. 2008). Generally, there are two statistical techniques used in the meta-analysis: the fixed effect or random effects model.

The assumption of the fixed effect model is that there is one true effect size in all the included studies, and our pooled effect size is the estimate of this shared effect size (Borenstein et al. 2009). Therefore, the only source of error in our pooled estimate is the random error (sampling or estimation) within-studies. In the fixed effect model the weights (share) of the individual studies are assigned based on the inverse variance, which is mainly dependent on the sample size and thus the smaller studies make little contribution to the pooled estimate and are therefore effectively ignored. In effect, the pooled effect size is pulled towards the results from the larger studies. This could be more problematic in case of the relatively extreme effect size (smaller or larger) in the larger studies. If all the factors influencing the effect size are equal in the included studies and our

aim is to estimate a pooled effect size for a specific population then the fixed effect model could be used (Borenstein et al. 2009).

In random effects model, the studies must have sufficient in common to be pooled together but the true effect varies from one study to another, and the cumulative effect size is the mean estimate of these different effect sizes. Therefore, the assumption of random effects model is that the included studies represent the population which vary from each other, such that the effect size varies (Borenstein et al. 2009). For instance, the effect size might vary among studies; as was measured more reliably or due to difference in age, socio-economic status, or presence of comorbidity, and so on. Therefore, in the random effects model there are two sources of errors to be dealt with; the random error (within-studies) and the true variations from study to study (between-studies). The fixed effect model uses inverse of variance in assigning weight to individual studies but this includes only within-studies variance. Similarly, the random effects model uses inverse of variance but this includes both within and between studies variance. Thus the relative share of individual studies is more balanced in random effects model as it is not only dependent on the sample size but also every study is important as it is drawn from a unique population. As a result, unlike the fixed effect model, the larger study does not have too much influence on the pooled estimate and the smaller study is not ignored.

The term heterogeneity is defined as “the variation in true effect sizes underlying the different studies” (Higgins 2008). Higgins has argued that heterogeneity is inevitable in the meta-analysis as the underlying studies are conducted by different researchers, using diverse methods and in different places. As such, the use of random effects model may be more justified in most cases. However, the random effects models has some disadvantages, including the non-realistic assumption that the effect sizes of the individual studies are drawn from a larger distribution of effect sizes, the failure of estimating the between-study variance in the case of a very small number of studies and if the studies are conducted in a particular population then it will not be generalizable to a wider population (Kelly GA & Kelly KS 2012). In these scenarios, the fixed effect model may be the only realistic option. Furthermore, the decision of using

the random effects model should not be based on the presence of statistically significant heterogeneity or first trying the fixed effect and then moving to random effects but should be based on our objectives and how the underlying studies are conducted (Borenstein et al. 2009).

For the meta-analysis the underlying published studies had similar study designs, same research questions, and tool of measuring subjective well-being. All studies adopted standardized BMI cut-offs but were from very different population (countries, ages, general population/disease), and had different level of adjustment for potential confounders. Therefore, based on the characteristics of the underlying studies I used the random effects model in this study.
The weighted mean differences (WMD) in SF-36 score was analysed between individual BMI categories and the normal weight category. I^2 statistics were calculated to determine the degree of heterogeneity (Higgins et al. 2003). Possible publication and small study biases were assessed visually using funnel plots of the WMD against their standard errors.

The funnel plot is widely used for the diagnosis of publication bias and small study effects in the meta-analyses. It is basically a scatter plot where usually a standard error (as a measure of individual study sample size) is plotted vertically on the Y-axis in descending order, and the effect size is plotted horizontally on the x-axis i.e., precision versus magnitude of the effect size (Sterne JAC 2009). Larger studies are plotted towards the bottom of the funnel (lower y values) because they produce smaller standard errors while smaller studies are plotted towards the top of the funnel (higher y values) because they produce larger standard errors. The results of the smaller studies are more dispersed, producing 95% confidence intervals, and therefore the funnel shape.

In the absence of bias or heterogeneity, the plot resembles the shape of a symmetric funnel. The asymmetry or other shapes of the funnel plot may indicate the reporting bias (publication bias, selective outcome or analysis reporting), poor methodology of the underlying studies, heterogeneity, artefact or chance (Egger et al. 1997). The diagonal lines in the funnel plots correspond to the pseudo 95% CI around the pooled estimate. In the absence of heterogeneity, 95% of the underlying studies are expected to lie within these

diagonal lines (Sterne & Harbord 2004). In case of small study bias, asymmetry is expected due to the wide spread of the smaller studies at the bottom. If there is publication bias, there will be a gap, for example, in the right bottom side of the funnel plot and so there could be an overestimated pooled estimate (Sterne & Harbord 2004).

The visual assessment of funnel plot may not be occasionally reliable (Sterne et al. 2011), and therefore the meta-analysts usually follow it by conducting the statistical test, such as Eggers test (based on the linear regression) or Begg's rank correlation test (Deeks et al. 2008). However, it is argued that these funnel asymmetry tests are very underpowered and therefore should be used only in minority of the cases. Generally, the results of these tests are not considered valid if the number of underlying studies is less than 10 (Higgins & Green 2011). All statistical analyses were performed using Stata version 11.2 (Stata Corporation, College Station, Texas, USA).

4.4 Results

The electronic search identified 968 publications. I used four different databases and when these were combined 396 duplicates were found and excluded. An additional 32 publications were identified from the reference lists. The abstracts of the 540 articles were reviewed, 466 articles were found not to fulfil the inclusion criteria and were excluded. Seventy four were deemed relevant, and the full manuscripts were reviewed. Of these, 53 were excluded because they did not fulfil the inclusion criteria. Among the remaining 21 publications that have used the SF-36 index, only eight studies reported the physical and mental summary scores and thus were included in the meta-analyses (Bentley et al. 2009; de Petersen et al. 2009; Doll et al. 2000; Hopman et al. 2007; Larsson et al. 2002; Mond & Baune 2009; Renzaho et al. 2010; Yancy et al. 2002). The eight studies were all cross-sectional (Table 4.1). They were published between 2000 and 2011 inclusive. Four (50%) of the studies were conducted in Europe (de Petersen et al. 2009; Doll et al. 2000; Larsson et al. 2002; Mond & Baune 2009), three (38%), in North America (Bentley et al. 2011; Hopman et al. 2007; Yancy et al.2002), and one (12%) in Australia (Renzaho et al. 2010). One study was conducted on only male participants (Yancy et al. 2002); the remainder included both sexes. The number of participants ranged from 640 (De wit et al.

2009) to 9,771 (Renzaho et al. 2010), with a total of 43,086 participants. Overall 23,097 (54%) participants were either overweight or obese. The eight studies all reported results for both the physical and mental health components of SF-36, and they provided a total of 42 estimates of effect size for each of these components. Overall, the majority of included studies were of good quality and fulfilled the quality satisfying criteria (Figure 4.2). The main limitations were the failure of reporting sufficient baseline information, appropriate description of analysis and controlling for confounders.

Figure 4.1 PRISMA flowchart of the SF-36 studies

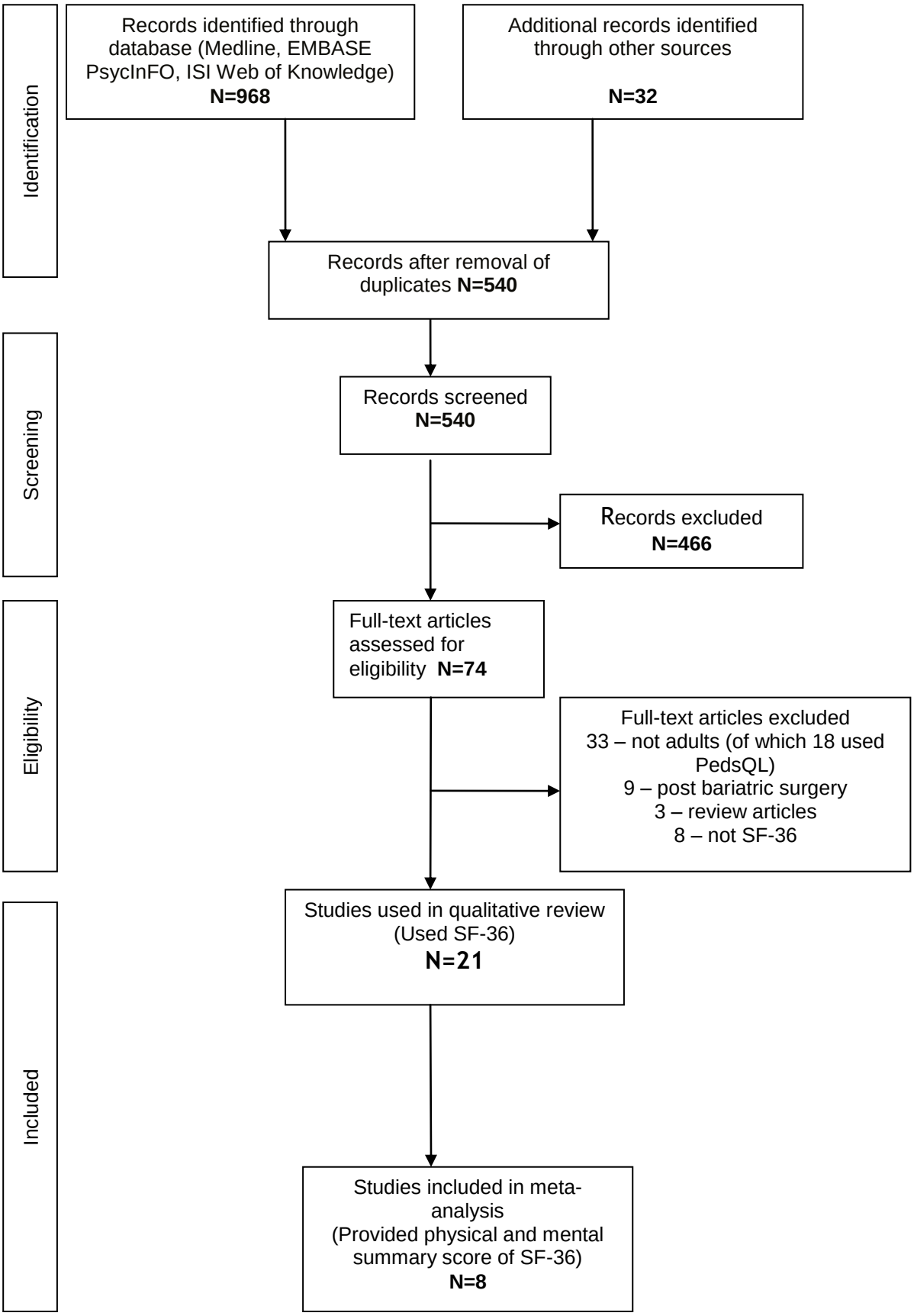


Figure 4.2 Results of quality assessment for all studies included in the review

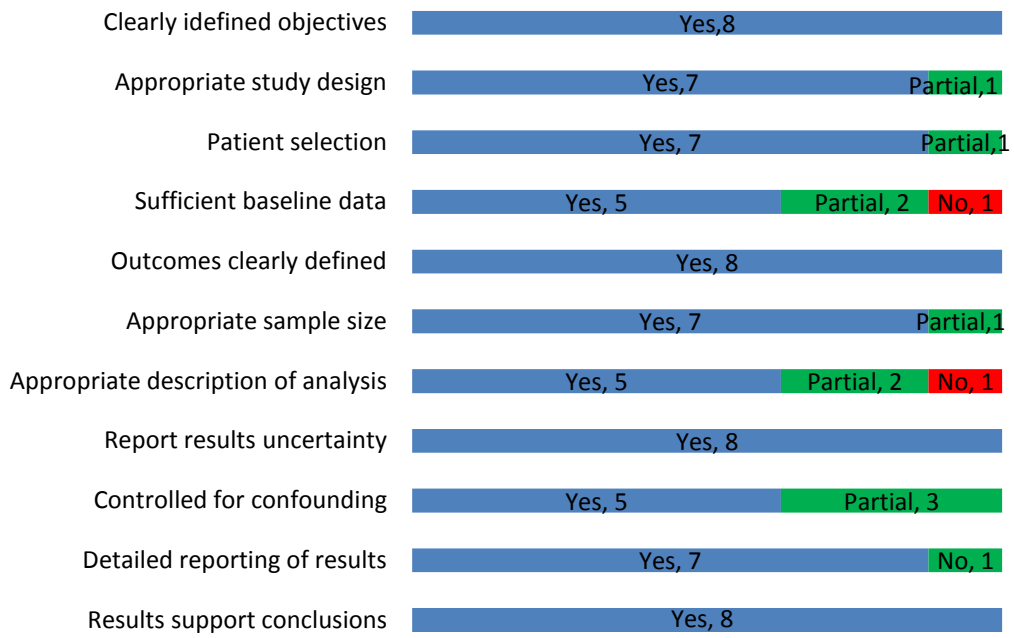


Table 4.1 Characteristics of studies examining the association between BMI and SF-36 physical and mental health scores.

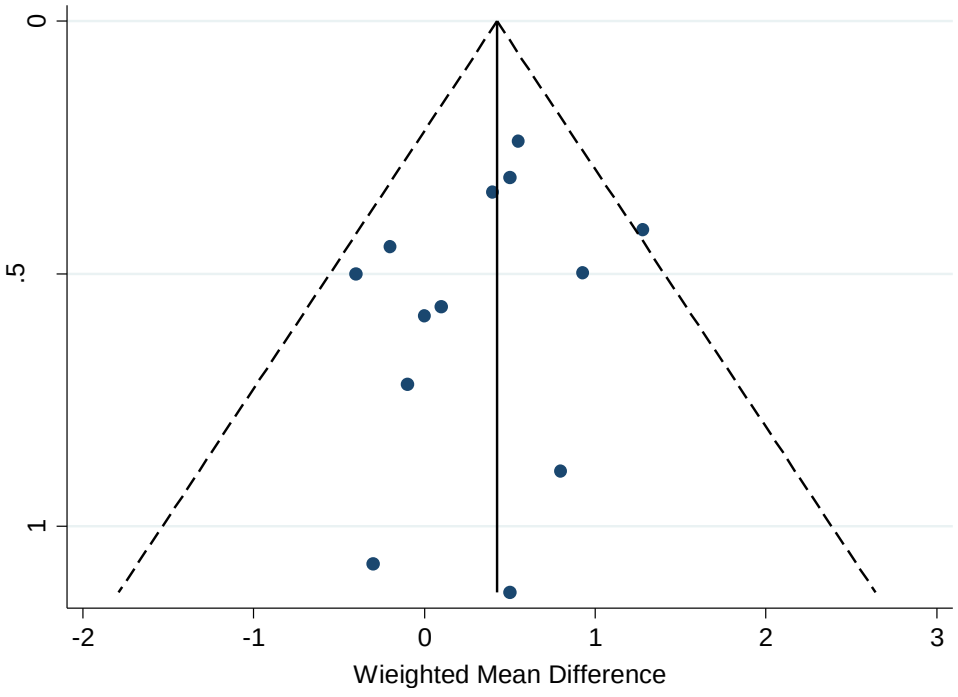
Author	Year	Country	N	Sex	Age (years)	Mean BMI	Overweight or obese (%)
Bentley	2011	USA	3,710	M&F	35-89	27.6 (28.1 M, 27.0 F)	68.9
Renzaho	2010	Australia	9,771	M&F	≥ 21	26.8 (27.1 M, 26.4 F)	65.9 M, 52.3 F
De ZM	2009	Germany	640	M&F	≥ 21	37.3	73.9
Johanthan	2009	Germany	4,181	M&F	18-65	26.3 (26.7 M, 25.9 F)	65.5 M, 48.3 F
Hopman	2007	Canada	9,094	M&F	≥25	26.8 (26.9 M, 26.6 F)	69.0 M, 60.4 F
Larsson	2002	Sweden	5,633	M&F	16-64	23.6 (24.1 M, 23.0 F)	31.6 M, 23.1 F
Yancy	2002	USA	1,168	M	48-60	-	79
Doll	2000	England	8,889	M&F	18-64	24.9	44

N number; BMI body mass index; USA United States of America; M male; F female

4.4.1 Mental health-related quality of life

Of the 42 individual estimates of the effect of BMI on mental HRQoL, only six achieved statistical significance (Figure 4.5). Of these, two suggested a higher score among overweight individuals (Doll et al. 2000; Mond et al. 2009), and one a reduced score among class III obese individuals (Hopman et al. 2007). The results for obese (class I and II) was different from the results of either class separately but all remained not significant. The Class I obese had not significantly better mental health similar to the overweight individuals. Studies have reported that people my underestimate their BMI (Krul et al. 2011; Madrigal et al. 2000), and therefore the Class I obese may consider themselves as overweight but not obese. Whereas, class II obese had not significant lower mental health than normal-weight individuals. Among obese individuals, two suggested a reduced score (Doll et al. 2000; Larsson et al. 2002) and one an increased score (Mond et al. 2009). On meta-analysis, overweight individuals had a significantly higher mental health score compared with normal weight individuals, and class III obese individuals had a significantly lower mental health score (Table 4.2). Between-study heterogeneity was low for the overweight category and moderate for the obese category. The funnel plots appeared reasonably symmetrical (Figure 4.3).

Figure 4.3 Funnel plot of the studies examining the association between adiposity and MCS score of SF-36



4.4.2 Physical health-related quality of life

Of the 42 individual estimates of the effect of BMI on physical HRQoL, 33 achieved statistical significance with all of these suggesting reduced scores among individuals with higher than normal BMI (Figure 4.6). On meta-analysis, compared with normal weight individuals, physical health scores were significantly lower in all raised BMI categories (Table 4.2). Furthermore, there was evidence of a dose-response relationship across the categories from normal weight to class III obese. Between studies heterogeneity was moderate in the overweight category and high in the other categories (Table 4.2). The funnel plots appeared reasonably symmetrical (Figure 4.4).

Figure 4.4 Funnel plot of the studies examining the association between adiposity and PCS score of SF-36

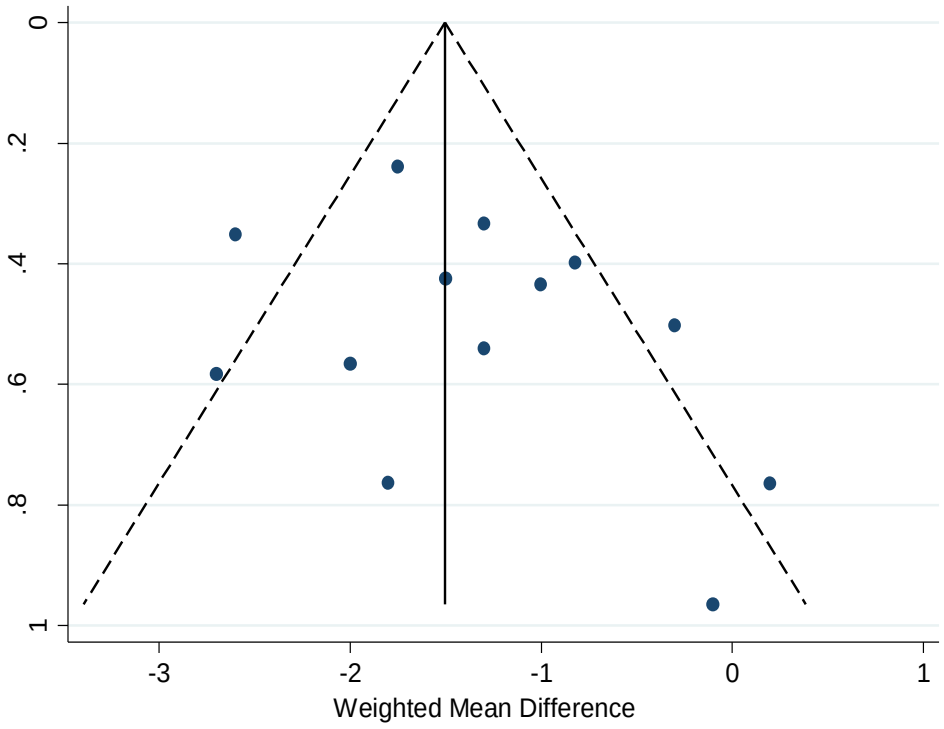


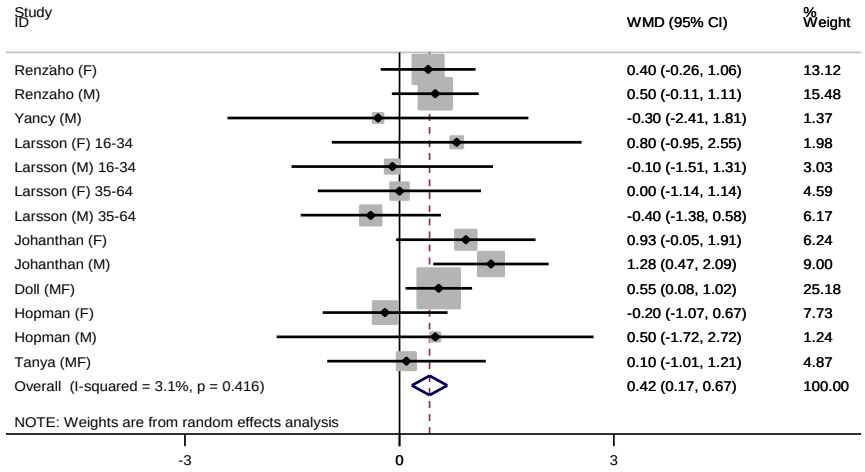
Table 4.2 Pooled estimates of the weighted mean difference in SF-36 physical and mental health scores by body mass index category referent to normal weight

	Mental health				Physical health			
	Pooled estimate		Heterogeneity		Pooled estimate		Heterogeneity	
	WMD (95% CI)	P value	I^2 (%)	P value	WMD (95% CI)	P value	I^2 (%)	P value
Overweight	0.42 (0.17, 0.67)	0.001	3.1	0.416	-1.40 (-1.82, -0.98)	<0.001	64.3	0.001
Obese	-0.98 (-1.98, 0.03)	0.058	28.2	0.233	-3.73 (-5.54, -1.92)	<0.001	83.6	<0.001
Class I	0.03 (-0.78, 0.83)	0.951	66.5	0.004	-2.54 (-3.93, -1.16)	<0.001	89.9	<0.001
Class II	-0.04 (-1.06, 0.99)	0.945	51.3	0.045	-3.91 (-5.10, -2.72)	<0.001	68.6	0.002
Class III	-1.75 (-3.33, -0.16)	0.031	59.6	0.016	-9.72 (-12.20, -7.24)	<0.001	87.3	<0.001

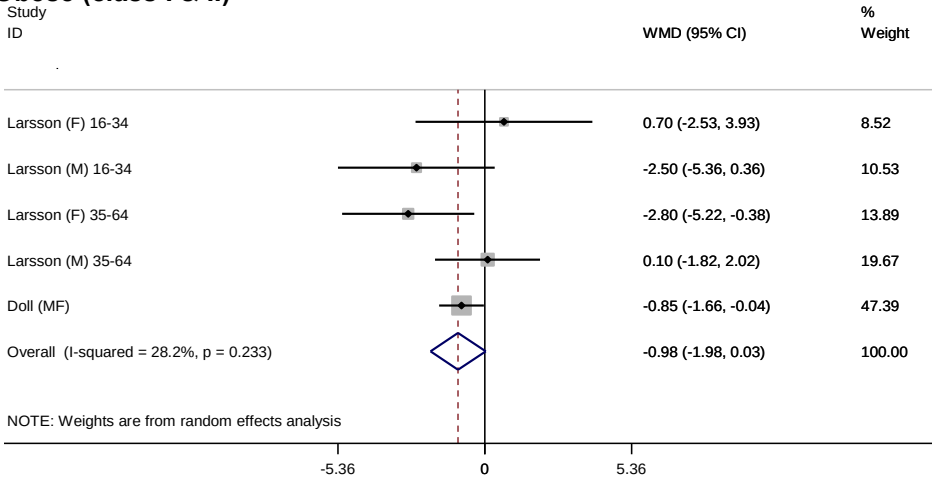
WMD weighted mean difference; CI confidence interval

Figure 4.5 Forest plots of the mental health scores

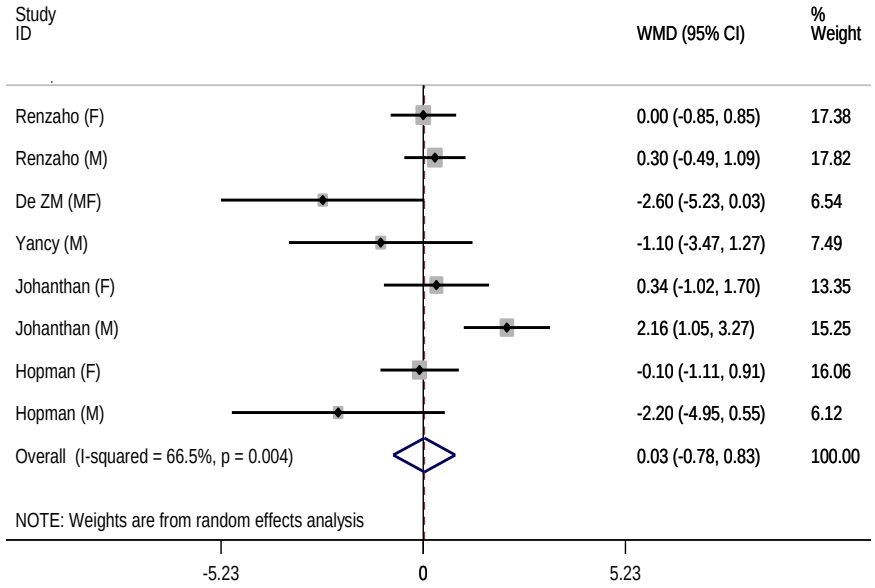
a. Overweight



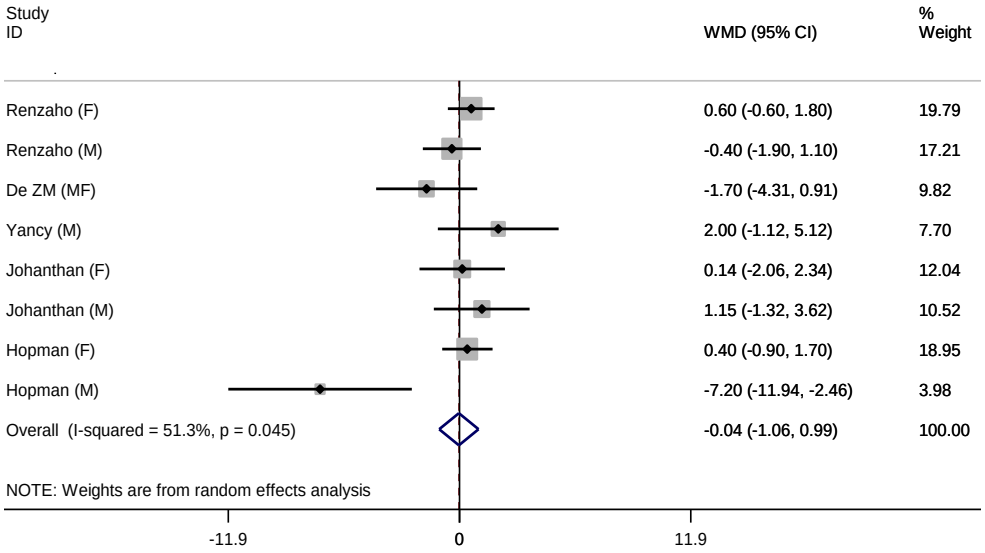
b. Obese (class I & II)



c. Class I Obese



d. Class II Obese



e. Class III Obese

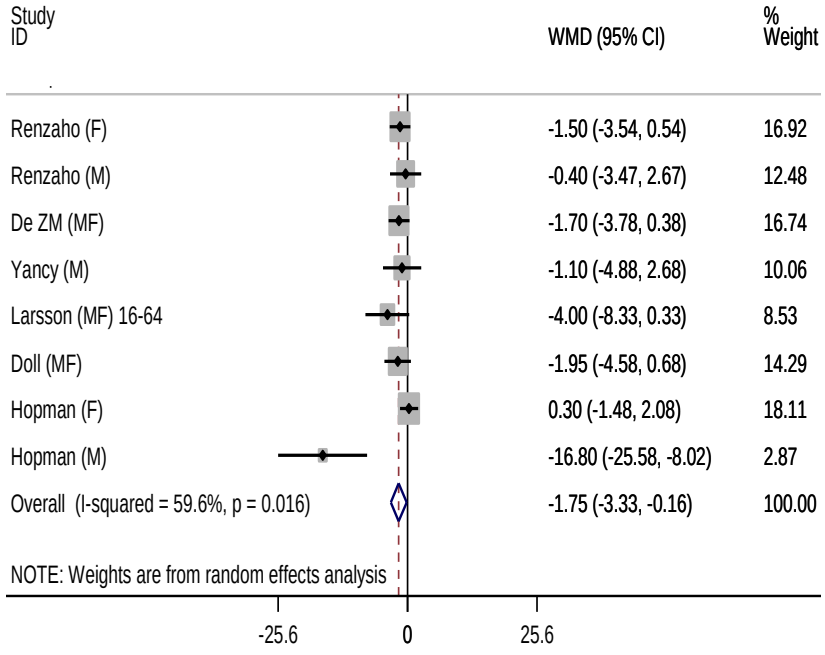
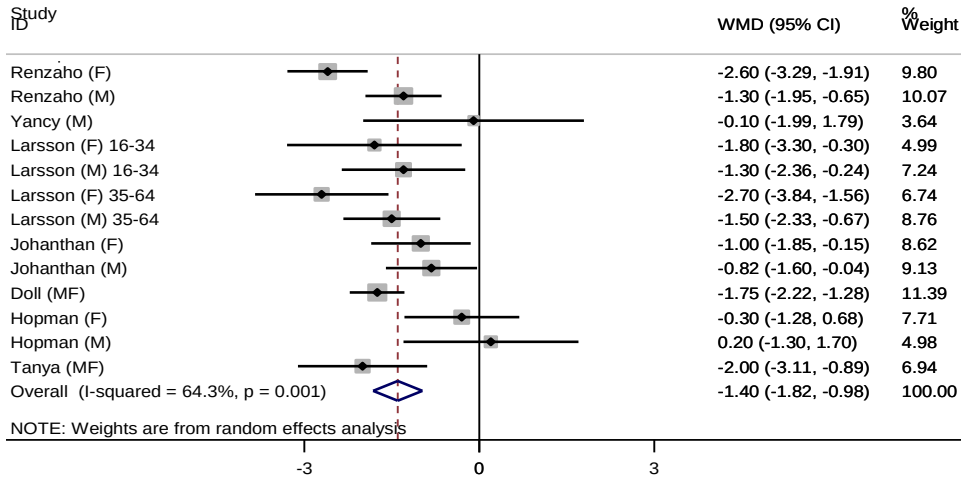
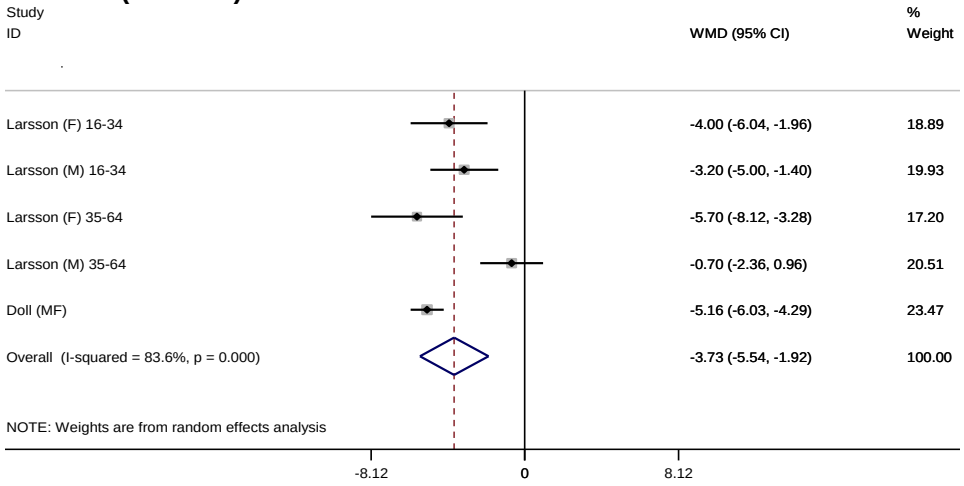


Figure 4.6 Forest plots of the physical health scores

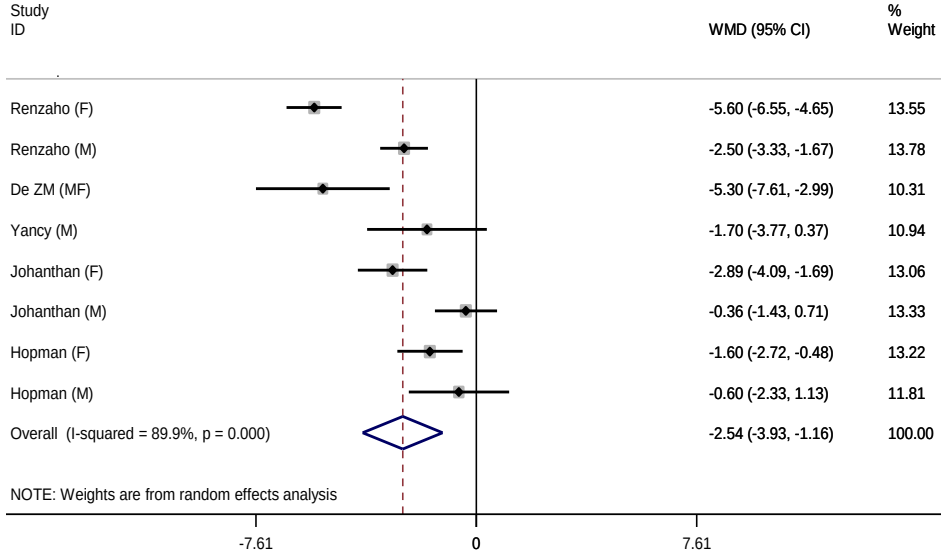
a. Overweight



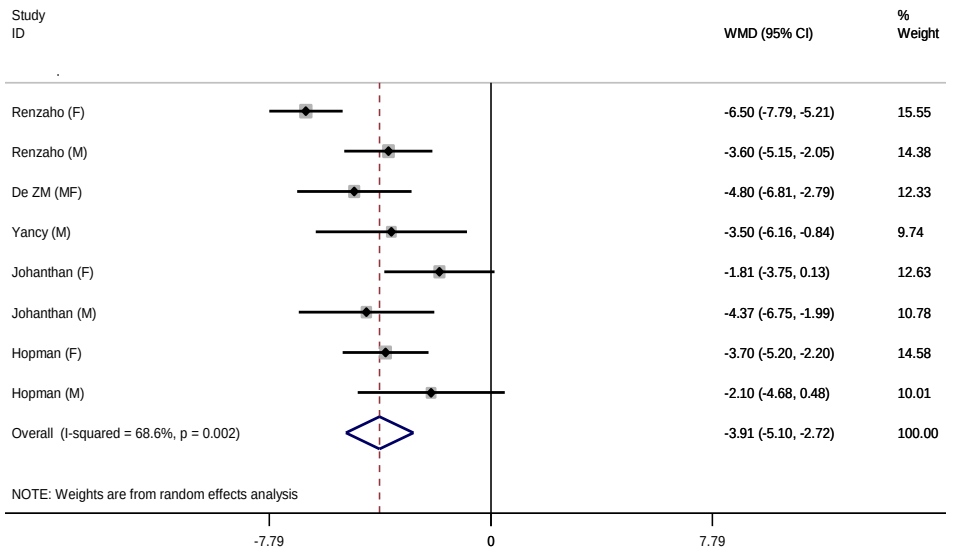
b. Obese (class I II)



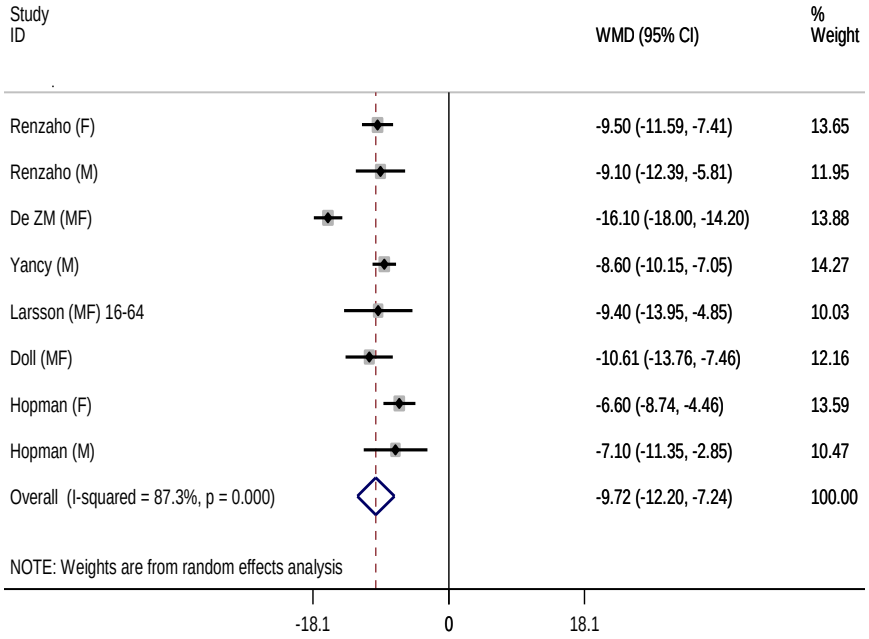
c. Class I Obese



d. Class II Obese



e. Class III Obese



4.5 Discussion

Different patterns were observed for physical and mental HRQoL. Compared with normal weight adults, those with higher BMI had significantly reduced physical HRQoL with clear evidence of a dose relationship across all the BMI categories. Mental HRQoL was also significantly reduced among class III obese adults, but was not significantly different among obese individuals and was significantly increased among overweight adults, compared to normal weight adults.

It has been shown that obese adults are at increased risk of a number of conditions, such as CVD (Bray 1992; Trakas et al. 1999; Visscher & Seidell 2001), have shorter life expectancy (Peeters et al. 2003), and have reduced overall HRQoL (Brown et al. 2000; Ford et al. 2001; Huang et al. 2006). There is now sufficient evidence to demonstrate that while physical HRQoL was reduced in both overweight and obese adults, mental HRQoL was only reduced among the class III obese. A between-groups difference of 5 points in individual SF-36 domains (Ware 1993), or 2-3 points in the overall physical and mental component is generally considered clinically significant (Ware 1994). Therefore, the reduction in physical HRQoL demonstrated for all above normal weight categories was clinically significant, as well as statistically significant. The reduction in mental HRQoL was only clinically and statistically significant in the class III obese. There is some evidence that BMI may be more negatively associated with mental HRQoL among women than men (Bentley et al. 2011).

Previous studies have suggested that overweight individuals have increased overall HRQoL (Bentley et al. 2011; Vasiljevic et al. 2008). This meta-analysis suggests that this is driven by an increase in the mental HRQoL component. The finding that mental HRQoL was higher in overweight than normal-weight individuals is consistent with some previous studies. The underlying reason is not yet clearly understood (Carpenter et al. 2000). Therefore I can only speculate. One possible reason is that generic measures of HRQoL might not be sensitive to the type of impairment in the mental HRQoL which is likely to be associated with overweight (Mond & Baune 2009). In some cultures overweight is still accepted as a symbol of a happy life (Huang et al. 2006). Also as the prevalence of overweight increases, perceptions may be changing such that being overweight is perceived as normal. Overeating may console some individuals,

especially those who are socioeconomically deprived (Crisp & McGuiness 1976). However, their physical HRQoL is reduced. This result is consistent with the increased risk of many conditions, such as CVD, diabetes, hypercholesterolemia, gallstones, osteoarthritis and musculoskeletal disease, demonstrated in overweight individuals (Field et al. 2001; Manson et al. 1995; Wyatt et al. 2006).

4.6 Strengths and limitations

There have been two previous systematic reviews, published in 1995 and 2001, of studies examining the association between BMI and physical and mental HRQoL (Fontaine & Barofsky 2001; Friedman & Brownell 1995) but, to my knowledge, this is the first meta-analysis of their results. Most of the published literature has reported a significant association between obesity and impairment in the physical domain of HRQoL but a comprehensive quantitative analysis is lacking. In particular, the results of published studies have not been consistent in relation to the association between the mental component of HRQoL and BMI. Some have reported a significant dose-response relationship between increasing BMI and decline in mental health (Friedman & Brownell 1995; Kim et al. 2007; Sullivan et al. 1987), while others have reported very weak or no association (de Petersen et al. 2009; Hopman et al. 2007; Le et al. 1998). This study was conducted in accordance with PRISMA guidelines and I searched four databases to ensure that I identified all relevant studies. My pooled estimates were derived from eight studies that comprised a total of 43,086 participants. Random effects meta-analyses were used to take account for heterogeneity in study design and populations and provide more conservative estimates of pooled effect sizes.

Of the 21 selected studies, only eight reported the physical and mental summary scores and were thus included in the quantitative analysis. Since I did not have access to individual level data I could not adjust for potential confounders at this level. The extent to which individual studies measured and adjusted for potential confounders varied. Many studies reported only unadjusted results. This might be a potential source of heterogeneity. Only published studies reporting SF-36 scores were included but there was no evidence of significant publication bias or small study bias as assessed by both funnel plots. SF-36 has been translated into and validated in more than 50 countries (http://www.sf36.org/tools/sf36.shtml) and was the most commonly used measure. Since all of

the studies were cross-sectional, it was not possible to determine the temporal relationship and therefore exclude the possibility of reverse causation.

4.7 Implications of this research

Both physical and mental HRQoL were impaired among class III obese individuals. There was a significant positive association between overweight and mental HRQoL. Physical HRQoL was impaired among overweight and obese, whereas mental HRQoL was only significantly impaired among individuals who were classified as class III obese. This meta-analysis provides further evidence to support the injurious effects of obesity on all aspects of health and supports the need to take action to reverse the higher prevalence of obesity.

In this Chapter, I collated the published evidence on the relationship between adiposity and HRQoL. The prevalence of adiposity is high, not only among adults, but also in children. Childhood obesity is important because obese children/adolescents are more likely to become obese adults (Cunningham et al. 2014). In the next chapter I will explore whether it is also important in its own right, in terms of an adverse effect on subjective well-being during childhood. A previous systematic review was published in 2009 (Tsiros et al. 2009), but that mainly focused on the impact of weight loss on HRQoL and, as yet, no meta-analysis has been conducted. Therefore, in the next Chapter (Chapter 5), I will update the systematic review and conduct a meta-analysis of the published studies to determine the association between childhood/adolescent adiposity and HRQoL.

5 Chapter 5: Adiposity and health-related quality of life among children

Published in;

Ul-Haq Z, Mackay DF, Fenwick E, Pell JP (2013). Meta-analysis of the association between body mass index and health-related quality of life among children and adolescents assessed, using the pediatric quality of life inventory index. *J Pediatr* **162**(2):280-286.

5.1 Chapter summary

To explore the relationships between BMI and overall, physical and psychosocial HRQoL in children and adolescents, a systematic review was conducted, in accordance with PRISMA guidelines. Medline, Embase, PsycINFO and the Web of Knowledge were used to search for relevant articles.

Inclusion was restricted to participants under 20 years of age, who had been assessed using the PedsQL index. Random effects meta-analysis was conducted. Heterogeneity was assessed using the I^2 statistic, and potential publication and small study bias using funnel plots.

Eleven eligible studies provided 35 estimates of effect size, derived from 13,210 study participants. Based on self-report, children and adolescents with higher than normal BMI had significantly reduced total, physical and psychosocial HRQoL with a clear dose relationship across all categories. Among obese children/adolescents, the overall score was reduced by 10.6 points (95% CI 14.0, 7.2, $p<0.001$). Parents reported the same pattern but a larger effect size. The overall parental score for obese children/adolescents was reduced by 18.9 points (95% CI 26.6, 11.1, $p<0.001$). No significant publication or small study bias was observed.

Parents over-estimate the impact of obesity on the HRQoL of their children. Nonetheless, obese children/adolescents themselves report reduced overall, physical and psychosocial HRQoL.

5.2 Introduction

Recent estimates suggest that around 43 million children under five years of age are overweight, including 35 million in developing and 8 million in developed countries (World Health Organization 2011). The prevalence of overweight and obesity in children and adolescents is high (Ogden et al. 2002; Wang & Lobstein 2006; Waxman & Norum 2004). Obesity in childhood predisposes to obesity in adulthood which, in turn, increases the risk of ill-health and reduced life expectancy (Guo et al. 2000; Whitaker et al. 1997). The relationship between adult obesity and HRQoL is complex. Physical HRQoL demonstrates a dose relationship, decreasing steadily as BMI increases from the normal range to obese (Chapter 4; Ul-Haq Z et al. 2013b). In contrast, mental HRQoL is significantly reduced in obese adults, but not in overweight adults. The relationship between childhood obesity and HRQoL is currently unclear. Individual studies have used a mixture of self and parental reporting, and have produced conflicting results. A systematic review was published in 2009 (Tsiros et al. 2009) and suggested that HRQoL improves with weight loss. The pooled results suggested that children's HRQoL can be predicted from parent-proxy reports, although parents tend to perceive HRQoL to be worse than their children. No meta-analysis has previously been conducted. I undertook an updated systematic review and meta-analysis of published studies to determine the association between childhood/adolescent BMI and overall, physical and psychosocial HRQoL.

5.3 Materials and methods

5.3.1 Systematic review

A systematic review of published articles was performed in accordance with the PRISMA guidelines (http://www.prisma-statement.org), which consists of 27-items checklist, aimed to improve the reporting of systematic reviews and meta-analysis (Moher et al. 2009). I adhered to most of the PRISMA checklist but not to item number 5 which is more relevant to clinical trials, and to item number 27 which is related to the statement of funding and was irrelevant to my study. I also could not adhere to PRISMA checklist items number 16 and 23; additional analyses; as these were not feasible due to the small number of underlying studies (Appendix 1). The relevant search terms (obes* OR BMI OR body mass index OR overweight) AND (HRQoL OR quality of life OR QoL) were applied to four electronic databases: Embase, Medline, ISI Web of Knowledge and PsycINFO. The last search was undertaken on 1 August 2011. The electronic search was limited to studies conducted on humans and written, or translated into, English. The identified articles were then reviewed manually, and their reference lists checked for any additional relevant studies. Articles were included in the meta-analysis if they were conducted on children or adolescents; defined as <20 years of age. The PedsQL was the most frequently used index. Therefore, inclusion in the meta-analysis was limited to studies that used the PedsQL Inventory, and reported the overall, physical and psychosocial summary scores or both. PedsQL is a generic HRQoL index developed for self-reporting by study participants aged 5-18 years, as well as parent-proxy reporting for participants aged 2-18 years (Varni et al. 1999; Varni et al. 2003). It comprises 23 items that encompass physical, emotional, social and school functioning (Schwimmer et al. 2003). It produces standardized scores for overall, physical and psychosocial HRQoL, ranging from 0 to 100, with higher scores indicating better HRQoL (Varni et al.1999). BMI was categorised, using the International Obesity Task Force (IOTF) (Cole et al. 2000) age-sex specific BMI cut-off values, into normal weight, overweight, obese and severely obese. Where studies used the CDC definition, I treated the normal, at risk of overweight, overweight and very overweight as equivalent to these four IOTF categories, respectively (Kuczmarski et al. 2000). The information collated from individual studies included study design, age, sex, region, year of publication, number of

participants and the mean PedsQL scores and SD by BMI category. No additional or individual level data were obtained from the study investigators. Risk of bias assessment was conducted for each study that was included in the systematic review using a generic validated checklist "QualSyst" for the quantitative studies (Kmet et al. 2004).

5.3.2 Meta-analysis

A random effects meta-analysis was conducted, of the weighted mean WMD in PedsQL scores for each BMI category referent to the normal weight category. Based on the characteristics of the underlying studies I used the random effects model in this study. As they were very different population (countries, ages, general population/disease), and had different level of adjustment for potential confounders. I^2 statistics were calculated to assess the degree of heterogeneity (Higgins et al. 2003). All statistical analyses were performed using Stata version 11.2 (STATA Corporation, College Station, Texas, USA).

5.4 Results

Electronic searching of the four databases identified 968 potentially eligible studies, of which 460 were excluded as duplicates. An additional 32 articles were identified from the reference lists (Figure 5.1). After reviewing the abstracts of the resultant 540 articles, 74 were considered relevant and the full articles were studied. Fifty two studies did not meet the inclusion criteria. Of the remaining 22 studies that have used the PedsQL index, only 11 provided the overall, physical and psychosocial summary scores by BMI category and were thus included in the meta-analysis. The 11 studies comprised a total of 13,210 children or adolescents (range of 93 to 5,543 participants per study), of whom 1,370 (10%) were either overweight or obese. The studies were published between 2003 and 2011 (Table 5.1). Five (45%) were conducted in North America (Schwimmer et al. 2003; Tyler et al. 2007; Varni et al. 2007; Zeller et al. 2006; Zeller & Modi 2006), three (27%) in Europe (de wit et al. 2007; Hughes et al. 2007; Riazi et al. 2010), two (18%) in Australia (Williams et al. 2005; Williams et al. 2011) and one (9%) in Asia (Pinhas-Hamiel et al. 2006). Nine studies were cross-sectional (de wit et al 2007; Hughes et al. 2007; Pinhas-Hamiel et al. 2006; Riazi et al. 2010; Schwimmer et al. 2003; Tyler et al. 2007; Varni et al. 2007;

Williams et al. 2005; Zeller et al. 2006) and two were cohort studies (Williams et al. 2011; Zeller & et al. 2006). All studies included both sexes and all reported results obtained from child-self assessment. Eight of the studies also reported results obtained from parent-proxy assessment (Hughes et al. 2007; Schwimmer et al. 2003; Tyler et al. 2007; Varni et al. 2007; Williams et al. 2005; Williams et al. 2011; Zeller et al. 2006; Zeller & Modi 2006).

Overall, the majority of included studies were well performed and fulfilled the quality satisfying criteria (Figure 5.2). However, there were some weaknesses such as lack of sufficient baseline information, patient selection, sample size, detailed reporting of results, inappropriate description of analysis and adjustment for potential confounders.

Figure 5.1 PRISMA flowchart of the PedsQL studies

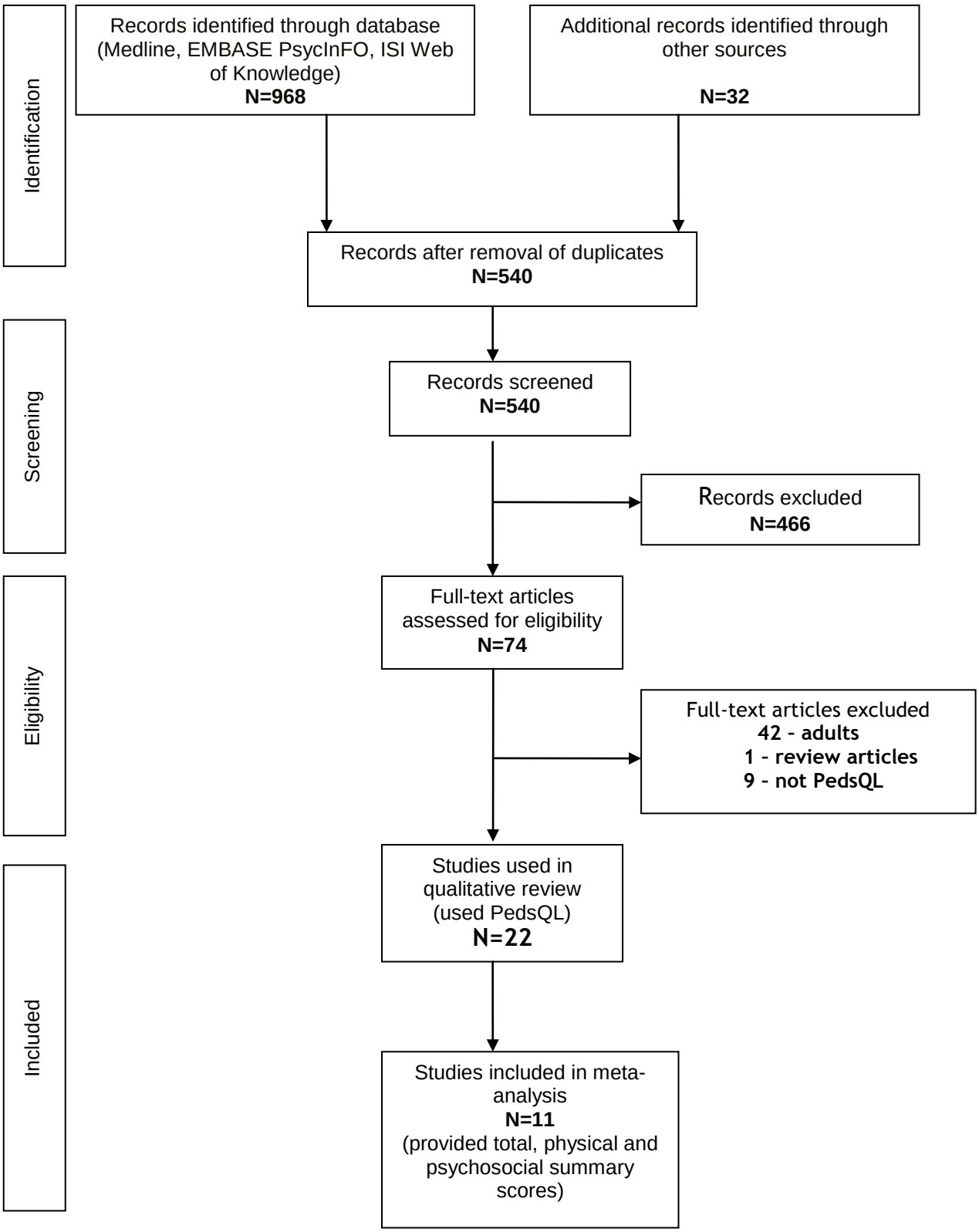


Figure 5.2 Results of quality assessment for all studies included in the review

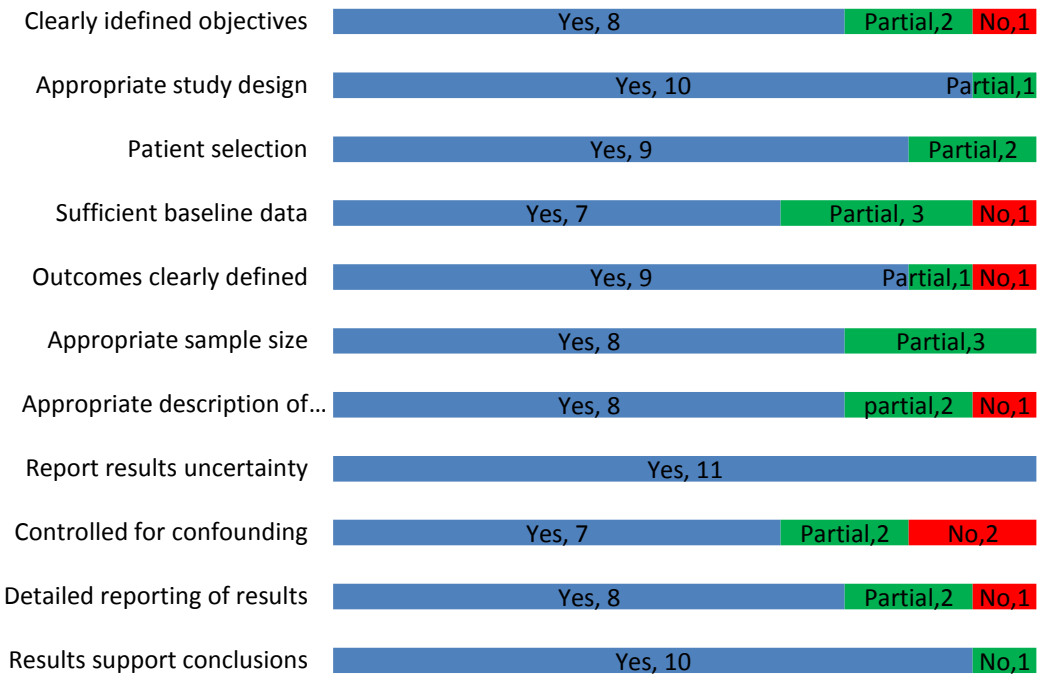


Table 5.1 Characteristics of studies examining the association between body mass index in children and adolescents and health-related quality of life

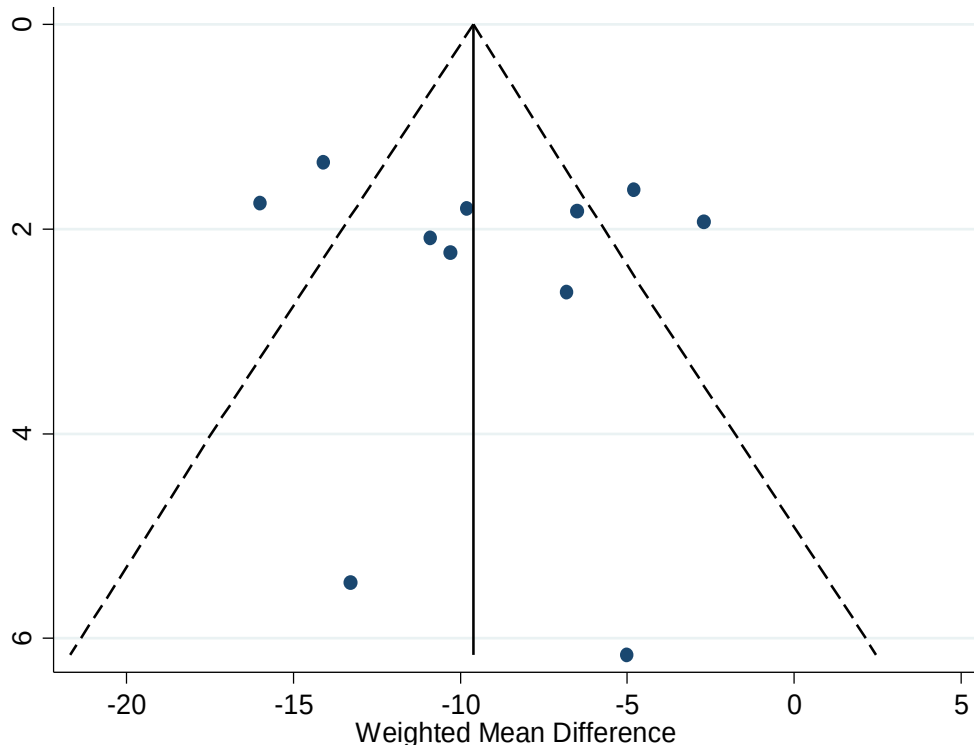
Author	Year	Country	Sex	Age (years)	Sample size all (OW/obese)	Sample	Comparison groups	Child-self report	Parent-proxy report
Williams1	2011	Australia	M&F*	08-18	851 (199)	From schools	Normal-weight vs† overweight & obese	Yes	Yes
Riazi	2010	England	M&F	05-16	540 (96)	Obese (clinic), control (schools)	Healthy control vs obese clinical	Yes	No
Varni	2007	USA	M&F	15-18	5,543 (63)	Obese (clinic), healthy (community)	Healthy control vs obese clinical	Yes	Yes
De beer	2007	Netherland	M&F	12-18	93 (31)	Obese (clinic), healthy (community)	Normal-weight vs obese	Yes	No
Hughes	2007	Scotland	M&F	05-11	197 (126)	Obese (clinic), control (schools)	Control vs obese	Yes	Yes
Tyler	2007	USA	M&F	02-18	175 (105)	From school	Normal vs overweight, obese & very obese	Yes	No
Pinhas	2006	Israel	M&F	02-18	182 (88)	Obese (clinics) & Healthy (OPD)	Normal-weight vs obese	Yes	Yes
Zeller	2006	USA	M&F	08-18	1,843 (166)	Obese (clinics), healthy (published)	Healthy control vs obese clinical	Yes	Yes
Williams2	2005	Australia	M&F	09-12	1,569 (357)	From schools	Normal-weight vs overweight & obese	Yes	Yes
Zeller2	2005	USA	M&F	13-18	1,710 (33)	Obese (clinics), healthy (published)	Normal-weight vs obese	Yes	Yes
Schwimer	2003	USA	M&F	05-18	507 (106)	Obese (clinics), healthy (published)	Normal-weight vs obese	Yes	Yes

*M: male, F: female †vs: versus Yes: provided; No: not provided

5.4.1 Child-self reporting

The 11 studies provided 35 estimates of the effect of obesity, of which 28 achieved statistical significance (p<0. 05) (Figure 5.4). Three studies provided 9 estimates of the effect of overweight and one achieved statistical significance. In comparison with normal weight children, obese children had significantly reduced overall HRQoL, as well as both significantly reduced physical and psychosocial HRQoL (Table 5.2). In relation to overall HRQoL, there was a clear dose relationship, whereby overall HRQoL was reduced slightly in overweight children and much more among obese children (Table 5.2). Similar patterns were observed for both physical and psychosocial HRQoL, although the reduction in psychosocial HRQoL in overweight children did not reach statistical significance. The reduction in physical HRQoL was slightly greater than that in psychosocial HRQoL but the differences were not statistically significant. Visual inspection of the funnel plots did not suggest asymmetry (Figure 5.3).

Figure 5.3 Funnel plot of the studies examining the association between adiposity and PedsQL score



5.4.2 Parent-proxy reporting

Eight studies provided 23 estimates of the effect of obesity, of which 22 achieved statistical significance ($p<0.005$) (Figure 5.5). Two studies provided 6 estimates of the effect of being overweight and two achieved statistical significance. Consistent with children's reports, the parents of obese children reported that they had significantly reduced overall, physical and psychosocial HRQoL (Table 5.2). There was a dose effect whereby HRQoL was reduced in overweight children but to a much lesser extent than among obese children (Table 5.2). As with children's reports, the reduction in psychosocial HRQoL reported by the parents of overweight children did not reach statistical significance. Across all three measures, parents consistently rated their overweight and obese children as suffering greater reductions in their HRQoL than that reported by the children themselves. Compared with children, parents tended to report a greater reduction in physical, compared with psychosocial, HRQoL for both overweight and obese. However, the differences were not statistically significant. There was no evidence of asymmetry in the Funnel plots.

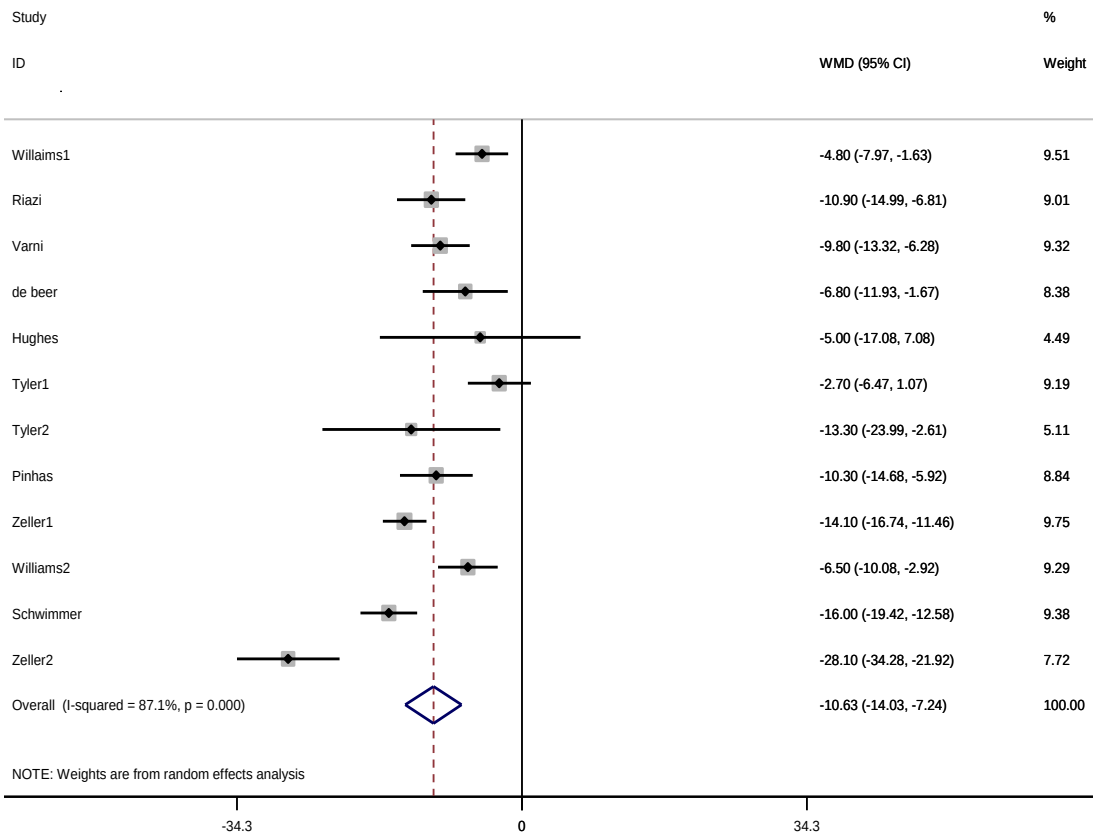
Table 5.2 Pooled estimates of the weighted mean difference in health-related quality of life score among obese and overweight children and adolescents referent to normal weight.

	Child-self report				Parent-proxy report			
	Pooled estimate		Heterogeneity		Pooled estimate		Heterogeneity	
	WMD* (95% CI¶)	P value	I^2 (%)	P value	WMD (95% CI)	P value	I^2 (%)	P value
Obese								
Total Score	-10.63 (-14.03, -7.24)	<0.001	87.1	<0.001	-18.87 (-26.60, -11.14)	<0.001	96.3	<0.001
Physical Summary	-11.93 (-15.13, -8.74)	<0.001	81.8	<0.001	-21.73 (-30.12, -13.35)	<0.001	95.4	<0.001
Psychosocial Summary	-9.99 (-13.98, -6.01)	<0.001	88.1	<0.001	-17.37 (-25.89, -8.85)	<0.001	96.4	<0.001
Overweight								
Total Score	-1.43 (-2.55, -0.32)	0.012	00.0	0.690	-2.60 (-4.00, -1.19)	<0.001	00.0	0.322
Physical Summary	-1.47 (-2.67, -0.28)	0.015	04.4	0.351	-4.16 (-6.57, -1.74)	0.001	45.1	0.177
Psychosocial Summary	-1.15 (-2.46, 0.16)	0.084	00.0	0.774	-1.32 (-2.79, 0.16)	0.080	00.0	0.748

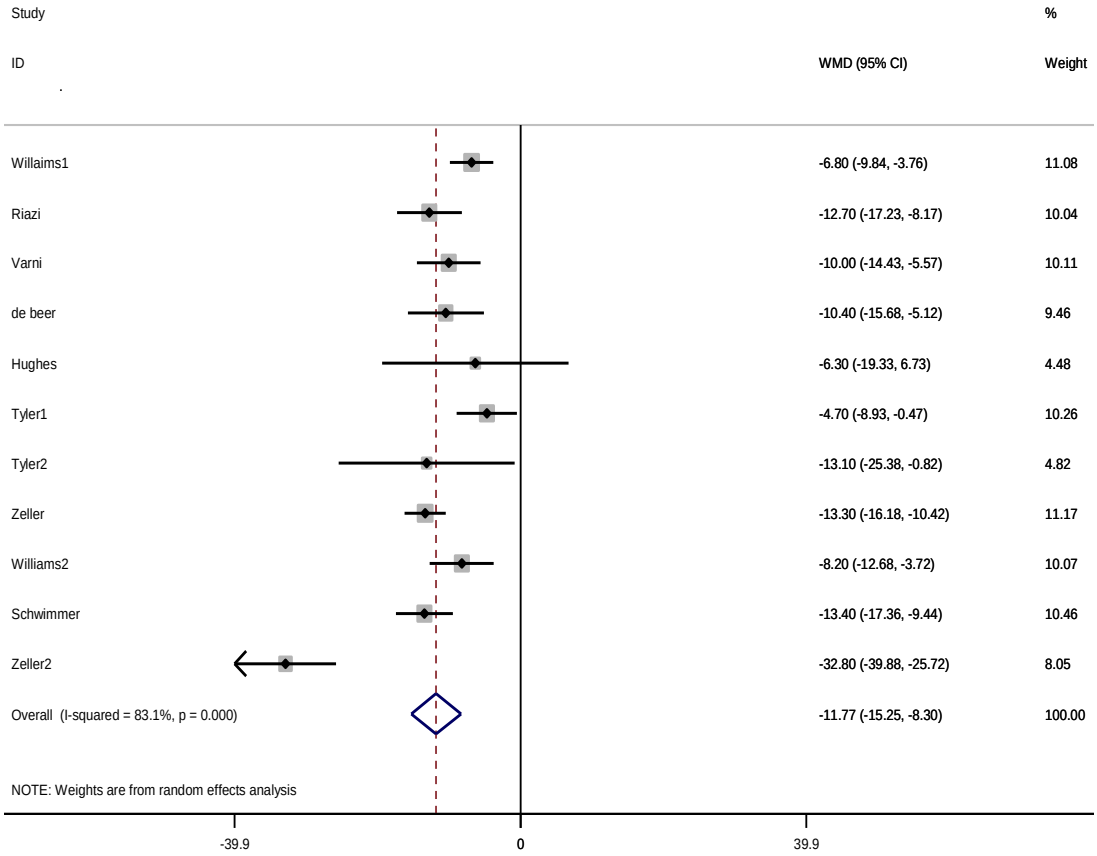
*WMD weighted mean difference; ¶CI confidence interval

Figure 5.4 Forest plots of the child-self reports from the obese participants compared with normal-weight participants.

a. **Total score**



b. **Physical summary**



C. Psychosocial summary

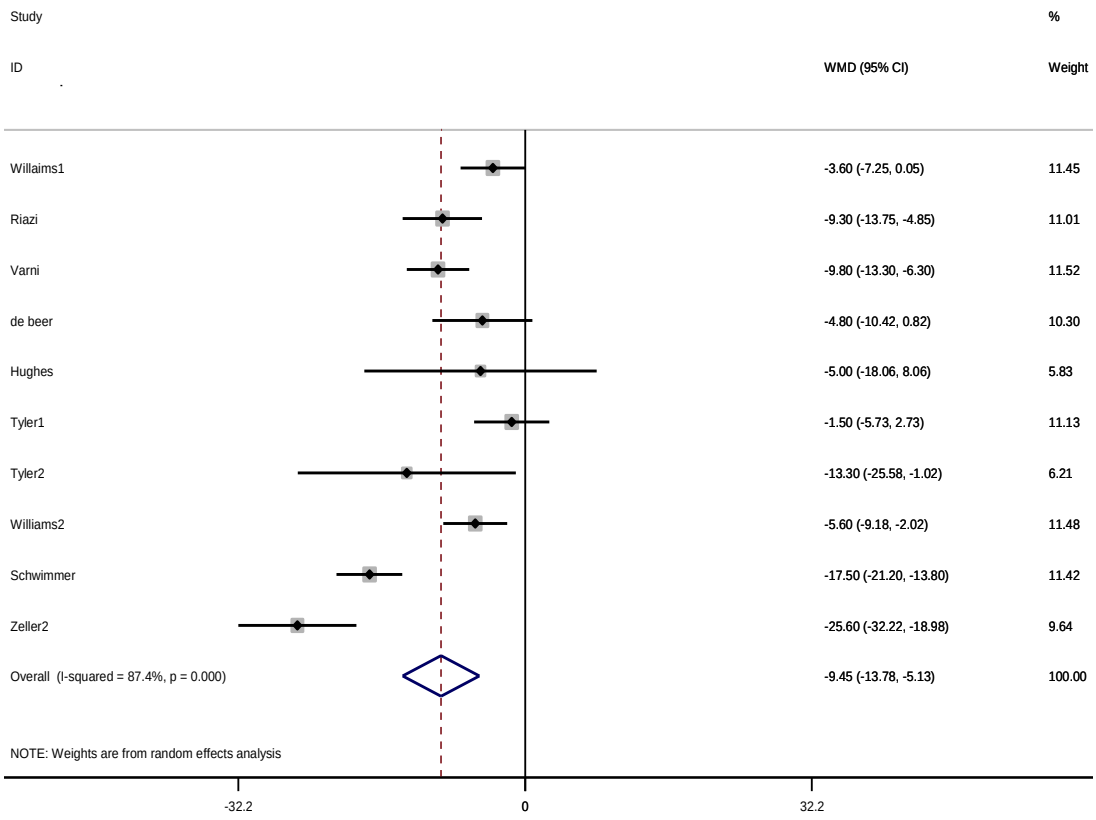
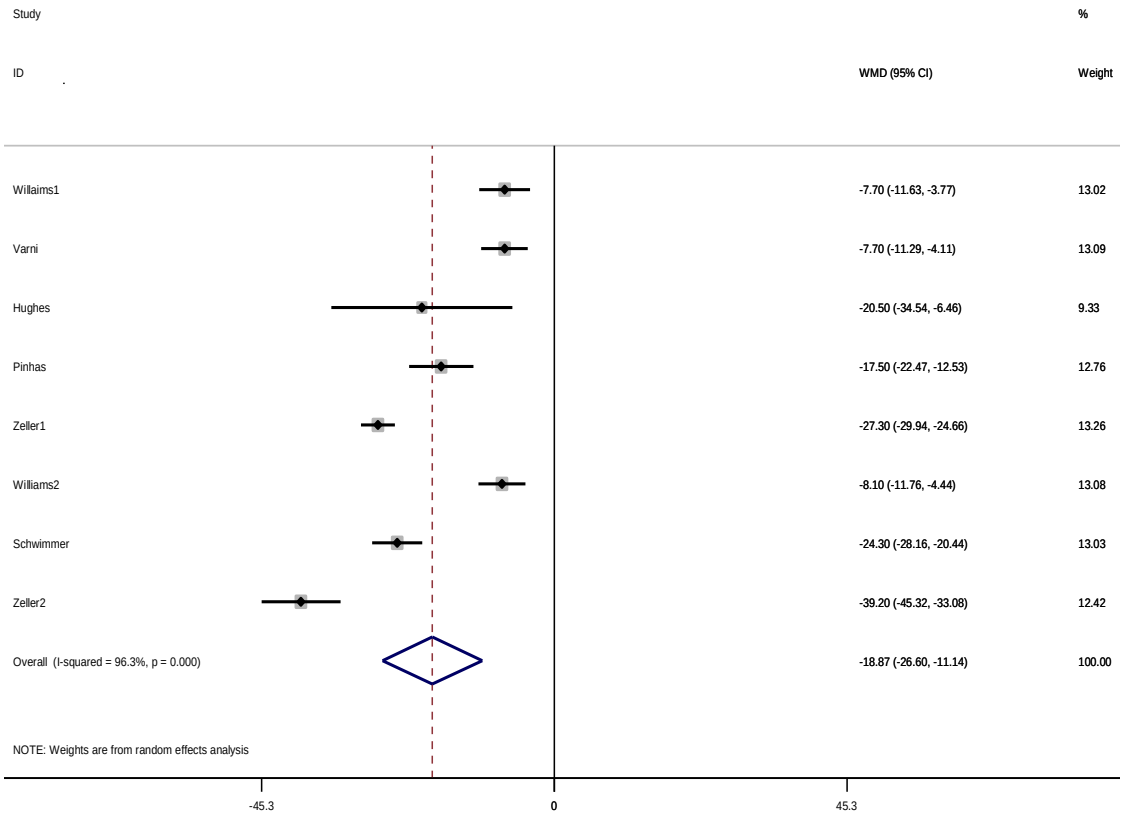
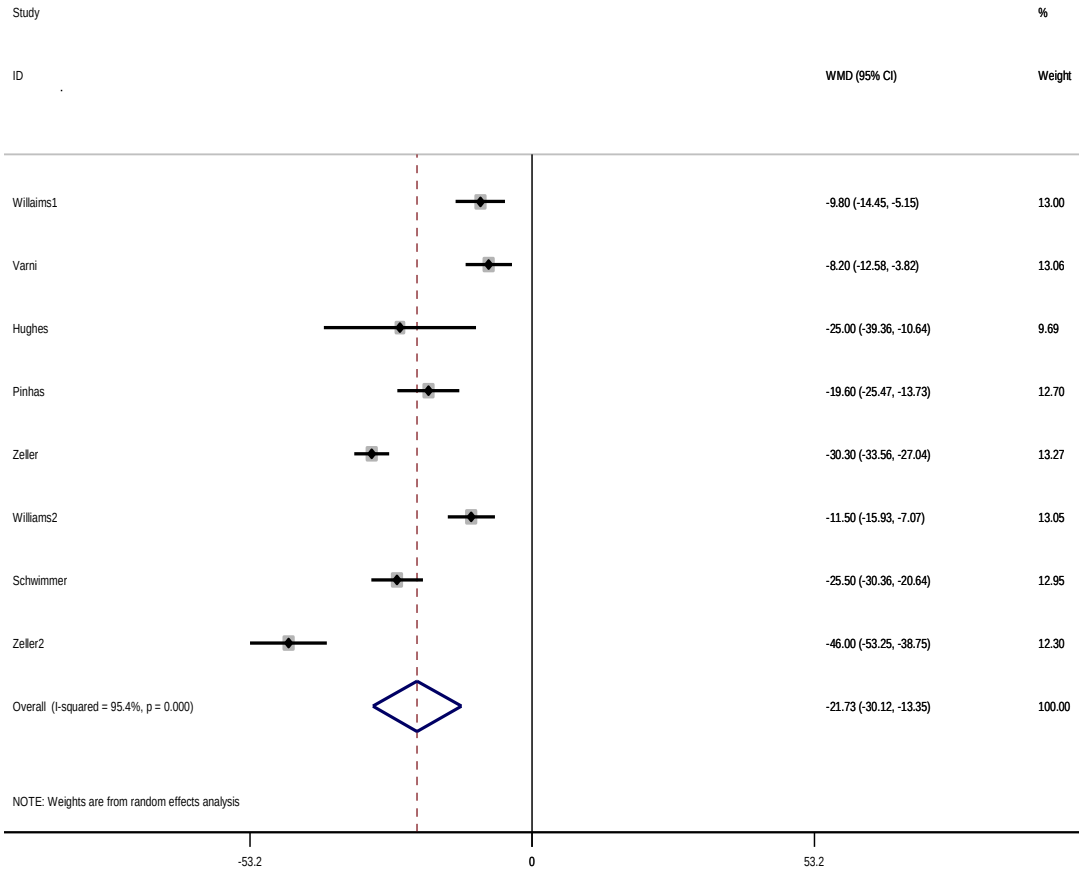


Figure 5.5 Forest plots of the parent proxy reports from the obese participants compared with normal-weight participants.

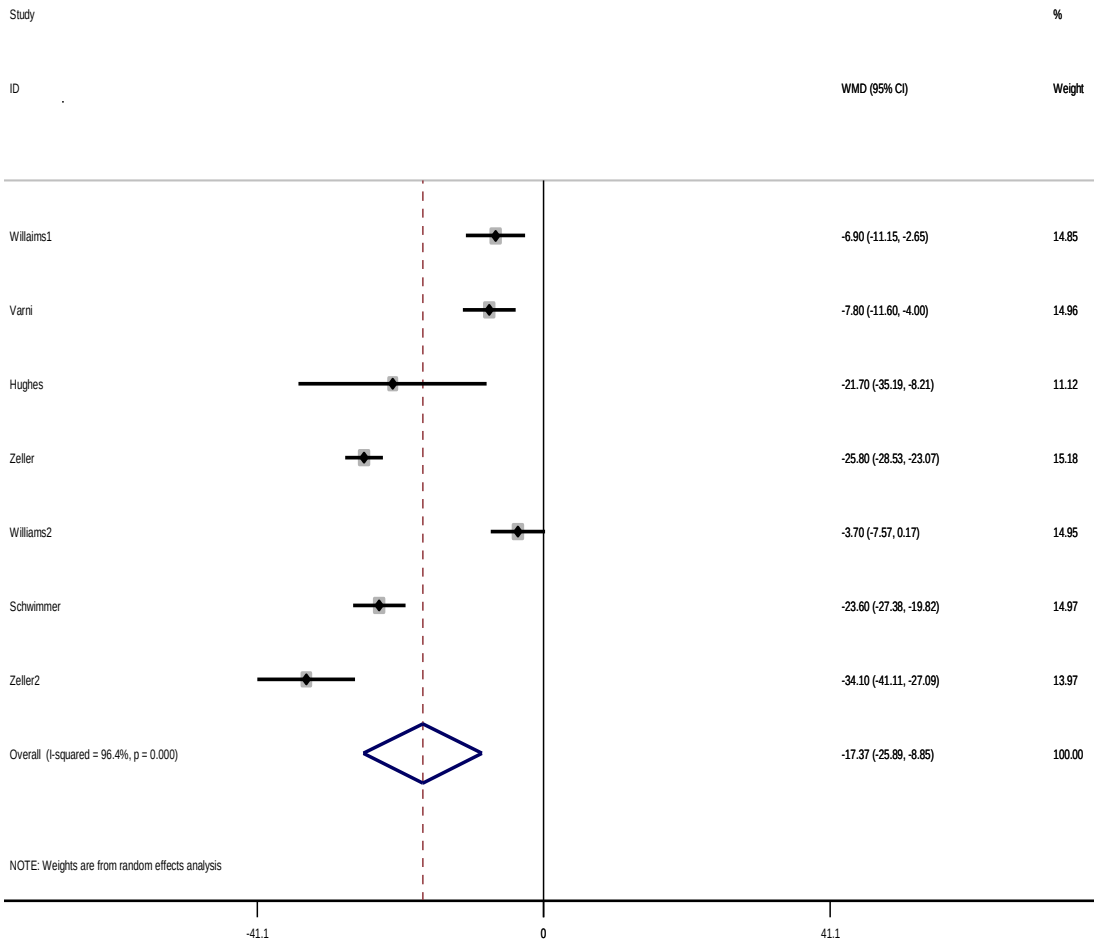
a. **Total score**



b. **Physical summary**



C. Psychosocial summary



5.5 Discussion

The evidence from published studies suggests that obese children and adolescents have significantly reduced overall HRQoL. The impact on physical HRQoL is non-significantly greater than the impact on psychosocial HRQoL but both are significantly reduced. Parents tend to over-estimate the extent to which their children's HRQoL is reduced. Nonetheless, there is a significant effect when based on child self-reporting. There is also evidence of a dose relationship whereby HRQoL decreases as BMI increases from normal weight, through overweight to obesity.

Childhood obesity is significantly associated with various morbidities (Ebbeling et al. 2002), including noninsulin-dependent diabetes mellitus (Scott et al. 1997), hypertension (Figueroa-Colon et al. 1997), dyslipidemia (Williams et al. 1992), sleep apnoea (Riley et al. 1976), gall bladder diseases (Acalovschi et al. 1997) and depression (Zeller et al.2006). There has been one previous systematic review of the effect of childhood BMI on HRQoL (Tsiros 2009) but, to my knowledge, this is the first meta-analysis to have been conducted in children. In the previous Chapter of meta-analysis of adults (Chapter 4; Ul-Haq Z et al. 2013b), I found a similar dose relationship whereby physical HRQoL fell with increasing BMI above normal weight. However, psychosocial HRQoL was only reduced significantly in morbidly obese adults. It was not significantly reduced in obese adults and it was significantly increased in overweight adults. In contrast, psychosocial HRQoL was significantly reduced in obese children and non-significantly reduced in overweight. This suggests that the psychosocial sequelae of increased BMI may be greater in children than in adults.

Parental over-estimation of the adverse effect on HRQoL is not restricted to obesity. Previous studies have shown that parents over-estimate the adverse effect on HRQoL of other conditions, such as cystic fibrosis (Modi & Quittner 2003; Verrips et al. 2000). The reasons that parents over-estimate the impact of childhood obesity are not known but may include parental distress (Vance et al. 2001), and greater awareness of future complications (Ingerski et al. 2007) and conversely, children have a short-term perspective (Eiser & Morse 2001). Also, the parents of obese children are more likely to be obese themselves (Lake et

al. 1997), and their own experiences of being obese may impact on their reporting.

5.6 Strengths and limitations

This meta-analysis was conducted in accordance with PRISMA guidelines and four major databases were searched to ensure that all relevant studies were identified. The pooled estimates were derived from eleven studies that comprised a total of 13,210 study participants. The majority of the individual studies were cross sectional which are inferior to cohort studies at inferring causality. The included studies were conducted on both clinical and community based samples. The former might be expected to over-estimate the association, but previous studies have demonstrated no significant differences in HRQoL between the two groups (Pinhas-Hamiel et al. 2006). I found no evidence of significant publication or small study bias but, because the individual studies were not conducted under identical conditions, I used the more conservative approach of random effects meta-analysis. I used the published results from individual studies and did not approach the investigators for access to individual level data. Some of the studies used IOTF and others used CDC classification of BMI which could be one of the reasons of the significant heterogeneity among the studies. The 10% prevalence of overweight and obese children in the underlying studies is very low than the general population. The corresponding prevalence in the UK is 30.6% (Figure 1.5). This may be because the majority of the included studies did not draw sample from the general population but from schools or OPD.

There was statistical heterogeneity among studies in both the chapters (4&5), as shown by the funnel plots (some of the studies are lying outside the pseudo 95% CI) (Figure 4.3, 5.3), forest plots (the confidence intervals of studies do not overlap well) and the standard chi-square statistics (Figure 4.5, 5.4). The level of heterogeneity was also explored using the Higgins I^2 statistics. This useful measure gives the percentage of inconsistency in the underlying studies effect size which cannot be explained by sampling error or chance (Higgins et al. 2003). In general, the findings of I^2 statistics are interpreted as; might not be important (I^2 = 0% to 40%), moderate (I^2 = 30% to 60%), substantial (I^2 = 50% to 90%), and considerable (75% to 100%) heterogeneity (Higgins & Green 2011). The advantage

of I^2 is that it is easy to measure and interpret, is accompanied by uncertainty level, and importantly not dependent on the sample size (number of underlying studies). The moderate to substantial significant heterogeneity in the pooled effect sizes were expected; as all of the individual studies are observational which are prone to confounding and selection bias and conducted by different researchers at different population and different places (Higgins 2008). However, all of the underlying studies had similar objectives, all used cross-sectional study designs, and had reasonably good quality and a same standardized cut-off for measuring both adiposity and HRQoL. Furthermore, there was significant heterogeneity but no inconsistency in the direction of the effect size was observed.

I conducted a robust search, quality assessments of the included studies, used the random effects meta-analysis, and produced funnel plots. However, the underlying heterogeneity has resulted in a wider confidence interval of the pooled effect size and due to the power issue I could not further explore the reasons of heterogeneity by cumulative meta-analysis or meta-regression, and so the conclusion of these meta-analyses should be interpreted with caution.

Heterogeneity can be further explored by using various plots, such as cumulative meta-analysis, L'Abbé funnel and re-ordering studies on forest plot (Sterne JAC 2009, L'Abbé et al. 1987). Cumulative meta-analyses plots could be used to explore changes over time in the pooled estimates of effect size. L'Abbé proposed a method of presenting the variations in the effect size by plotting the control group on the x-axis and the intervention group on the Y-axis. Between-study heterogeneity may be explored by sub-group analysis (Naggara at al. 2011), and regression method (Sterne JAC 2001).

Meta-analysis of a subset of a studies or subset of participants within studies is allowed, and the effect size of various sub-groups can be informally compared by considering each sub-group independently. However, it could result in misleading conclusion if not commenced carefully. The clear definitions of sub-group are crucial and should be pre-specified based on a scientific rationale. If the overall result of one sub-group is significant, and the other is not, it does not mean that there is a statistically significant difference between the two sub-

groups, as they are not directly compared (Borenstein et al. 2009). It should be restricted to a hypothesis-generating tool.

In the presence of significant heterogeneity, the meta-regression may be a useful tool for exploring the cause of heterogeneity (Borenstein et al. 2009). In simple terms, the outcome variable (WMD in this case) from each underlying study is regressed on the independent variable of interest. The variable which is significantly associated with effect size is assumed to be the major cause of heterogeneity. In meta-analysis, the unit of analysis is the study, and thus the validity of a meta-regression is dependent on the number of studies (≥ 10).

5.7 Implications of this research

Overweight children are more likely to develop into overweight adults (Whitaker et al.1997) and are at increased risk of many conditions. This study suggests that they also suffer from impaired HRQoL. Therefore, childhood obesity is an important public health problem and effective interventions are needed urgently to stem the higher prevalence. These findings will enable clinicians, public health physicians and others to educate children and their parents about the potential adverse effect of obesity on their HRQoL.

In Chapters 4 and 5, I collated the existing literature. In the subsequent chapters, I will undertake a series of primary data studies in which I can address a number of the limitations of previous studies, including adjustment for potential confounders, testing for interactions with comorbidity and sex, and checking the robustness of the relationship using a variety of measures of adiposity and subjective well-being.

6 Chapter 6: Adiposity, comorbidity and health-related quality of life

Published in;

Ul-Haq Z, Mackay DF, Fenwick E, Pell JP (2012). Impact of metabolic comorbidity on the association between body mass index and health-related quality of life: a Scotland-wide cross-sectional study of 5,608 participants. *BMC Public Health* 12:143

6.1 Chapter summary

The prevalence of obesity is rising in Scotland and globally. Overall, obesity is associated with increased morbidity, mortality and reduced health HRQoL. Studies suggest that “healthy obesity” (obesity without metabolic comorbidity) may not be associated with morbidity or mortality. Its impact on HRQoL of life is unknown.

Data from the SHeS were extracted on self-reported HRQoL, BMI, demographic information and comorbidity. SF-12 responses were converted into a utility score (indicating the overall HRQoL of the individuals ranges from 0 “death” to 1 “full health). Linear regression analyses were used to explore the association between BMI and health utility, stratified by the sex and presence or absence of metabolic comorbidity (diabetes, hypertension, hypercholesterolemia or CVD), and adjusted for potential confounders (age, sex, deprivation quintile and smoking, drinking status).

Of the 5,608 individuals, 3,744 (66.8%) were either overweight or obese and 921 (16.4%) had metabolic comorbidity. There was an inverted U-shaped relationship whereby health utility was highest among overweight individuals and fell with increasing BMI. There were significant interactions of BMI with sex ($p<0.001$) and with metabolic comorbidity ($p=0.007$). Being overweight was associated with significantly higher utility scores in men only. In contrast, being underweight and obese was associated with significantly lower utility score in women only. Individuals with metabolic comorbidty had lower utility scores and a steeper decline in utility with increasing BMI (morbidly obese, adjusted coefficient: -0.064, 95% CI -0.115, -0.012, $p=0.015$ for metabolic comorbidity versus -0.042, 95% CI -0.067, -0.018, $p=0.001$ for no metabolic comorbidity).

Overall, the negative association between obesity and HRQoL is greater among individuals with metabolic comorbidity. However, increased BMI is associated with reduced HRQoL even in the absence of metabolic comorbidity, casting doubt on the notion of “healthy obesity”.

6.2 Introduction

In Scotland, around two-thirds of adult men and more than one-half of adult women are either overweight or obese (http://www.scotland.gov.uk/Topics/Statistics/Browse/Health/TrendObesity). Overall, obesity is associated with an increased risk of many conditions including hypertension, hypercholesterolemia, type II diabetes and CVD (Bray 1992; Colditz 1992; Rippe et al. 1998; Trakas et al. 1999). It is also associated with reduced life-expectancy (Flegal et al. 2005; Hu et al. 2004; Olshansky et al. 2005; Peeters et al. 2003). There is growing evidence that the association between obesity and fatal or non-fatal events is mediated via these other conditions and that isolated obesity may not be injurious to health. In the United States of America, around 29% of obese men and 45% of obese women (totalling 19.5 million individuals) do not have metabolic comorbid conditions (Wildman et al. 2008). They do not appear to be at increased risk of cardiovascular events (Wildman 2009), and it has been suggested that weight loss will not be beneficial and may even increase their risk of cardio-metabolic outcomes (Iacobellis et al. 2005; Sims 2001; Stefan et al. 2008; Velho et al. 2010; Wildman et al. 2008; Wildman 2009). This had led to the term “healthy obesity.”

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However, there is no standardized definition for categorizing an individual in this unique category of obesity. Generally, it is defined as the absence of cardio-metabolic disease such as type 2 diabetes, hypercholesterolemia and hypertension in an obese individual (Pataky et al. 2010). In addition, the

associations of cardio-metabolic risk factors and insulin sensitivity are also used to determine it, but different studies have used different cut-off value of these factors. The lack of a harmonized definition and standardized cut-off values have made the between studies comparison difficult (Van et al. 2014). The other factors such as age, sex, family history, and ethnicity can also influence the prevalence of healthy obesity (Velho et al. 2010). Consequently, due to the variation in definition and cut-off values, different studies have given different prevalence of "healthy obese", ranges from 6% (Kuk & Ardern 2009) to as high as 35% (Aguilar et al. 2008). To know the prevalence of healthy obesity, one recent study used a harmonized definition across the 10 cohort studies from 7 European countries, including the UK with a total of 163,517 participants (Van et al. 2014). The study revealed significant variations in the prevalence of healthy obesity in different cohorts even after the use of uniform definitions and cut-off values; from 7% to 28% among women, and 2% to 19% in men. Overall, the total of 3,387 (12%) obese participants had no metabolic comorbidity. The prevalence was significantly higher in woman than men. Among all the 10 cohorts, the prevalence decreases with increasing age.

The mechanisms that delay or protect obese people from developing comorbidties are not exactly known. Very recently a study which is published in "Cell" demonstrated the anti-inflammatory role of heme oxygenase-1 (HO-1) in the development of metabolic disease (Jais et al. 2014). HO-1 was the strong independent predictor of developing comorbidity in humans and its deletion in mice showed promising results of preventing the secondary diseases. This development could have important implications for the stratification of obesity with and without comorbidity, and may lead to the therapeutic role of HO-1 inhibition in obese individuals (Jais et al. 2014).

However, a recently published meta-analysis suggest that "healthy obese" is a "myth" as they are at significantly higher risk of developing CVD events and death on a longer follow-up (Kramer eta l 2013). The pooled estimate of the included studies showed that obese individuals with no metabolic comorbidity had 24% higher risk of developing CVD events and all-cause mortality on a ten year follow-up (RR 1.24, 95% CI 1.02, 1.55), compared to normal-weight individuals without metabolic comorbidity. The corresponding risk for unhealthy obese was also significantly higher (RR 2.65, 95% CI 2.18, 3.12). It is argued that

the “healthy” obese might have subclinical disease which could emerge with time (Hill & Wyatt 2013). It is also premature to claim that weight loss in not beneficial in healthy obese group, as to date there are very few studies to support this (Pataky et al. 2010). The lack of weight loss effect may be explained as; the cardio-metabolic and inflammatory parameters of healthy obese group are already in normal range.

Overall, obesity is associated with anxiety, depression and impaired HRQoL (Fontaine & Barofsky 2001; Jia & Lubetkin 2005; Kolotkin et al. 2001; Morrison et al. 2011). Previous research suggests that deterioration in HRQoL in overweight and obese individuals may be due to the presence of comorbidity (Doll et al. 2000). It is currently unknown whether isolated or “healthy” obesity is associated with HRQoL. In this study, I used data from a Scotland-wide survey to compare HRQoL across BMI categories in the presence and absence of metabolic comorbidity.

6.3 Material and methods

6.3.1 Data source

The SHeS has been conducted at regular intervals, of 3-5 years, since 1995. The Survey uses multi-stage, stratified probability sampling to ensure a representative sample of the general population. The trained staff collected data via face to face interview (including age, sex, postcode of residence, lifestyle risk factors, medication, past medical history and current health) and measured weight, height and blood pressure and obtained blood samples for assays (including total cholesterol concentrations) (http://www.esds.ac.uk/government/shes/). I used an extract of data from the 2003 Survey, the focus of which was CVD and risk factors.

6.3.2 Inclusion criteria and definitions

The analyses were restricted to participants aged ≥20 years and those included were categorised into three age groups: 20-44, 45-64 and ≥65 years. Postcode of residence was used to allocate individuals to a socioeconomic quintile of the general population using the 2004 SIMD (http://www.scotland.gov.uk/Publications/2005/01/20458/49127). The index is

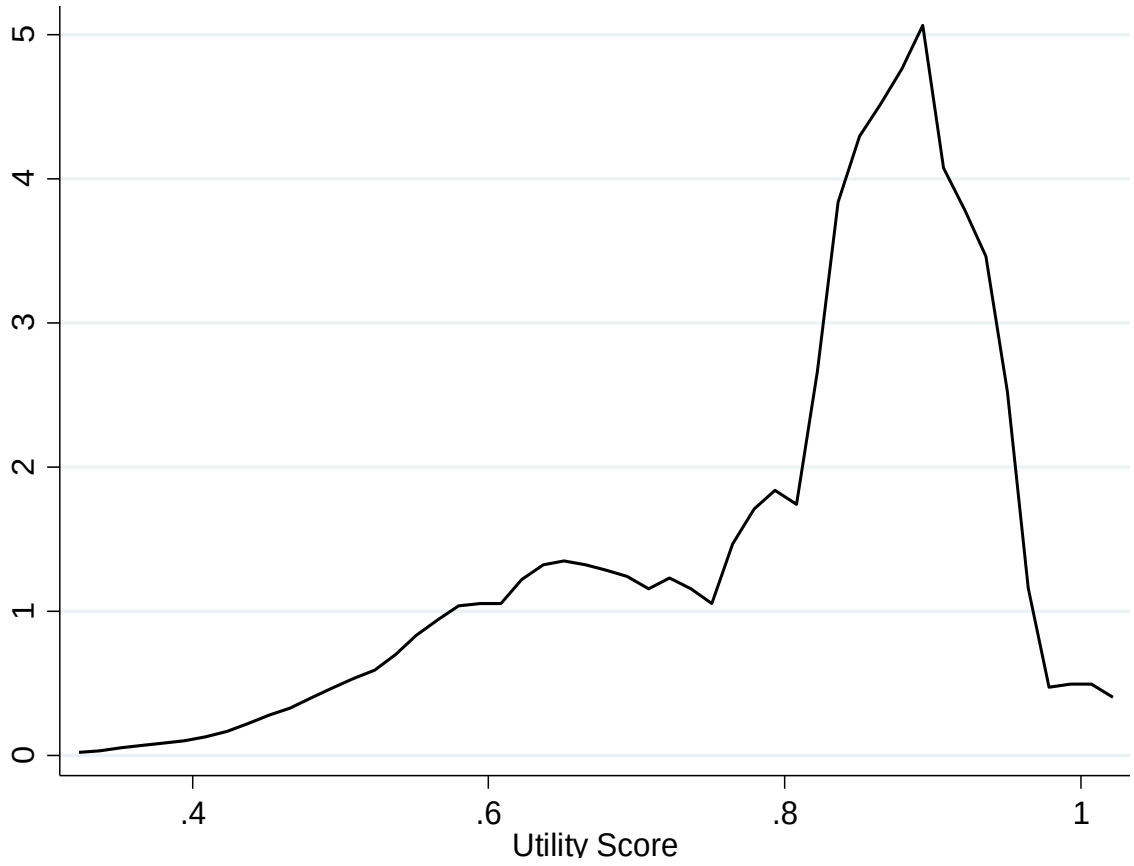
derived from 31 markers of deprivation relating to health, education, housing, current income, employment access and crime, that are applied to each postcode data zones. There are 6,505 data zones in Scotland with a mean population of 750. BMI was categorised according to the WHO (World Health Organization 2000): underweight (BMI <18.5 kg/m^2), normal weight (BMI 18.5-24.9 kg/m^2), overweight (BMI 25.0-29.9 40 kg/m^2), and obese (BMI 30.0-39.9 kg/m^2), with the addition of a category for morbidly obese (BMI ≥40 kg/m^2). Metabolic comorbidity was defined as the presence of one or more of the following conditions known to be associated with obesity: diabetes, hypertension, CVD or hypercholesterolemia. CVD was defined as angina or a past history of stroke or myocardial infarction and was based on participants reporting diagnosis by a doctor. Hypertension was defined as a blood pressure measurement of ≥140/90 mmHg, or anti-hypertensive medication. Hypercholesterolaemia was defined as a total cholesterol concentration ≥5.2mmol/L, or lipid-lowering medication. Diabetes was self-reported of doctor diagnosis or on blood glucose lowering agents. Smoking status was self-reported and classified as never, ex- or current smoker. Alcohol consumption was self-reported and categorised as never, ex-, sensible and excessive, with the cut-off between sensible and excessive drinking defined as more than 14 units/week for women and 21 units/week for men. The responses obtained from the SF-12 questionnaires were converted into a single utility score using an algorithm developed by Brazier and colleagues at the University of Sheffield (http://www.shef.ac.uk/scharr/sections/heds/mvh/sf-6d/revisions.html) (Brazier et al. 2002).

6.3.3 Statistical analyses

All statistical analyses were performed using Stata version 11.2 (Stata Corporation, College Station, Texas, USA). Categorical data were summarized using frequencies and percentages and groups were compared using chi-square tests, or chi-square tests for trend for ordinal data. I used univariate and multivariate linear regression models to examine the association between BMI category and utility score, adjusting for the potential confounding effects of age, sex, deprivation quintiles, smoking status and alcohol consumption. Normal weight was used as the referent category. I tested whether there were statistically significant interactions by applying likelihood ratio test between BMI

and both sex and metabolic comorbidity and stratified the analyses accordingly. The utility score was skewed, so the robustness of standard errors was checked using the bootstrapping method (Figure 6.1).

Figure 6.1 Kerned density plot of the utility score



6.4 Results

Of the 10,470 individuals who participated in the SHeS, 7,097 were aged ≥20 years. Of these 6,559 (92%) had sufficient data to calculate a utility score. Participants who completed the SF-12 instrument were not significantly different in terms of BMI category (p=0.225) and sex (p=0.197), but were younger (p<0.001), less socioeconomically deprived (p<0.001), and more likely to have metabolic comorbidity (p<0.001). Among the 6,559 participants with a utility score, 5,608 (86%) also had BMI recorded and they comprised the study population. These individuals were not significantly different in term of metabolic comorbidity (p=0.582) but were younger (p<0.001), more likely to be male (p<0.001) and less socioeconomically deprived (p=0.020).

Of the 5,608 individuals, 2,531 (45.1%) were men and the mean age was 50 years (standard deviation 16 years). Nine hundred and twenty one (16.4%) had metabolic comorbidity and the mean utility score was 0.80 (standard deviation 0.14). One thousand seven hundred and ninety seven (32.0%) were normal weight, 2,276 (40.6%) overweight, 1,319 (23.5%) obese, 149 (2.7%) morbidly obese, and 67 (1.2%) underweight. There were significant differences between the BMI categories in terms of age and sex (Table 6.1). The percentage belonging to the most deprived quintile increased significantly from normal weight to morbidly obese, as did the percentage with metabolic comorbidity (Table 6.1).

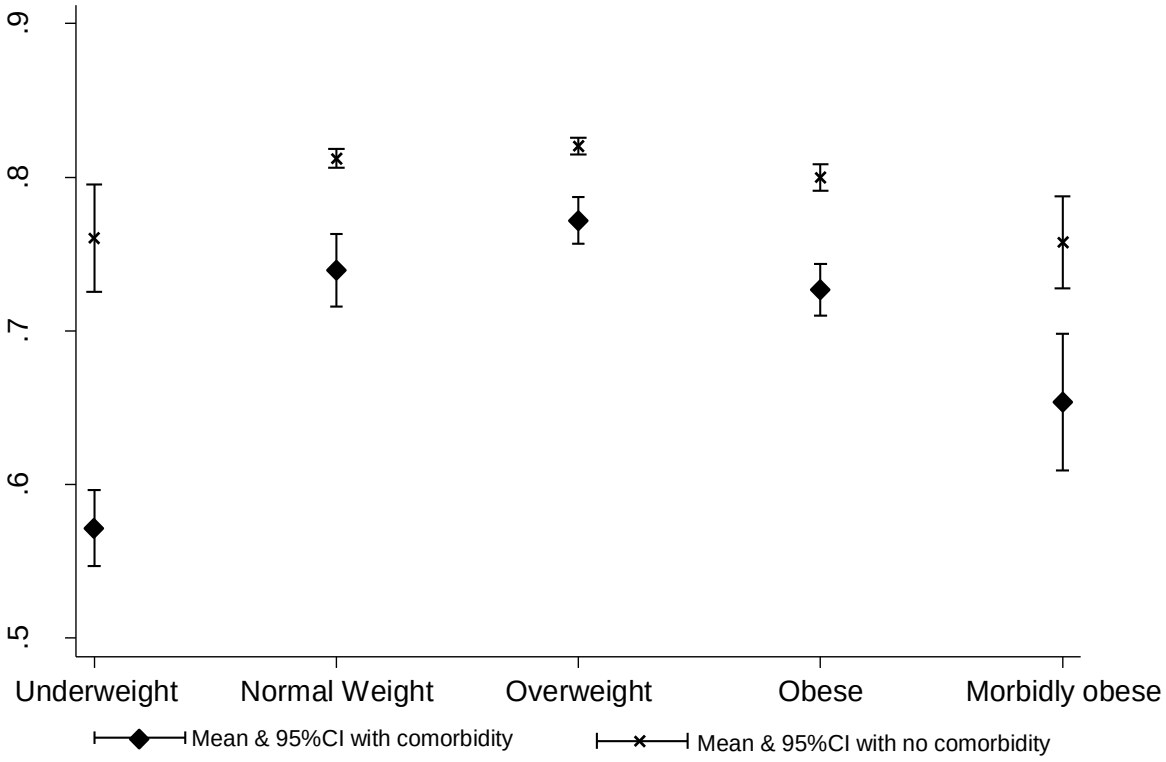
Table 6.1 Characteristics of participants by body mass index category

	Underweight N=67 N (%)	Normal-weight N=1,797 N (%)	Overweight N= 2,276 N (%)	Obese N=1,319 N (%)	Morbidly obese N=149 N (%)	p-value¶	Overall N= 5, 608 N (%)
Age (years)							
20-44	32 (47.8)	937 (52.1)	858 (37.7)	440 (33.4)	54 (36.2)	<0.001	2,321 (41.4)
45-64	21 (31.3)	562 (31.3)	916 (40.3)	549 (41.6)	75 (50.3)		2,123 (37.9)
≥65	14 (20.9)	298 (16.6)	502 (22.1)	330 (25.0)	20 (13.4)		1, 164 (20.8)
Sex							
Men	26 (38.8)	688 (38.3)	1,183 (52.0)	598 (45.3)	36 (24.2)	<0.001	2,531 (45.1)
Women	41 (61.2)	1,109 (61.7)	1,093 (48.0)	721 (54.7)	113 (75.8)		3,077 (54.9)
Deprivation quintile							
1	14 (20.9)	389 (21.7)	498 (21.9)	218 (16.5)	16 (10.7)	<0.001	1,135 (20.2)
2	11 (16.4)	413 (23.0)	537 (23.6)	258 (19.6)	30 (20.1)		1,249 (22.3)
3	9 (13.4)	385 (21.4)	503 (22.1)	337 (25.6)	29 (19.5)		1,263 (22.5)
4	14 (20.9)	322 (17.9)	427 (18.8)	276 (20.9)	26 (17.6)		1,065 (19.0)
5	19 (28.4)	288 (16.0)	311 (13.7)	230 (17.4)	48 (32.2)		896 (16.0)
Metabolic comorbidity							
No	59 (88.1)	1,632 (90.8)	1,899 (83.4)	990 (75.0)	107 (71.8)	<0.001	4,687 (83.6)
Yes	8 (12.0)	165 (9.2)	377 (16.6)	329 (25.0)	42 (28.2)		921 (16.4)
Smoking status							
Never	21 (31.3)	748 (41.6)	1, 002 (44.0)	599 (45.4)	60 (40.3)	<0.001	2, 430 (43.3)
Ex	7 (10.5)	409 (22.8)	737 (32.4)	447 (33.9)	56 (37.6)		1, 656 (29.5)
Current	39 (58.2)	640 (35.6)	537 (23.6)	273 (20.7)	33 (22.2)		1, 522 (27.1)
Drinking status							
Never	12 (17.9)	89 (5.0)	106 (4.7)	72 (5.5)	8 (5.4)	<0.001	287 (5.1)
Ex	5 (7.5)	83 (4.6)	85 (3.7)	62 (4.7)	14 (9.4)		249 (4.4)
Sensible*	39 (58.2)	1, 266 (70.5)	1, 560 (68.5)	936 (70.9)	100 (67.1)		3, 901 (69.5)
Excessive	11 (16.4)	352 (19.7)	522 (23.0)	246 (18.7)	27 (18.1)		1, 158 (20.7)
Missing	0 (0)	7 (0.39)	3 (0.13)	3 (0.23)	0 (0)		13 (0.23)

¶chi-square tests for trend, *< 21 units/week for men, <14 units /week for women , deprivation quintile; 1 least deprived; 5 most deprived

In relation to the association between BMI category and utility score, there was a significant interaction with metabolic comorbidity (p=0.007). In every BMI category, the utility score was lower among those with metabolic comorbidity (Figure 6.2). Among both individuals with and without metabolic comorbidity, there was an inverted U-shaped relationship whereby health utility was highest among overweight individuals and fell with increasing BMI, with the decline steepest among those with metabolic comorbidity (Figure 6.2). HRQoL was significantly reduced among obese individuals regardless of the presence or absence of metabolic comorbidity.

Figure 6.2 Mean utility score by body mass index category and presence of metabolic comorbidity (unadjusted).



After adjustment for the potential confounding effects of age, sex, deprivation smoking status and alcohol consumption, the utility score was not significantly higher among overweight than normal weight individuals, irrespective of the presence of metabolic comorbidity (Table 6.2). Compared with normal weight individuals, utility scores were significantly lower among both morbidly obese and underweight individuals in both groups (Table 6.2).

In the association between BMI category and utility score, there was also a significant interaction with sex ($p<0.001$). Being overweight was associated with significantly higher utility scores in men only. In contrast, being underweight and obese was associated with significantly lower utility score in women only (Figure 6.3).

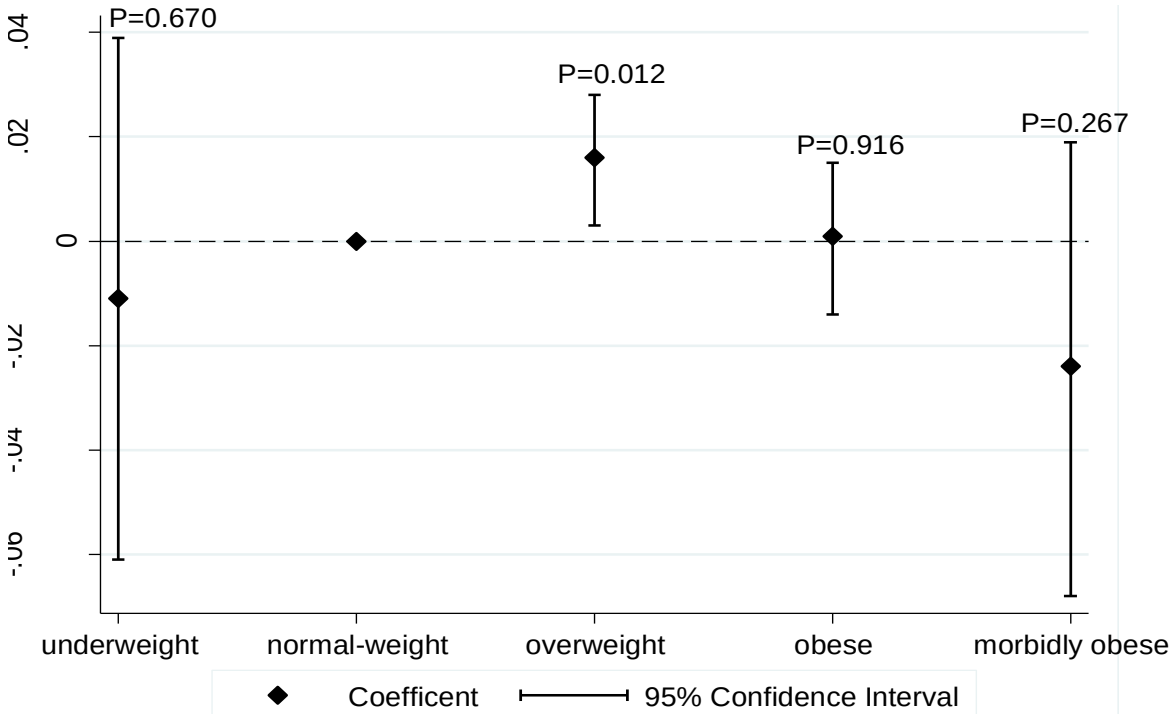
Table 6.2 Characteristics of studies examining the association between body mass index and health-related quality of life

		Univariate				Multivariate			
		No metabolic comorbidity		With metabolic comorbidity		No metabolic comorbidity		With metabolic comorbidity	
		Coefficient (95% CI)	*P*	Coefficient (95% CI)	*P*	Coefficient (95% CI)	*P*	Coefficient (95% CI)	*P*
BMI category	Underweight	-0.051 (-0.084, -0.018)	0.002	-0.167 (-0.275, -.059)	0.002	-0.036 (-0.069, -0.004)	0.027	-0.141 (-0.245, -0.037)	0.008
	Normal-weight*	-	-	-	-	-	-	-	-
	Overweight	0.008 (-0.000, 0.016)	0.059	0.032 (0.004, 0.060)	0.023	0.001 (-0.008, 0.009)	0.900	0.026 (-0.002, 0.053)	0.064
	Obese	-0.012 (-0.022, -0.002)	0.015	-0.012 (-0.041, 0.015)	0.380	-0.016 (-0.026, -0.006)	0.001	-0.015 (-0.043, 0.013)	0.290
	Morbidly obese	-0.054(-0.079, -0.029)	<0.001	-0.085 (-0.137, -0.034)	0.001	-0.045 (-0.069, -0.020)	<0.001	-0.077 (-0.128, -0.026)	0.003
Age (yrs)	20-44	0.002 (-0.005, 0.010)	0.500	0.001 (-0.036, 0.039)	0.924	0.005 (-0.002, 0.013)	0.190	0.007 (-0.030, 0.043)	0.714
	45-64	-	-	-	-	-	-	-	-
	≥65	-0.007 (-0.018, 0.003)	0.191	0.004 (-0.016, 0.025)	0.663	-0.009 (-0.020, 0.002)	0.106	0.004 (-0.017, 0.024)	0.718
Sex	Men*	-	-	-	-	-	-	-	-
	Women	-0.020 (-0.028, -0.013)	<0.001	-0.009 (-0.029, 0.010)	0.357	-0.020 (-0.027, -0.013)	<0. 001	-0.005 (-0.025, 0.015)	0.629
Deprivation quintiles									
	1	-	-	-	-	-	-	-	-
	2	-0.012 (-0.023, -0.001)	0.030	-0.016(-0.048, 0.015)	0.313	-0.008 (-0.019, 0.002)	0.132	-0.009 (-0.040, 0.021)	0.546
	3	-0.026 (-0.037, -0.015)	<0.001	-0.053(-0.085, -0.021)	0.001	-0.019 (-0.030, -0.008)	0.001	-0.036 (-0.068, -0.004)	0.027
	4	-0.036 (-0.047, -0.024)	<0.001	-0.070(-0.103, -0.038)	<0.001	-0.026 (-0.038, -0.015)	<0.001	-0.050 (-0.082, -0.017)	0.003
	5	-0.070 (-0.082, -0.058)	<0.001	-0.117(-0.150, -0.084)	<0.001	-0.052 (-0.064, -0.040)	<0.001	-0.084 (-0.117, -0.051)	<0.001
Smoking	Never smoker*	-	-	-	-	-	-	-	-
	Ex-smoker	-0.012 (-0.021, -0.004)	0.005	-0.031 (-0.053, -0.009)	0.006	-0.008 (-0.016, 0.001)	0.095	-0.031 (-0.053, -0.009)	0.006
	Current smoker	-0.051 (-0.060, -0.042)	<0.001	-0.085 (-0.113, -0.058)	<0.001	-0.041 (-0.050, -0.032)	<0.001	-0.067 (-0.095, -0.038)	<0.001
Drinking	Never*	-	-	-	-	-	-	-	-
	Ex	-0.058 (-0.083, -0.033)	<0.001	-0.066 (-0.118, -0.013)	0.014	-0.050 (-0.075, -0.026)	<0.001	-0.043 (-0.094, 0.008)	0.098
	Sensible¶	0.010 (-0.008, 0.028)	0.281	0.033 (-0.002, 0.069)	0.067	0.003 (-0.014, 0.021)	0.710	0.032 (-0.02, 0.067)	0.068
	Excessive	0.005 (-0.014, 0.024)	0.623	0.056 (0.015, 0.097)	0.007	-0.001 (-0.020, 0.018)	0.925	0.052 (0.010, 0.093)	0.014
	Missing	-0.059 (-0.136, 0.018)	0.133	0.029 (-0.186, 0.244)	0.793	-0.054 (-0.130, 0.021)	0.156	0.033 (-0.173, 0.239)	0.754

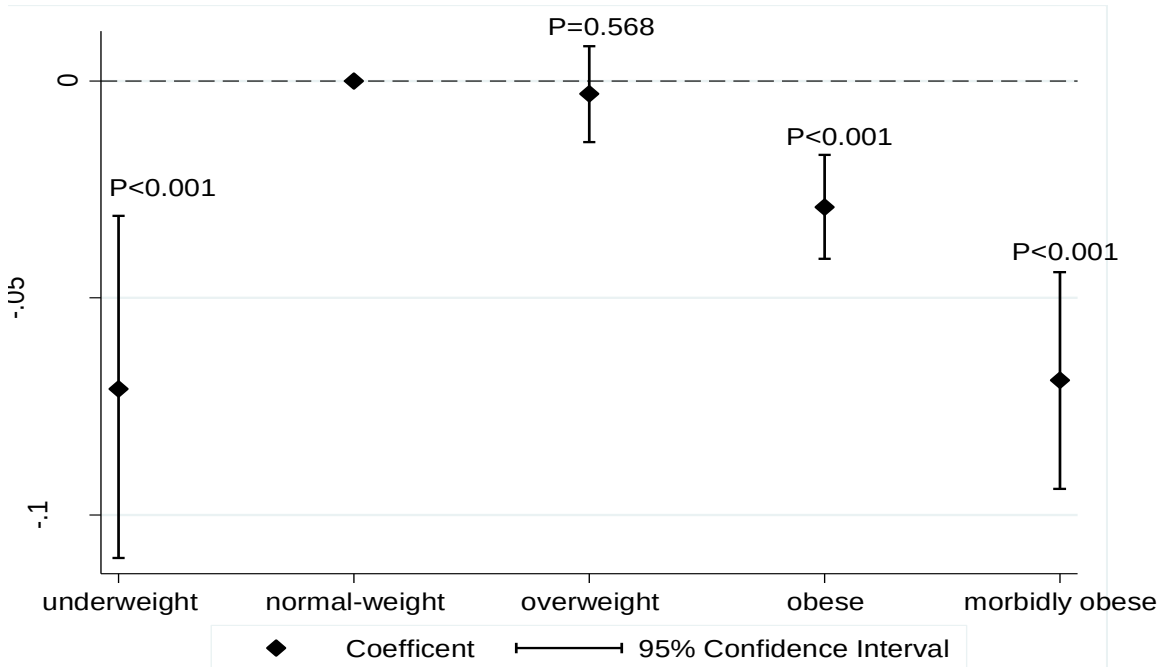
*Referent category, CI confidence interval, ¶<21 units/week for men, <14 units /week for women, deprivation quintiles 1 least deprived, 5 most deprived

Figure 6.3 Adjusted* coefficient for the association between utility score (overall HRQoL) and body mass index category by sex.

a. men



b. women



Utility score; SF-12 response *adjusted by age, deprivation quintile, comorbidity, smoking and drinking status.

6.5 Discussion

Overweight men had better overall HRQoL than normal-weight men whereas being underweight and obese is associated with significantly lower overall HRQoL in women only. Individuals with metabolic comorbidity have a poorer HRQoL than those without, irrespective of their BMI. However, HRQoL is significantly reduced among obese individuals even in the absence of metabolic comorbidity, suggesting that "healthy obesity" is a misnomer.

My findings are consistent with previous studies that have demonstrated reduced HRQoL among obese individuals (Castres et al. 2010; Fontaine & Barofsky 2001; Ford et al. 2001; Garcia-Mendizabal et al. 2009; Hassan et al. 2003; Hopman et al. 2007; Kolotkin et al. 2001; Yan et al. 2004). However, these studies have only considered obese individuals as a whole. Historically, normal weight was associated with the lowest risk of CVD and type II diabetes, and the highest HRQoL (Fontaine & Barofsky 2001; Friedman & Brownell 1995). This has changed over time, and my finding of significantly better overall HRQoL among overweight men is consistent with other recent studies (Bentley et al. 2011; Hopman et al. 2007; Lopez-Garcia et al. 2003; Vasiljevic et al. 2008). Previous studies have also shown poorer HRQoL among individuals with a low BMI (Hopman 2007; Sach et al. 2007; Wee et al. 2008). This is likely to be due, in part, to reverse causation due to conditions other than those that I included in my definition of metabolic comorbidity.

There is a growing consensus that the increased risk of cardiometabolic events associated with obesity is mediated, largely, via the increased risk of intermediate conditions such as hypertension, hypercholesterolemia and type II diabetes (World Health Organization 2000). A number of studies have identified a sub-group of obese individuals who do not develop these intermediate conditions (Wildman 2009). They are not at significantly increased risk of cardiometabolic events, and weight loss does not improve their natural history (Iacobellis et al 2005; Sims 2001; Stefa et al. 2008; Velho et al. 2010;Wildman et al. 2008; Wildman 2009). These findings have led to the label "healthy" obesity.

Health extends beyond clinical events, to encompass psychological well-being. A number of studies have shown that HRQoL is reduced among obese individuals

(Fontaine & Barofsky 2001; Friedman & Brownell 1995; Kushner & Foster 2000; Sarlio-Lahteenkorva et al. 1995). It was not previously known whether, as with clinical events, this risk was specific to obese individuals with metabolic comorbidity. This study demonstrated that, whilst HRQoL was lower among individuals with metabolic comorbidity, it was nonetheless significantly reduced among obese individuals with no metabolic comorbidity.

6.6 Strengths and limitations

The study used data from a large pan-Scotland survey that was representative of the general population. Due to incomplete data on BMI or utility score in 14% of participants, the study population was younger, more affluent and healthier than the overall survey population. However, this is unlikely to affect the generalisability of the results. Access to information on metabolic comorbidity enabled me to undertake sub-group analyses. BMI and blood pressure measurements were made by trained fieldworkers using standard operating procedures and the presence of hypercholesterolemia was based on blood assays. Presence of diabetes and CVD were based on clinician diagnosis but reported by participants. Since the study was conducted retrospectively, this is unlikely to have led to reporting bias, because certain information such as use of medications, current exposure to risk factors or the eliminated exposure factors may be recorded more accurately at the time of interview than a personal interview. In a cross-sectional study, a temporal relationship cannot be established. Therefore, reverse causation is possible. This is particularly so among individuals who are below normal weight in whom other conditions may be causing both poor HRQoL and weight loss. Survival bias may also occur in cross-sectional studies. These findings should be corroborated within the context of a cohort study.

6.7 Implications of this research

This study suggests that obesity is not only a risk for fatal and non-fatal clinical events but also reduced HRQoL, even in the absence of comorbid conditions. These findings cast doubt on the notion of “healthy” obesity and reinforce the need for population and individual interventions to reverse the higher prevalence of obesity.

In this Chapter I have shown that obesity is associated with reduced overall HRQoL. However, overall HRQoL covers physical and mental domains. The adverse impact of obesity on physical HRQoL is much clearer than before, as demonstrated in my two meta-analyses (Chapter 4 and 5). In contrast, the relationship between BMI and mental health is not well understood. There are inconsistencies in the existing evidence and whether the associations vary by sex, and there is a paucity of studies using the full spectrum of BMI. I am going to address these questions in the next Chapter (Chapter 7)

7 Chapter 7: Adiposity and mental health

Published in;

Ul-Haq Z, Mackay DF, Fenwick E, Pell JP (*2014)*. Association between body mass index and mental health among Scottish adult population: a cross-sectional study of 37,272 participants. *Psych Med 44,* 1-10.

7.1 Chapter summary

The evidence is conflicting as to whether BMI is associated with mental health and, if so, to what extent it varies by sex. I studied mental health across the full spectrum of BMI among the general population, and conducted subgroup analyses by sex.

I undertook a cross-sectional study of a representative sample of the Scottish adult population. The SHeS provided data on mental health, measured by the GHQ, BMI, demographic and lifestyle information. Good mental health was defined as a GHQ score <4, and poor mental health as a GHQ score ≥4. Logistic regression models were applied.

Of the 37,272 participants, 5,739 (15.4%) had poor mental health. Overall, overweight participants had better mental health than the normal-weight group (adjusted OR 0.93, 95% CI 0.87, 0.99, p=0.049), and individuals who were underweight, class II or class III obese had poorer mental health (class III obese group: adjusted OR 1.26, 95% CI 1.05, 1.51, p=0.013). There were significant interactions between BMI and sex (p=0.013). Being overweight was associated with significantly better mental health in men only. In contrast, being underweight and obese was associated with significantly poorer mental health in women only.

The adverse associations between adiposity and mental health are specific to women. Underweight women who are obese have poorer mental health. In contrast, overweight men have better mental health.

7.2 Introduction

There is a higher prevalence of both obesity and depression in the UK (Low et al. 2009; Olfson & Marcus 2009; Reid & Barbui 2010; Rennie & Jebb 2005). In Scotland, 28% of adults are obese, and a further 36% are overweight (Keenan et al. 2011). Around one in six adults in the United Kingdom experience common mental disorders (Adult psychiatric morbidity in England 2009). More than 50% of these have mixed depression and anxiety disorder, and one in three has generalised anxiety disorder or depression. According to the WHO "there is no health without mental health" (World Health Organization 2013).

Both overweight and obesity predispose to a number of physical conditions, including CVD (Lavie et al. 2009; Wannamethee et al. 2005), type II diabetes (Mokdad et al. 2003), hypertension (Jarvinen et al. 2007), musculoskeletal diseases (Janke et al. 2007; Lohmander et al. 2009), and many cancers (Renehan et al. 2008). All-cause mortality is higher among classes II and III obese individuals but reduced among adults who are overweight (Flegal et al. 2013). Increased BMI has also been shown to be associated with reduced overall HRQoL (Chapters 4, 5 & 6; Ul-Haq Z et al. 2012; Ul-Haq Z et al. 2013b; Ul-Haq Z et al. 2013c). However, overall HRQoL covers different domains; physical and mental. The adverse impact of increased BMI on physical HRQoL is now relatively clear, as demonstrated in my meta-analyses (Chapter 4; Ul-Haq, Z et al. 2013b; Chapter 5 Ul-Haq, Z et al. 2013c). In contrast, the relationship between BMI and mental health remains inconclusive. Some studies have reported that increased BMI is associated with poor mental health (Baumeister & Harter 2007; Luppino et al. 2010; Ohayon 2007; Petry et al. 2008; Strine et al. 2008), whereas others have reported no association or a protective role (Crisp & McGuiness 1976; Goldney et al. 2009; Jorm et al. 2003; Palinkas et al. 1996).

In Chapter 4, I conducted a meta-analysis of the association between BMI and HRQoL, assessed using the SF-36, among adults (Chapter 4; Ul-Haq, Z 2013b). The pooled estimate for the mental health component of SF-36 demonstrated significantly reduced mental HRQoL among class III obese individuals and increased mental HRQoL among overweight adults. However, many of the individual studies included in the meta-analysis had not been adjusted for potential confounders, such as socio-economic status, marital status, smoking

and alcohol consumption. Also, many population based studies could not be included in the meta-analysis because they categorised BMI into two groups only: obese (≥30 kg/m^2) and non-obese (<30 kg/m^2), rather than examining the relationship across the whole range from underweight to class III obese. Underweight, in particular, has been associated with poor mental health, and it has been highlighted that it should be included as a separate category but, as yet, very few studies have done so (Mond et al. 2011). In addition to the conflicting findings in relation to the overall association between BMI and mental health, there is also a lack of consensus on whether the relationship varies by sex. Studies commonly do not test or report interactions. Some studies have reported no significant interaction with sex and, in those that have, the direction of effect has not been consistent (McCrea et al. 2012). For instance, one recent study found significant association between BMI and poor mental health among women (Brandheim et al. 2013). In contrast, others have reported significant associations among men (Carroll et al. 2010; Rosmond & Bjorntorp 2000).

In summary, there are inconsistencies in the existing evidence in relation to the overall associations between BMI and mental health, and whether the associations vary by sex, and there is a paucity of studies using the full spectrum of BMI. In this study I investigate the relationship between BMI (across its whole range) and mental health (measured using the GHQ-12), and whether it varies by sex among a representative sample of Scottish adults, after adjustment for a range of potential confounding factors.

7.3 Material and methods

7.3.1 Data source

The SHeS was undertaken periodically in 1995, 1998 and 2003, and annually from 2008 (http://www.scotland.gov.uk/Topics/Statistics/Browse/Health/scottish-health-survey). Each survey recruited a representative sample of the Scottish general population from different households. Different samples were drawn for each survey using identical methodology. Household response rate was 81% in 1995, 76% in 1998, 68% in 2003, and 61-64% in SHeS 2008-2010. For the current study, I combined data from the six surveys conducted up to, and including, 2010. Participants under 16 years of age were excluded from the study. As part of the surveys, face to face interviews were conducted in participants' homes to collect information on demographics (including age, sex, marital status and postcode of residence) and health-related behaviours (including smoking status and alcohol consumption), as well as measurements (including height and weight). Participants were asked to complete a GHQ-12. During a second visit, a survey nurse collected self-reported information on diagnosis, by a doctor, of medical conditions (including diabetes, hypertension, CHD, CVD, musculoskeletal diseases and cancer) and obtained urine, saliva and blood samples for biochemical analyses.

7.3.2 Definitions

Age was categorised into four groups: 16-29, 30-44, 45-59, and ≥60 years. BMI was categorised into underweight (<18.5 kg/m^2), normal weight (18.5-24.9 kg/m^2), overweight (25-29.9 kg/m^2), class I obese (30-34.9 kg/m^2), class II obese (35-39.9 kg/m^2), and class III obese (>40 kg/m^2) (World Health Organization 1995). Hypertension was defined as greater than >140/90 mmHg or administration of anti-hypertensive therapy. Medical comorbidity was defined as the presence of one or more of the following conditions: diabetes, hypertension, CHD (angina or myocardial infarction), CVD (CHD or stroke), musculoskeletal disease or cancer. Smoking status was categorized as never-smoker, ex-smoker or current smoker. Alcohol consumption was classified as never-drinker, ex-drinker, drinker within limits (<21 units/week for men; <14 units/week for women) or excessive-drinker. Marital status was categorized as married,

cohabitees, single/never married, married but living separate, divorced or widowed. GHQ-12 is a validated and widely-used measure of mental health suitable for use in the general population (Goldberg et al.1997). The 12 questions ask about relevant experiences over the previous few weeks (including sleep disturbance, feelings of tension, anxiety, stress, depression, lack of confidence and failure to cope). The responses to each question are summated producing an overall score ranging from 0 to 12. Good mental health was defined as a GHQ-12 score <4 and poor mental health as a score ≥4 (Goldberg et al. 1998). This definition has been validated, and is strongly linked with different mental health disorders such as anxiety and depression (Aalto et al. 2012; Holi et al. 2003). Scotland is divided into 6,505 datazones using postcode of residence; each contains around 350 households and has a mean population of 800. The SIMD for each datazone is constructed using information on seven domains: income, employment, health, education (including skills and training), housing, crime, and access to services. The SIMD is used to derive quintiles of socioeconomic status for the Scottish population; ranging from 1 (most deprived) to 5 (least deprived) (http://www.scotland.gov.uk/Topics/Statistics/SIMD).

7.3.3 Statistical analyses

Differences in the characteristics of participants by BMI category were analysed using the x^2 test for categorical data and x^2 test for trend for ordinal data. I examined the association between BMI category and mental health using univariate and multivariate logistic regression models with adjustment for age, sex, deprivation quintile, presence of medical comorbidity, marital status, study year, smoking status and alcohol consumption. I tested whether there were statistically significant interactions by applying likelihood ratio test between BMI and sex, conducting sub-group analyses accordingly. All statistical analyses were performed using Stata version 12.1 (StataCorp, College Station, Texas). Statistical significance was defined as $p<0.05$.

7.4 Results

Of the 37,272 participants, 530 (1.4%) were underweight, 13,176 (35.4%) normal-weight, 14,161 (38%) overweight, 6,560 (17.6%) class I obese, 2,060 (5.5%) class II obese, and 785 (2.1%) class III obese. Overall, the mean age was 47 years (standard deviation 16 years), 16,727 (44.9%) were men, 4,673 (12.5%) had at least one medical comorbidity, 11,010 (29.5%) were current smokers and 8,233 (22.1%) drank excessively. All of these characteristics varied significantly by BMI category (Table 7.1). There were no statistically significant differences in participant demographic characteristics between individual surveys.

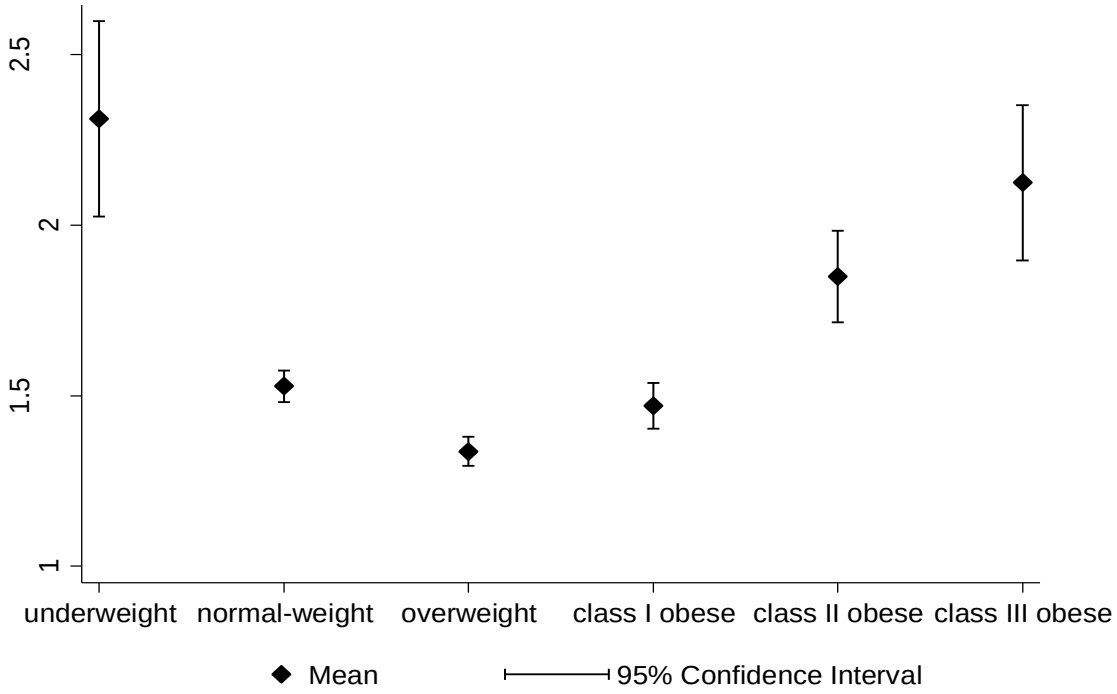
Overall, 5,739 (15.4%) participants had poor mental health (GHQ≥4) but the prevalence differed significantly by BMI category. It was lowest (13.6%) among overweight participants and highest among the underweight (25.3%) and class III obese (23.3%) groups (Table 7.1). There was also a U-shaped relationship between BMI category and mean GHQ-12 score (Figure 7.1). The percentage with poor mental health varied significantly by sex (12.8% of men versus 17.6% of women, $p<0.001$).

Table 7.1 Characteristics of the participants by body mass index category

	Underweight	Normal-weight	Overweight	Class I Obese	Class II Obese	Class III Obese	‡*P*-value
	N = 530 N (%)	N = 13176 N (%)	N = 14161 N (%)	N = 6560 N (%)	N = 2060 N (%)	N = 785 N (%)	
Mental health							
Good	396 (74.7)	11078 (84.1)	12237(86.4)	5563 (84.8)	1657 (80.4)	602 (76.7)	<0.001
Poor	134 (25.3)	2098 (15.9)	1924 (13.6)	997 (15.2)	403 (19.6)	183 (23.3)	
Age (Years)							
16-29	231 (43.6)	3578 (27.1)	1 749 (12.4)	619 (9.5)	213 (10.3)	80 (10.2)	<0.001
30-44	113 (21.3)	4280 (32.5)	3972 (28.1)	1648 (25.1)	545 (26.5)	228 (29.0)	
45-59	84 (15.9)	2940 (22.3)	4280 (30.2)	2031 (31.0)	642 (31.2)	288 (36.7)	
≥60	102 (19.3)	2378 (18.1)	4160 (29.4)	2262 (34.4)	660 (32.1)	189 (24.1)	
Sex							
Men	173 (32.6)	5190 (39.4)	7277 (51.4)	3180 (48.5)	731 (35.5)	176 (22.4)	<0.001
Women	357 (67.4)	7986 (60.6)	6884 (48.6)	3380 (51.5)	1329 (64.6)	609 (77.6)	
Deprivation quintile							
1	150 (28.3)	2520 (19.1)	2542 (18.0)	1267 (19.3)	472 (22.9)	201 (25.6)	<0.001
2	101 (19.1)	2657 (20.1)	2808 (19.8)	1322 (20.2)	452 (21.9)	164 (20.9)	
3	97 (18.3)	2656 (20.2)	3108 (20.0)	1510 (23.0)	453 (22.0)	174 (22.2)	
4	92 (17.4)	2704 (20.5)	3000 (21.2)	1368 (20.9)	424 (20.6)	158 (20.1)	
5	90 (17.0)	2639 (20.0)	2703 (19.1)	1093 (16.7)	259 (12.6)	88 (11.2)	
Smoking status							
Never	199 (37.6)	5726 (43.5)	6224 (44.0)	2899 (44.2)	959 (46.7)	372 (47.4)	<0.001
Ex	43 (8.1)	2602 (19.8)	4223(29.8)	2112 (32.2)	662 (32.1)	241 (30.7)	
Current	288 (54.3)	4848 (36.8)	3714 (26.2)	1549 (23.6)	439 (21.3)	172 (22.0)	
Drinking status							
Never	68 (12.8)	686 (5.2)	638 (4.5)	376 (5.7)	146 (7.1)	56 (7.1)	<0.001
Ex	45 (8.5)	591 (4.5)	682 (4.8)	412 (6.3)	149 (7.2)	73 (9.3)	
Sensible*	333 (62.8)	8921 (67.7)	9467 (66.9)	4426 (67.4)	1410 (68.4)	560 (71.3)	
Excessive	84 (15.9)	2978 (22.6)	3374 (23.9)	1346 (20.6)	355 (17.2)	96 (12.2)	
Medical comorbidity							
No	482 (90.9)	12416 (94.3)	12397 (87.7)	5262 (80.3)	1509 73.3)	533 (68.0)	<0.001
Yes	48 (9.0)	760 (5.7)	1764 (12.4)	1298 (19.8)	551 (26.7)	252 (32.0)	
Marital status							
Married	146 (27.6)	5969 (45.3)	8563 (60.5)	3926 (59.9)	1208 (58.6)	395 (50.3)	<0.001
Cohabitees	34 (6.4)	1007 (7.6)	947 (6.7)	420 (6.4)	137 (6.7)	51 (6.5)	
Single	245 (46.2)	3909 (29.7)	2188 (15.5)	956 (14.6)	311 (15.1)	157 (20.0)	
Separated	27 (5.1)	571 (4.3)	492 (3.5)	260 (4.0)	63 (3.1)	43 (5.5)	
Divorced	35 (6.6)	939 (7.1)	922 (6.5)	413 (6.3)	162 (7.9)	81 (10.3)	
Widowed	43 (8.1)	778 (5.9)	1047 (7.4)	584 (8.9)	179 (8.7)	58 (7.4)	

GHQ; General Health Questionnaire-12 score; ‡P-value; chi-square tests; *<21 units/week for men, <14 units /week for women; Deprivation quintile: 1 most deprived, 5 least deprived

Figure 7.1 Mean GHQ-12 score by body mass index category



On univariate logistic regression analysis, there was a significant association between BMI category and poor mental health (p<0.001). After adjusting for the potential confounding effects of age, sex, deprivation quintile, medical comorbidity, marital status, smoking and drinking status, the overall association remained statistically significant (p<0.001). Specifically, overweight participants had significantly reduced odds of having poor mental health in comparison with normal-weight participants, whilst individuals who were underweight, class II or class III obese had significantly increased odds of having poor mental health (Table 7.2).

There were significant interactions of BMI with sex (p=0.013). When the overall interaction term was disaggregated I observed that it was mainly driven by overweight, possibly due, in part, to larger numbers in this sub-group. The sex differences in underweight and class I obesity were also statistically significant. The sex difference in class II and class III obese were in the same direction as class I obese but failed to reach statistical significance, possibly due to smaller numbers in these sub-groups; OR (95% CI); underweight*female 1.77 (1.10, 2.85, p=0.018), overweight*female 1.24 (1.08, 1.42, p=0.002), class I obese*female 1.18 (1.00, 1.40, p=0.052), class II obese*female 1.24 (0.96, 1.60, p=0.104), and class III obese*female 1.05 (0.69, 1.61, p=0.823), compared to the sex difference in the normal-weight group.

The sub-group analyses by sex demonstrated that overweight men had a significantly lower risk of poor mental health than men of normal-weight (adjusted OR 0.85, 95% CI 0.75, 0.95, p=0.004) (Figure 7.2). The overall increased risk of poor mental health among class III obese individuals did not reach statistical significance in men (adjusted OR 1.25, 95% CI 0.84, 1.86, p=0.277).

In contrast, overweight women did not differ significantly from normal-weight women (adjusted OR 1.01, 95% CI 0.93, 1.11, p=0.778), while underweight, class II and class III obese women had a significantly higher risk of poor mental health (class III obese women relative to normal weight women: adjusted OR 1.37, 95% CI 1.11, 1.68, p=0.003) (Figure 7.2).

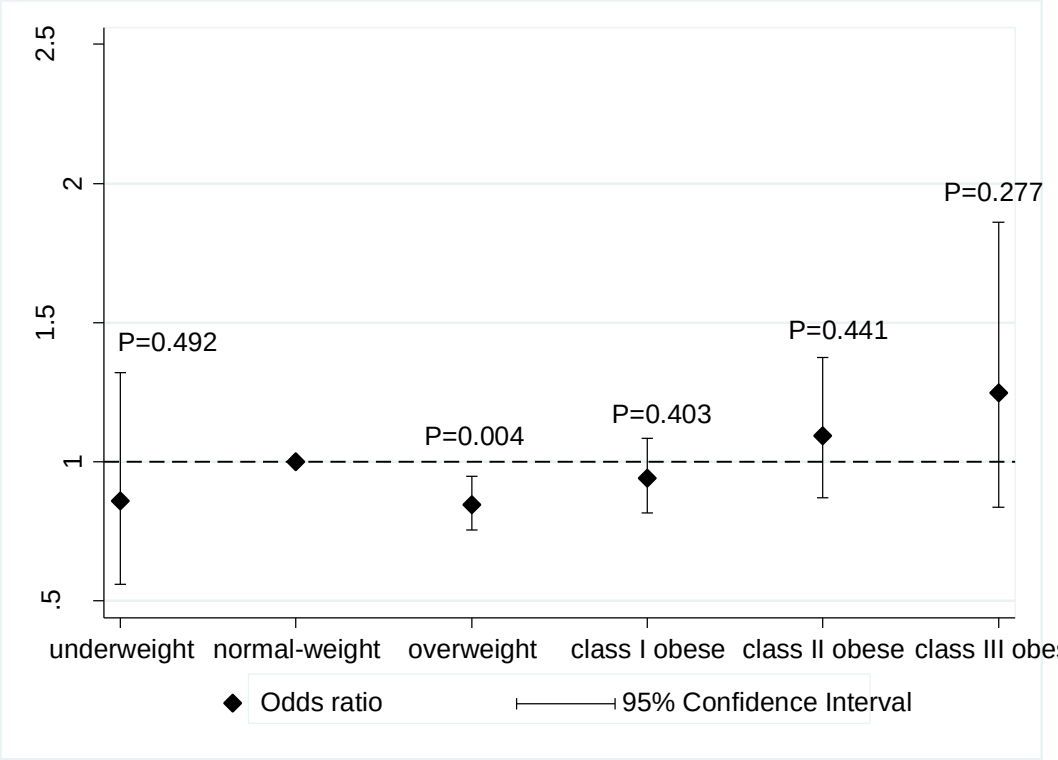
Table 7.2 Multiple logistic regression analysis of the participant characteristics associated with having poor mental health (GHQ≥4)

		Univariate		Multivariate	
		Odds ratio (95% CI)	P-value	Odds ratio (95% CI)	P-value
BMI category	Underweight	1.79 (1.46, 2.19)	<0.001	1.46 (1.18, 1.80)	<0.001
	Normal-weight	1	-	1	-
	Overweight	0.83 (0.78, 0.89)	<0.001	0.93 (0.87, 0.99)	0.049
	Class I Obese	0.95 (0.87, 1.03)	0.187	0.99 (0.92, 1.09)	0.984
	Class II Obese	1.29 (1.14, 1.45)	<0.001	1.22 (1.07, 1.38)	0.002
	Class III Obese	1.61 (1.35, 1.91)	<0.001	1.26 (1.05, 1.51)	0.013
Age (years)	16-29	1	-	1	-
	30-44	1.07 (0.99, 1.17)	0.098	1.12 (1.02, 1.23)	0.017
	45-59	1.13 (1.04, 1.23)	0.004	1.07 (0.96, 1.18)	0.214
	≥60	0.76 (0.69, 0.83)	<0.001	0.57 (0.50, 0.64)	<0.001
Sex	Men	1	-	1	-
	Women	1.46 (1.37, 1.54)	<0.001	1.41 (1.32, 1.49)	<0.001
SIMD	1(Most deprived)	1	-	1	-
	2	0.72 (0.66, 0.78)	<0.001	0.81 (0.75, 0.89)	<0.001
	3	0.64 (0.59, 0.70)	<0.001	0.76 (0.70, 0.83)	<0.001
	4	0.54 (0.49, 0.59)	<0.001	0.68 (0.62, 0.75)	<0.001
	5(Least deprived)	0.61 (0.56 0.67)	<0.001	0.79 (0.72, 0.87)	<0.001
Smoking status	Never smoker	1	-	1	-
	Ex-smoker	1.03 (0.95, 1.11)	0.468	1.03 (0.95, 1.11)	0.489
	Current smoker	1.94 (1.82, 2.07)	<0.001	1.63 (1.52, 1.74)	<0.001
Drinking status	Never drinker	1	-	1	-
	Ex-drinker	1.77 (1.51, 2.06)	<0.001	1.56 (1.33, 1.84)	<0.001
	Within limits*	0.81 (0.72, 0.92)	0.001	0.84 (0.74, 0.95)	0.008
	Excessive drinker	0.91 (0.80, 1.04)	0.165	0.95 (0.82, 1.09)	0.435
Comorbidity	No	1	-	1	-
	Yes	1.99 (1.85, 2.14)	<0.001	2.49 (2.28, 2.72)	<0.001
Marital status	Married	1	-	1	-
	Cohabitees	1.28 (1.14, 1.44)	<0.001	1.12 (0.99, 1.26)	0.070
	Single	1.50 (1.39, 1.61)	<0.001	1.34 (1.23, 1.46)	<0.001
	Separated	2.92 (2.59, 3.30)	<0.001	2.27 (2.0, 2.58)	<0.001
	Divorced	2.35 (2.13, 2.60)	<0.001	1.81 (1.63, 2.0)	<0.001
	Widowed	1.70 (1.53, 1.88)	<0.001	1.68 (1.49, 1.89)	<0.001

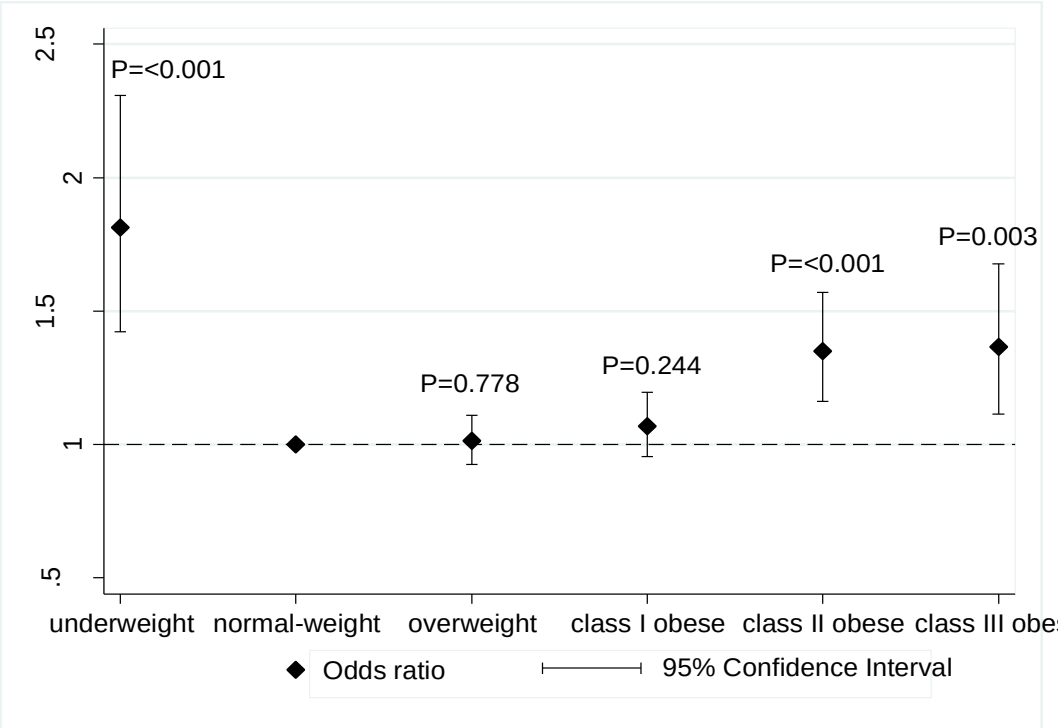
GHQ: General health questionnaire 12, CI; confidence interval, BMI; body mass index *<21 units/week for men, <14 units /week for women.

Figure 7.2 Adjusted* odds ratio for the association between poor mental health and body mass index category by sex.

a. men



b. women



GHQ: General health questionnaire-12; *adjusted by age, deprivation quintile, medical comorbidity, marital status, survey year, smoking and drinking status.

7.5 Discussion

Overall, compared with normal weight individuals, overweight participants were significantly less likely to have poor mental health, and those who were underweight or severely obese were significantly more likely to have poor mental health, even after adjustment for potential confounders. However, the relationship between BMI and mental health varied by sex. The protective role of overweight was confined to men. There was no evidence of a protective effect among women. Furthermore, neither underweight nor obesity was associated with poor mental health in men. In contrast, underweight and obese women had higher risk of poor mental health, compared to normal-weight women.

There is now a substantial body of evidence suggesting an adverse effect of both overweight and obesity on physical HRQoL with a dose-relationship (Chapters 4, 5 & 6; Ul-Haq, Z et al. 2012; Ul-Haq, Z et al. 2013b; Ul-Haq, Z et al. 2013c). In contrast, the published evidence is conflicting in relation to the association between BMI and mental health. A meta-analysis, conducted in 1995, found no association between obesity and depression in adults (Friedman & Brownell 1995a). In 2010, Wit et al published a meta-analysis of 17 population studies comprising a total of 204,507 participants (de wit et al. 2010). The majority of the included studies used self-reported BMI dichotomised into obese (≥30 kg/m^2) and non-obese (<30 kg/m^2). None used the GHQ as an indicator of mental health and none were conducted in United Kingdom. The meta-analysis reported a significant overall association between obesity and depression (pooled OR 1.18, 95% CI 1.01, 1.37). On sub-group analysis, the association was statistically significant among women (pooled OR 1.31, 95% CI 1.27, 1.40) but not men (pooled OR 1.12, 95% CI 0.96, 1.30).

In Chapters 4 and 5, I conducted two meta-analyses of the association between BMI and HRQoL; one in children and adolescents (Chapter 4; Ul-Haq Z et al. 2013c), and the other in adults (Chapter 5; Ul-Haq, Z et al. 2013b). The meta-analysis of children and adolescents used the PedsQL, and demonstrated that physical HRQoL was significantly reduced in both overweight and obese children but mental HRQoL was only impaired in obese children. The meta-analysis of adults used the SF-36 index, and demonstrated that there was an inverse dose-

response relationship with physical HRQoL across the BMI categories from normal weight to obese. In contrast, mental HRQoL was significantly reduced only in class III obese adults and was increased in overweight adults. The overall results of this current study corroborate these findings, using a different measure of mental health, and suggest that the relationship cannot be explained by confounding since the associations persisted after statistical adjustment.

This current study demonstrated a significant interaction with sex; such that obesity impacts adversely on mental health among women but not men. This finding is consistent with some previous individual studies (Palinkas et al. 1996; Scott et al. 2008). Whilst both men and women compare their bodies with the "ideal," women are more likely to feel dissatisfied with their bodies (Sheldon 2010). The female body has more socio-cultural importance than the male body, and women report feeling greater external pressure to conform to media-portrayed ideals (Cattarin & Thompson 1994; Connor-Greene 1998; Harrison & Cantor 1997; Sheldon 2010).

I found a significant dose-response relationship with poor mental health across classes I, II and III obese women (adjusted ORs 1.20, 1.38 and 1.63 respectively) (Table 7.3). Similarly, McCrea *et al* recently reported that there was a linear relationship between level of obesity and common mental disorder; classes I and class II obese had adjusted odd ratios for common mental disorder of 1.38 and 1.40 respectively (McCrea et al. 2012). A recent Swedish study of 68,000 adults from the general population reported a significant linear relationship with poor mental health (based on GHQ 12) among classes I and II obese women (ORs 2.58 and 2.71 respectively). Another larger study based on the World Mental Health Survey conducted in 13 different countries found a significantly higher risk among obese women but not men (Scott et al. 2008, Heo et al. 2006). Conversely, other studies have reported no significant interactions with sex (Morris et al. 2010, Scott et al. 2008) in relation to the association between BMI and mental health.

In the current study overweight participants had better mental health than normal-weight participants but, on further scrutiny, the association was confined to men. This corroborates previous studies on the association between body weight and subjective well-being (Linna et al. 2013). The overall finding of

improved mental health among overweight people is consistent with my previous studies in Chapters 4 and 6. A study conducted in Goteborg, Sweden, exclusively on middle aged men, reported that overweight participants had better psychosocial health but worse physical health than normal-weight (Rosmond & Bjorntorp 2000).

There is evidence that some overweight people may underestimate their BMI and classify themselves as normal weight (Krul et al. 2011; Madrigal et al. 2000). Also, it is possible that as the BMI distribution in the general population has shifted to the right over time, people's belief as to what constitutes "normal" weight has changed. In this obesogenic environment maintaining a healthy weight might be stressful, and thus mental health may be better in overweight men. BMI is a poor measure of adiposity in individuals with a high muscle mass and some men in the overweight category may have a low lean body mass. Whereas women feel pressure to reduce weight, men are more likely to feel pressure to increase their BMI, by increasing their muscle mass (Harrison & Cantor 1997; Sheldon 2010). There is also growing evidence that being overweight may not, necessarily, be associated with reduced mortality compared to normal-weight individuals (Flegal et al.2013).

In this study, being underweight was associated with significantly poorer mental health overall, but the sub-group analysis showed that this relationship was driven by women, and was not significant in men. The majority of previous studies have focused on the association between increased BMI and mental health, and either excluded underweight individuals or included them in the normal-weight category (Mond et al. 2011). These findings support a U-shaped association between BMI and poor mental health, even after controlling for potential confounders, particularly in women (de Wit et al. 2009). My findings highlight the importance of studying the full-spectrum of BMI, as merging or excluding the underweight category might not only increase the risk of weakening the association between BMI and mental health but also missing the valuable information associated with being underweight. Mond *et al* recently reported that underweight women had significantly reduced mental health compared to normal-weight women (Mond et al. 2011). They have further shown that this association was not because of increased body dissatisfaction or eating

disorders, and argued that the notion of “underweight associated with body dissatisfaction or eating disorders” is not supported by enough evidence.

7.6 Strengths and limitations

This study examined the association with mental health across the full spectrum of BMI categories in a large, nationally representative sample of adults in the general population, taking account of obvious confounders such as age, sex, deprivation, smoking status, drinking status, marital status and medical comorbidity. Many of the published studies have not reported appropriately adjusted results. Where statistical adjustment has been undertaken, it has usually been restricted to only age and sex. Most previous studies have examined overall associations only. I tested for interactions with sex, demonstrating differences in the relationship between BMI and mental health between men and women. The SHeS is a large, representative sample of the Scottish population. Height, weight and blood pressure were measured by trained staff using standard operating procedures. BMI is a poor measure of adiposity in individuals with a high muscle mass. Presence of medical comorbidity was self-reported but based on physician diagnoses. Availability of various potential confounders including demographic data, deprivation, smoking and drinking status, marital status and medical comorbidity enabled me to do the adjustment and subgroup analysis. The GHQ-12 is the most widely-used measure of mental health in UK. It is intended and validated for adults aged 16 years and above in both clinical and general population (Goldberg et al. 1997). Notable limitations of the study include the use of cross-sectional data with BMI and recent experiences of mental health recorded at the same time and, thus it is impossible to detect causation. There is possibility of reverse causation that poor mental health might lead to increased weight among women. Over the course of clinical treatment, a psychotropic drug may cause 2-17 kg increase in body weight (Nihalani et al. 2011). These findings should be confirmed within the context of a cohort study. GHQ is a short screening tool, not a detailed assessment of mental health. There were fewer people in underweight and class III obese category compared to the other BMI groups, so my statistical power to detect differences in these groups is less. Furthermore, I have adjusted my analysis for several confounders but there is always a possibility of unobserved heterogeneity. Further research is needed to look for the incidence of BMI

related diseases in overweight participants who have better mental health and vice versa.

7.7 Implications of this research

Having a BMI well above normal values is associated with significantly poorer mental health in women only. Being underweight is associated with poor mental health among women, but not men. Conversely, the apparently protective role of overweight was confined to men only, and was not significant in women. This study further supports the need to consider sex variation and use the full spectrum of BMI (from underweight to class III obese) in future studies of BMI and mental health. These findings suggest that health care providers should be aware that obese and underweight women are more likely to suffer poor mental health and may require intervention.

In this Chapter, I focused on the association between adiposity and mental health. However, I used GHQ as a measure of mental health which is a short screening tool, not a detailed assessment of mental health. There was also lack of information regarding the use of psychotropic drugs. In the next Chapter (Chapter 8), I am going to explore this association further, examining the relationship between adiposity and mood disorder adjusting for various confounders, including the use of psychotropic drugs.

8 Chapter 8: Adiposity and probable major depression

Published in;

Ul-Haq Z, Smith D, Nicholl Barbara, *et al*. *(*2014). Gender differences in the association between adiposity and probable major depression: a cross-sectional study of 140,564 UK Biobank participants. *BMC Psychiatry* 14:153.

8.1 Chapter summary

Previous studies on the association between adiposity and mood disorder have produced contradictory results, and few have used measurements other than BMI. I examined the association between several measurements of adiposity (BMI, WC, WHR, and BF%) and probable major depression.

A cross-sectional study was conducted using baseline data on the sub-group of UK Biobank participants who were assessed for mood disorder. Multivariate logistic regression models were used, adjusting for potential confounders including: demographic and life-style factors, comorbidity and psychotropic medication.

Of the 140,564 eligible participants, evidence of probable major depression was reported by 30,145 (21.5%). The fully adjusted OR for obese participants were: 1.16, 95% CI 1.12, 1.20 using BMI; 1.15, 95% CI 1.11, 1.19 using WC; 1.09, 95% CI 1.05, 1.13 using WHR and 1.18, 95% CI 1.12, 1.25 using BF% (all $p<0.001$). There was a significant interaction between adiposity and sex ($p=0.001$). Overweight women were at increased risk of depression with a dose response relationship across the adiposity categories: fully adjusted ORs of 1.14, 1.20, 1.29 and 1.48 for overweight and obese I, II and III respectively (all $p<0.001$). In contrast, only obese III men had significantly increased risk of depression (OR 1.29, 95% CI 1.08, 1.54, $p=0.006$).

Adiposity was associated with probable major depression, irrespective of the measurement used. The association was stronger in women than men. Physicians managing overweight and obese women should be alert to this increased risk.

8.2 Introduction

Both depression and obesity are major public health problems. Worldwide, more than 350 million individuals suffer from depression (World Health Organisation 2013). As a contributor to the burden of morbidity, it is ranked third globally and first in middle and high income countries, with morbidity expected to rise further (World Health Organisation 2008). In the United Kingdom alone, around 1 in 20 adults experience an episode of depression annually, and it is the third most common reason for patients to consult their general practitioner (National Institute for Health and Clinical Excellence 2013). Major depression carries a significant economic and health burden (Stewart et al. 2001; Wang et al. 2003). It is associated with increased physical comorbidity (Moussavi et al. 2007), reduced HRQoL (Strine et al. 2008), and impaired function in work, school and family life (Cox et al. 1987), as well as increased mortality (Abas et al. 2002), including suicides (Miret et al. 2013). The prevalence of obesity is high both in the UK and worldwide (Rennie & Jebb 2005), leading to suggestions of an "obesity pandemic" or "globesity". In common with depression, adiposity is associated with reduced physical well-being (Canoy et al. 2013), higher societal costs (Tigbe et al. 2013) and, as shown in Chapters 4,5, and 6, poorer HRQoL (Chapter 4, 5, 6; Ul-Haq, Z et al. 2012; Ul-Haq, Z et al. 2013b; Ul-Haq, Z et al. 201c).

The relationship between these two important public health problems has been the focus of an increasing number of studies over recent years, but these studies have produced inconsistent results (Mcelroy et al. 2004; Stunkard et al. 2003). I have reported positive associations (Chapter 7; Ul-Haq et al. 2013a) whilst others have reported negative (Goldney et al. 2009) or no associations (John et al. 2005). In Chapters 4 and 6, I showed that adiposity was significantly associated with poor overall HRQoL, but this was largely due to reductions in the physical component of HRQoL, with the mental component reduced only among morbidly obese and increased among overweight (Chapter 4 Ul-Haq, Z et al. 2013b). Furthermore, in Chapter 7, I found that poor mental health was confined to obese women, and the apparent protective role of being overweight was confined to men (Chapter 7; Ul-Haq, Z et al. 2013a).

A meta-analysis of population studies reported a pooled OR of 1.26 (95% CI 1.17, 1.36) for the association between obesity and depression (Luppino et al. 2010). This association was only significant in women (OR 1.32). Of the 17 studies included, 16 used BMI as a measure of obesity. Another recent meta-analysis reported a pooled OR of 1.38 (95% CI 1.22, 1.57) for the association between central obesity and depression (Xu Q et al. 2011). A total of 15 studies were included in this review, of which 14 used WC as the measure of central obesity. Several studies, including my study in Chapter 7, have shown that the association between obesity and depression is stronger in women (Chapter ; Ul-Haq, Z et al. 2013a; Wild et al. 2012). In contrast, a recent large study demonstrated that adiposity was a significant predictor of depression but only in men (Gariepy et al. 2010).

In these two recent meta-analyses, most investigators used self-reported adiposity measurements, and many were not adjusted for important potential confounders such as socio-economic status, physical comorbidity, and the use of psychotropic medications. Only BMI and WC have been used as measures of adiposity, and they were simply dichotomized into obese and not obese, thereby losing information on the relationship across the spectrum of adiposity such as whether there is a dose relationship. There is some evidence that the relationship between adiposity and depression varies according to the level of adiposity (Onyike et al. 2003), and that WHR and BF% may also be associated with depression (Wyshak 2011). One recent, comparatively smaller German study (N=4,907) examined the association between obesity and depression, using BMI, WC and WHR as continuous variables, but did not have data on BF% (Wiltink et al. 2013). Overall, there is a paucity of larger studies that have used measures other than BMI in exploring this association.

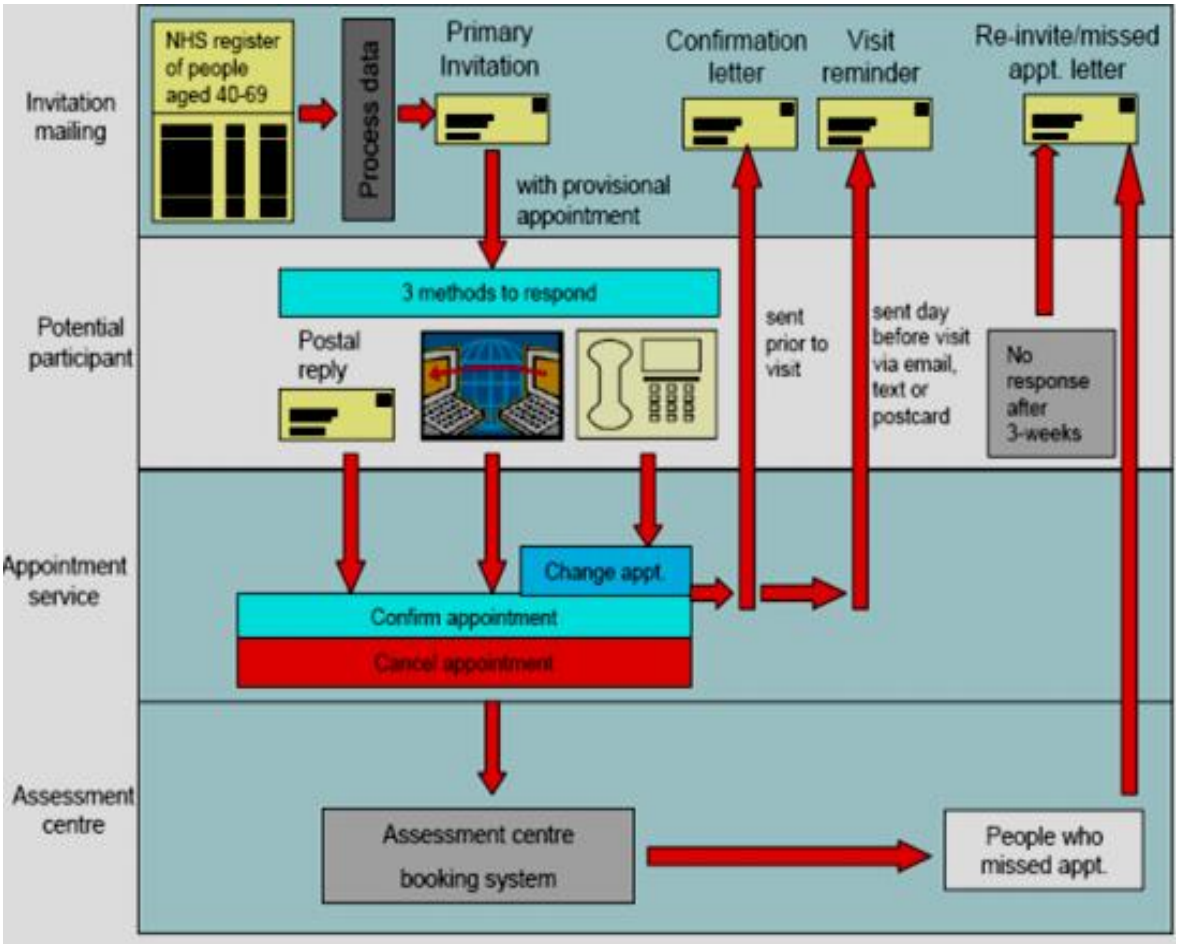
The study included in this chapter aimed to investigate the association between probable major depression and four different measurements of adiposity (BMI, WC, WHR and BF%), measured by trained staff using standard procedures and tools, across the whole range of adiposity (from underweight to class III obese). It is also to explore whether the associations varied by sex among a very large sample from the UK middle to old aged population, after adjusting for potential confounding factors, including medical comorbidity, use of psychotropic drugs, social deprivation and ethnicity.

8.3 Material and methods

8.3.1 Data source

I conducted a cross-sectional study using baseline data collected on UK Biobank participants. NHS UK maintains the records of almost all individuals of the general population through general practitioners. Based on these records, about 5 million primary invitations were sent to the eligible individuals who were living within a reasonable travelling distance from the assessment centres. UK Biobank recruited 502,682 participants, aged 40-69 years, via 22 assessment centres across the United Kingdom between 2006 and 2010 (Figure 8.1). The assessment of mood disorders was included only in the last two years, during which 172,751 participants were recruited (UK Biobank 2007).

Figure 8.1 Schematic of UK biobank invitation and appointment system



Source: from UK Biobank website: http://www.ukbiobank.ac.uk/wp-content/uploads/2011/11/UK-Biobank-Protocol.pdf

8.3.2 Data collection

Participants completed a series of computer based questionnaires followed by a face to face interview with trained research staff. The information collected included demographics (including sex, age, ethnicity, employment status, and postcode of residence), lifestyle factors (including smoking status and alcohol consumption), self-reported physician-diagnosed comorbidities (CVD, hypertension, diabetes and cancer), current medication and past or current experience of depressive and manic symptoms.

Anthropometric measurements (including height, weight, WC, hip circumference and BF%) were measured by trained data collectors, using standard operating procedures. BF% was calculated using a Tanita BC-418MA body composition analyser. WHR was derived by dividing WC (measured by a Wessex non-stretchable sprung tape at the level of the umbilicus) by hip circumference (measured at the widest point using the same device). BMI was derived by dividing weight in kilograms (measured after removal of shoes and heavy outer clothing using a Tanita BC-418MA device) by the square of height in metres (measured without shoes using the Seca 202 device) (UK Biobank 2007).

8.3.3 Definitions

BMI was classified using WHO cut-offs as; underweight (<18.5 kg/m^2), normal-weight (18.5-24.9 kg/m^2), overweight (25.0-29.9 kg/m^2), and obese (≥30 kg/m^2). Obesity was further classified as class I (30.0-34.9 kg/m^2), class II (35.0-39.9 kg/m^2) or class III obese (≥40 kg/m^2). Among men, WC was classified as normal-weight (<94 cm), overweight (94-101 cm), and obese (≥102 cm). The corresponding cut-off values for women were <80, 80-87 and ≥88 cm, respectively. WHR was classified among men as; normal weight (<0.90), overweight (0.90-0.99) or obese (≥1) and the corresponding cut-off values for women were <0.80, 0.80-0.84 and ≥0.85, respectively. BF% was classified among men as; normal weight (<18%), overweight (18-25%) and obese (>25%). The equivalent cut-off values for women were <25, 25-32 and >32, respectively.

Age was categorised into three groups; 39-49, 50-60, and 61-70 years. Townsend score quintile (from 1 least deprived to 5 most deprived) was used as an indicator of the participant's socio-economic status. This is a validated measure

which is determined on the basis of postcode of residence, and is derived from the following household information collected in the most recent census; car ownership, the number of people living in a house, home ownership, and employment status (Townsend 1987). The census based deprivation index, including Townsend index score are validated using ill health and income (Gordon D 1995, ONS 2012). Frequency of alcohol consumption (daily/almost daily, 3-4 times/week, 1-2 times/week, 1-3 times/month, special occasions and never), smoking status (never, former and current), ethnic group (white, mixed, Asian/Asian British [Indian, Pakistani, Bangladeshi and other Asian background], black/black British, Chinese and other) and employment status (in paid employment, retired, looking after home, unemployed, not working due to sickness or disability and student) were all self-reported. Comorbidity was defined as self-report of a doctor's diagnosis of one or more of the following conditions; CVD (CHD or stroke), hypertension, diabetes or cancer. Text information on all current medications was used to identify participants taking "any psychotropic medication" based on a list of 125 eligible generic and proprietary names. Text information on all current medications was used to identify participants taking "any psychotropic medication" based on a list of 125 eligible generic and proprietary names. This information was provided by the UK Biobank mental health group (Smith et al. 2013).

My classification of depression was based on criteria published previously by UK Biobank mental health group (Smith et al. 2013). Briefly, depression was defined using information collected via the Patient Health Questionnaire (PHQ) (Spitzer et al. 1999) on past help-seeking behaviour for mental health, and specific questions on the severity and duration of both depressed mood and anhedonia. Participants were classified as having probable major depression if they had ever seen a general practitioner or psychiatrist for 'nerves, anxiety, depression" and had either ever had mood that was depressed/down for at least two weeks or had been unenthusiastic/disinterested for at least two weeks. I included participants who reported one or more eligible episode but participants with probable bipolar I or II disorders were excluded from this study.

This study was conducted under generic approval from the NHS National Research Ethics Service (17th June 2011, Ref 11/NW/0382). Participants provided electronic consent for the baseline assessments, biochemical samples and future

linkage to routine databases. Participants are not provided with individual level information nor benefit from any future commercial developments.

8.3.4 Statistical analyses

The differences in depression and other covariates by adiposity were analysed using the x^2 test for categorical data, and x^2 test for trend for ordinal data. I examined the associations between anthropometric measurements (BMI, WC, WHR and BF%) and probably major depression, as the outcome, using multivariate logistic regression models. The association was first adjusted for age, sex, socio-economic status and ethnicity (model 1), and was then further adjusted for employment, alcohol consumption, smoking, presence of comorbidity (CVD, hypertension, diabetes, cancer) and use of psychotropic medications (model 2). I tested whether there were statistically significant interactions by applying likelihood ratio test between adiposity and sex, and conducted sub-group analyses accordingly. The logistic regression model was repeated using BMI, WC, WHR and sex-specific deciles of BF%. All statistical analyses were performed using Stata version 12.1 (StataCorp, College Station, Texas). Statistical significance was defined as $p<0.05$.

8.4 Results

Of the 172,751 UK Biobank participants who were recruited during the last two years, complete information on mood disorders was available for 140,564 (81.4%). Overall, the mean age was 57 years (SD 8 years), and 75,093 (53.4%) were women. 30,145 (21.5%) participants satisfied the criteria for probable major depression: 19,493 (26.0%) women and 10,652 (16.3%) men. Based on BMI, 33,857 (24.1%) were obese. Using the other measures, the percentage classified as obese were 46,504 (33.1%) for WC, 33,049 (23.5%) for WHR, and 91,166 (64.9%) for BF%. Depression was significantly more prevalent among women than men (19,493 [25.7%] versus 10,652 [16.3%], $p<0.001$).

Those with probable major depression were more likely to be obese and were more likely to be women, younger, deprived, unemployed, white, smoke, report comorbidity, and use psychotropic medication, but they consumed alcohol less frequently (all $p<0.001$) (Table 8.1). There was a positive association whereby

major depression was less common in the lower deciles of adiposity and more common in the higher deciles, and this was more marked among women (Figure 8.2). In women, the prevalence of depression in the top decile of adiposity was very consistent across the different anthropometric measurements; 31.6%, 33.5%, 31.2% and 30.6% using BMI, WC, WHR, and BF% respectively. The corresponding proportions for men were 20.4%, 20.2%, 18.6% and 24.3%, respectively (Figure 8.2).

Table 8.1 Characteristics of the participants by body mass index category

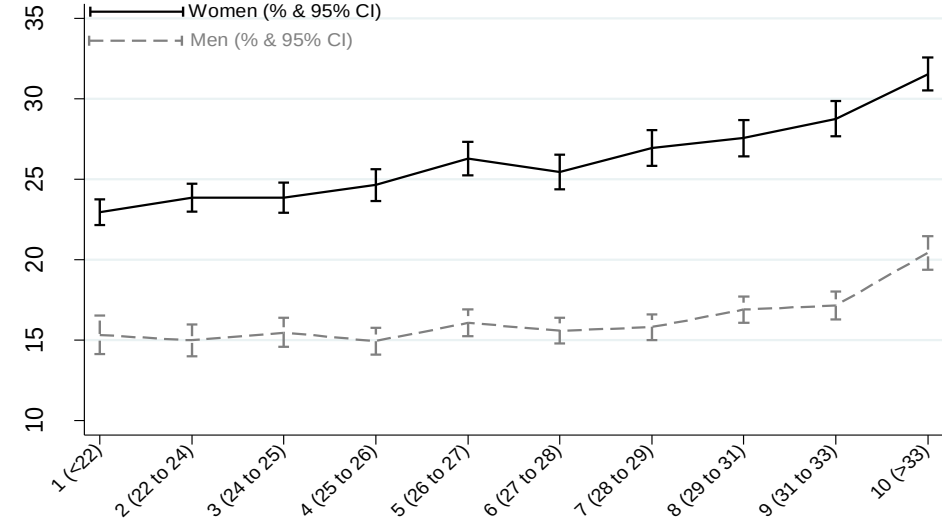
				Obese				
	Underweight N= 654 N (%)	**Normal-weight** N= 46,121 N (%)	**Overweight** N= 59,932 N (%)	**Overall** N= 33,857 N (%)	**Class I** N= 24,458 N (%)	**Class II** N= 6,852 N (%)	**Class III** N= 2,547 N (%)	**P-value**
Probable major depression								
No	508 (77.7)	36,622 (79.4)	47,641 (79.5)	25,648 (75.8)	18,912 (77.3)	5,022 (73.3)	1,714 (67.3)	<0.001
Yes	146 (22.3)	9,499 (20.6)	12,291 (20.5)	8,209 (24.3)	5,546 (22.7)	1,830 (26.7)	833 (32.7)	
Sex								
Women	517 (79.1)	29,748 (64.5)	27,380 (45.7)	17,448 (51.5)	11,634 (47.6)	4,089 (59.7)	1,725 (67.7)	<0.001
Men	137 (21.0)	16,373 (35.5)	32,552 (54.3)	16,409 (48.5)	12,824 (52.4)	2,763 (40.3)	822 (32.3)	
Age (years)								
39-49	170 (26.0)	12,200 (26.5)	12,958 (21.6)	7,119 (21.0)	4,970 (20.3)	1,478 (21.6)	671 (26.3)	<0.001
50-60	283 (43.3)	16,955 (36.8)	21,091 (35.2)	12,652 (37.4)	8,937 (36.5)	2,654 (38.7)	1,061 (41.7)	
61-70	201 (30.7)	16,966 (36.8)	25,883 (43.22)	14,086 (41.6)	10,551 (43.1)	2,720 (39.7)	815 (32.0)	
Townsend score quintile								
1	107 (16.4)	8,289 (18.0)	10,552 (17.6)	4,795 (14.2)	3,718 (15.2)	818 (11.9)	259 (10.2)	<0.001
2	108 (16.5)	9,580 (20.8)	12,377 (20.7)	6,115 (18.1)	4,632 (18.9)	1,126 (16.4)	357 (14.0)	
3	111 (17.0)	9,563 (20.7)	12,795 (21.4)	6,734 (19.9)	4,956 (20.3)	1,314 (19.2)	464 (18.2)	
4	160 (24.5)	10,541 (22.9)	13,232 (22.1)	7,828 (23.1)	5,578 (22.8)	1,646 (24.0)	604 (23.7)	
5	168 (25.7)	8,148 (17.7)	10,976 (18.3)	8,385 (24.8)	5,574 (22.8)	1,948 (28.4)	863 (33.9)	
Employment status								
Employed	339 (51.8)	27,597 (59.8)	34,155 (57.0)	18,733 (55.3)	13,651 (55.8)	3,704 (54.1)	1,378 (54.1)	<0.001
Retired	186 (28.4)	14,798 (32.1)	21,733 (36.3)	11,743 (34.7)	8,676 (35.5)	2,333 (34.1)	734 (28.8)	
Look after home	56 (8.6)	1,796 (3.9)	1,350 (2.3)	813 (2.4)	530 (2.2)	190 (2.8)	93 (3.7)	
Unemployed	32 (4.9)	1,113 (2.4)	1,509 (2.5)	1,031 (3.1)	673 (2.8)	245 (3.6)	113 (4.4)	
Not working	39 (6.0)	681 (1.5)	1,041 (1.7)	1,431 (4.2)	854 (3.5)	355 (5.2)	222 (8.7)	<0.001
Student	2 (0.3)	136 (0.3)	144 (0.2)	106 (0.3)	74 (0.3)	25 (0.4)	7 (0.3)	
Alcohol consumption								
Daily	139 (21.3)	10,604 (23.0)	13,137 (21.9)	5,337 (15.8)	4,296 (17.6)	846 (12.4)	195 (7.7)	<0.001
3-4 times/week	127 (19.4)	11,283 (24.5)	14,456 (24.1)	6,528 (19.3)	5,122 (20.9)	1,077 (15.7)	329 (12.9)	
1-2 times/week	123 (18.8)	11,419 (24.8)	15,411 (25.7)	8,677 (25.6)	6,398 (26.2)	1,720 (25.1)	559 (21.6)	
1-3 times/month	71 (10.9)	4,775 (10.4)	6,345 (10.6)	4,643 (13.7)	3,152 (12.9)	1,065 (15.5)	426 (16.7)	
Special occasions	94 (14.4)	4,587 (10.0)	6,270 (10.5)	5,306 (15.7)	3,299 (13.5)	1,358 (19.8)	649 (25.5)	
Never	100 (15.3)	3,453 (7.5)	4,313 (7.2)	3,366 (9.9)	2,191 (9.0)	786 (11.5)	389 (15.3)	

Smoking status								
Never	387 (59.2)	27,887 (60.5)	32,729 (54.6)	17,652 (52.1)	12,614 (51.6)	3,652 (53.3)	1,386 (54.4)	<0.001
Previous	151 (23.1)	13,590 (29.5)	21,537 (35.9)	13,154 (38.9)	9,575 (39.2)	2,638 (38.5)	941 (37.0)	
Current	116 (17.7)	4,644 (10.1)	5,666 (9.5)	3,051 (9.0)	2,269 (9.3)	562 (8.2)	220 (8.6)	
Ethnicity								
White	591 (90.4)	42,911 (93.0)	55,312 (92.3)	30,838 (91.1)	22,382 (91.5)	6,191 (90.4)	2,265 (88.9)	<0.001
Mixed	10 (1.5)	377 (0.8)	381 (0.6)	235 (0.7)	161 (0.7)	47 (0.7)	27 (1.1)	
Asian	28 (4.3)	1,426 (3.1)	1,893 (3.2)	863 (2.6)	653 (2.6)	162 (2.4)	48 (1.9)	
Black	3 (0.5)	651 (1.4)	1,521 (2.5)	1,451 (4.3)	926 (3.8)	355 (5.2)	170 (6.7)	
Chinese	6 (0.9)	291 (0.6)	169 (0.3)	38 (0.1)	34 (0.1)	3 (0.0)	1 (0.0)	
Other	16 (2.5)	465 (1.0)	656 (1.1)	432 (1.3)	302 (1.2)	94 (1.4)	36 (1.4)	
Comorbidity								
No	503 (76.9)	35,056 (76.0)	38,488 (64.2)	16,354 (48.3)	12,551 (51.3)	2,920 (42.6)	883 (32.7)	<0.001
Yes	151 (23.1)	11,065 (24.0)	21,444 (35.8)	17,503 (51.7)	11,907 (48.7)	3,932 (57.4)	1,664 (65.3)	
Psychotropic medication								
No	605 (92.5)	43,487 (94.3)	56,091 (93.6)	30,475 (90.0)	22,263 (91.0)	6,059 (88.4)	2,153 (84.5)	<0.001
Yes	49 (7.5)	2,634 (5.7)	3,841 (6.4)	3,382 (10.0)	2,195 (9.0)	793 (11.6)	394 (15.5)	

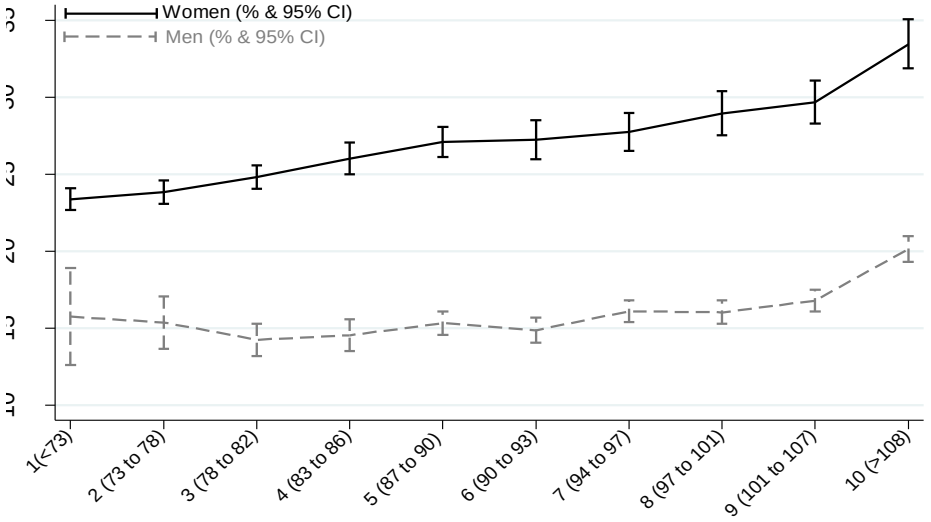
BMI: body mass index category (kg/m^2); underweight (<18.5), normal-weight (18.5-24.9), overweight (25-29.9), obese (≥30), class I (30-34), class II (35-39), class III obese (>40), Townsend score, a measure of socio-economic status, p-value; χ^2 test for categorical data & p-value for test of trend for ordinal data, Comorbidity (CVD, hypertension, diabetes, cancer)

Figure 8.2 Frequency (%) of probable major depression by measures of adiposity and sex.

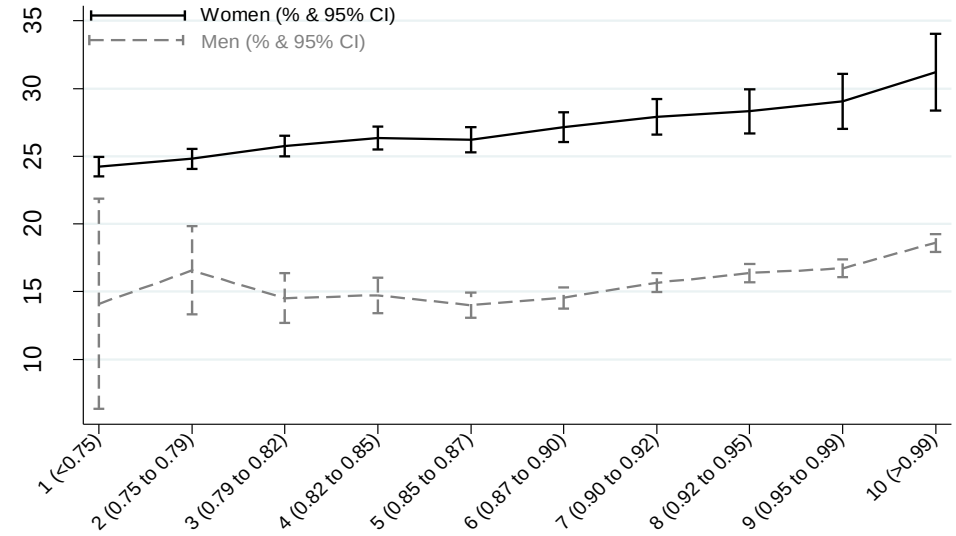
a. Body Mass Index deciles (kg/m^2)



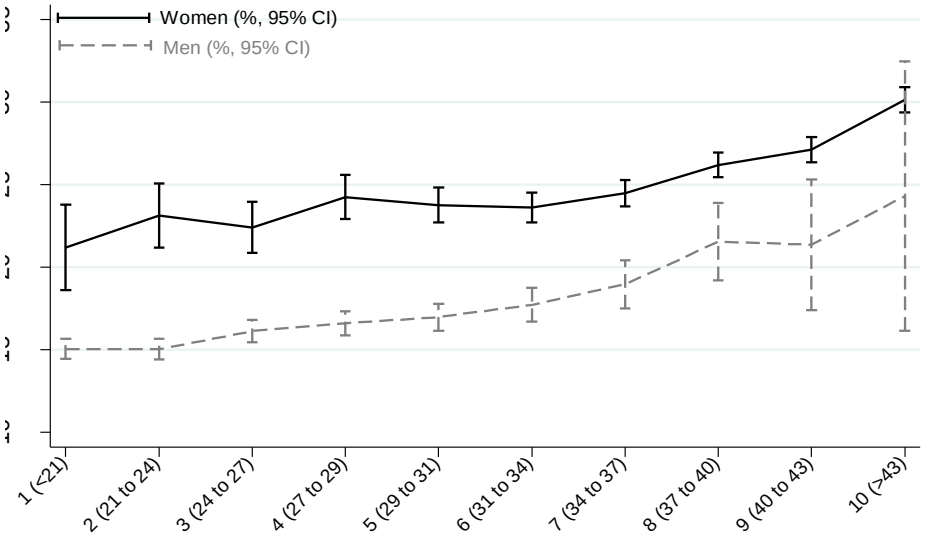
b. Waist Circumference deciles (cm)



c. Waist to hip ratio deciles



d. Body fat % deciles



In the overall logistic regression analyses, adjusted for age, sex, socio-economic status and ethnicity (model 1) there were significant associations between all anthropometric measures and major depression (all p-value <0.001) (Table 8.2). Being overweight or obese was significantly associated with major depression, and the OR of major depression in obese participants was consistent across the anthropometric measurements; 1.36 (95% CI 1.32, 1.41), 1.34 (95% CI 1.30, 1.39), 1.30 (95% CI 1.26, 1.35), and 1.32 (95% CI 1.25, 1.40) for BMI, WC, WHR and BF%, respectively (Table 8.2). When further adjusted for the potential confounding effects of employment, alcohol consumption, smoking, comorbidity (CVD, hypertension, diabetes, and cancer) and use of psychotropic medications (model 2), the associations were slightly attenuated. Nonetheless, participants classified as overweight or obese (class I, II or III) based on BMI still had significantly higher odds of having major depression, compared to normal weight participants, with evidence of a linear relationship. The OR of major depression were; 1.09 (95% CI 1.06, 1.13), 1.12 (95% CI 1.08, 1.17), 1.21 (95% CI 1.14, 1.29), and 1.39 (95% CI 1.27, 1. 53) (all p-value <0.001) for overweight, class I, II and III obese, respectively. Similarly, using WC, WHR, and BF%, overweight and obese participants had significantly higher odds of major depression than normal-weight participants, with a dose-response relationship. The OR for the association between overweight and major depression compared to normal weight remained very consistent across the anthropometric measurements; 1.09 (95% CI 1.06, 1.13), 1.07 (95% CI 1.03, 1.10), 1.05 (95% CI 1.02, 1.09), and 1.06 (95% CI 1.00, 1.13) for BMI, WC, WHR and BF% respectively. The corresponding OR for obese participants were 1.16 (95% CI 1.12, 1.20), 1.15 (95% CI 1.11, 1.19), 1.09 (95% CI 1.05, 1.13) and 1.18 (95% CI 1.12, 1.25), respectively (Table 8.2).

There was a significant interaction between adiposity and sex (p=0.001). Sub-group analyses by sex showed that the overall associations were largely driven by women (Table 8.2). In contrast, men classified as overweight, overall, class I or class II obese on the basis of their BMI were not at significantly increased risk of with major depression. Only class III obese men had significantly higher odds of major depression, compared to normal weight men. Similarly, using WC and BF%, there was no association between being overweight and major depression in men. Only obese men had significantly higher odds of major depression. In contrast, using WHR, both overweight and obese men were at significantly

increased risk of major depression (Table 8.2). Underweight individuals were not at significantly increased risk of depression either overall or by gender-specific sub-group.

When the logistic regression model was repeated using the BMI, WC, WHR and BF% sex-specific deciles, the adjusted OR in women illustrated the similar positive association (Figure 8.3) as was observed for the crude frequencies (Figure 8.2). The adjusted OR for the top decile of BMI, WC, WHR and BF% were; 1.38, 1.35, 1.16 and 1.67, respectively. In contrast, among men, other than the top decile of BMI (>33 kg/m^2), there was a straight line indicating no significant relationship with major depression in all anthropometric measurements.

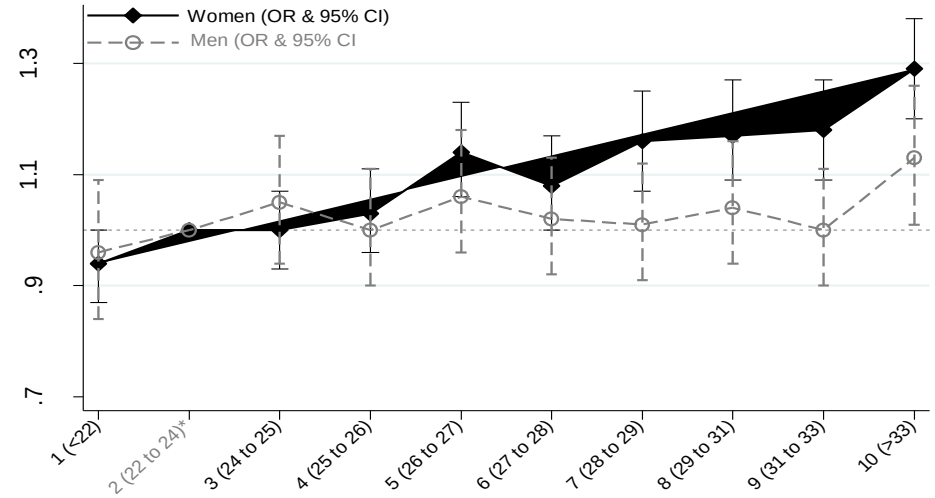
Table 8.2 Logistic regression analysis of the adiposity measurements associated with major depression.

	Overall				Women				Men			
	Model 1		Model 2		Model 1		Model 2		Model 1		Model 2	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
BMI category												
Underweight	1.00 (0.83, 1.20)	0.972	0.93 (0.77, 1.13)	0.480	0.92 (0.74, 1.13)	0.428	0.89 (0.71, 1.10)	0.281	1.47 (0.98, 2.21)	0.061	1.25 (0.82, 1.93)	0.302
Normal-weight	1	-	1	-	1	-	1	-	1	-	1	-
Overweight	1.15 (1.11, 1.18)	<0.001	1.09 (1.06, 1.13)	<0.001	1.20 (1.15, 1.24)	<0.001	1.14 (1.10, 1.19)	<0.001	1.07 (1.01, 1.12)	0.018	1.02 (0.97, 1.08)	0.480
Obese (overall)	1.36 (1.32, 1.41)	<0.001	1.16 (1.12, 1.20)	<0.001	1.43 (1.37, 1.50)	<0.001	1.24 (1.19, 1.30)	<0.001	1.24 (1.17, 1.32)	<0.001	1.05 (0.99, 1.12)	0.134
Class I	1.29 (1.24, 1.34)	<0.001	1.12 (1.08, 1.17)	<0.001	1.35 (1.29, 1.42)	<0.001	1.20 (1.14, 1.26)	<0.001	1.18 (1.11, 1.26)	<0.001	1.02 (0.96, 1.10)	0.489
Class II	1.47 (1.38, 1.56)	<0.001	1.21 (1.14, 1.29)	<0.001	1.51 (1.41, 1.63)	<0.001	1.29 (1.20, 1.40)	<0.001	1.38 (1.25, 1.53)	<0.001	1.10 (0.99, 1.23)	0.081
Class III	1.82 (1.66, 1.98)	<0.001	1.39 (1.27, 1.53)	<0.001	1.84 (1.66, 2.04)	<0.001	1.48 (1.32, 1.65)	<0.001	1.76 (1.50, 2.08)	<0.001	1.29 (1.08, 1.54)	0.006
WC category												
Normal-weight	1	-	1	-	1	-	1	-	1	-	1	-
Overweight	1.13 (1.10, 1.17)	<0.001	1.07 (1.03, 1.10)	<0.001	1.15 (1.10, 1.20)	<0.001	1.09 (1.04, 1.14)	<0.001	1.11 (1.05, 1.17)	0.096	1.04 (0.98, 1.10)	0.161
Obese	1.34 (1.30, 1.39)	<0.001	1.15 (1.11, 1.19)	<0.001	1.39 (1.33, 1.44)	<0.001	1.21 (1.16, 1.26)	<0.001	1.28 (1.22, 1.35)	<0.001	1.07 (1.02, 1.13)	0.010
WHR category												
Normal-weight	1	-	1	-		-	1	-	1	-	1	-
Overweight	1.14 (1.10, 1.18)	<0.001	1.05 (1.02, 1.09)	0.002	1.12 (1.08, 1.17)	<0.001	1.05 (1.01, 1.10)	0.024	1.18 (1.13, 1.24)	<0.001	1.06 (1.01, 1.12)	0.018
Obese	1.30 (1.26, 1.35)	<0.001	1.09 (1.05, 1.13)	<0.001	1.26 (1.21, 1.31)	<0.001	1.09 (1.04, 1.13)	<0.001	1.46 (1.36, 1.56)	<0.001	1.12 (1.04, 1.20)	0.002
BF% category												
Normal-weight	1	-	1	-	1	-	1	-	1	-	1	-
Overweight	1.07 (1.01, 1.14)	0.016	1.06 (1.00, 1.13)	0.039	1.08 (1.00, 1.18)	0.061	1.10 (1.00, 1.20)	0.039	1.06 (0.98, 1.14)	0.156	1.03 (0.95, 1.12)	0.469
Obese	1.32 (1.25, 1.40)	<0.001	1.18 (1.12, 1.25)	<0.001	1.37 (1.26, 1.48)	<0.001	1.26 (1.16, 1.37)	<0.001	1.27 (1.17, 1.36)	<0.001	1.09 (1.00, 1.18)	0.038

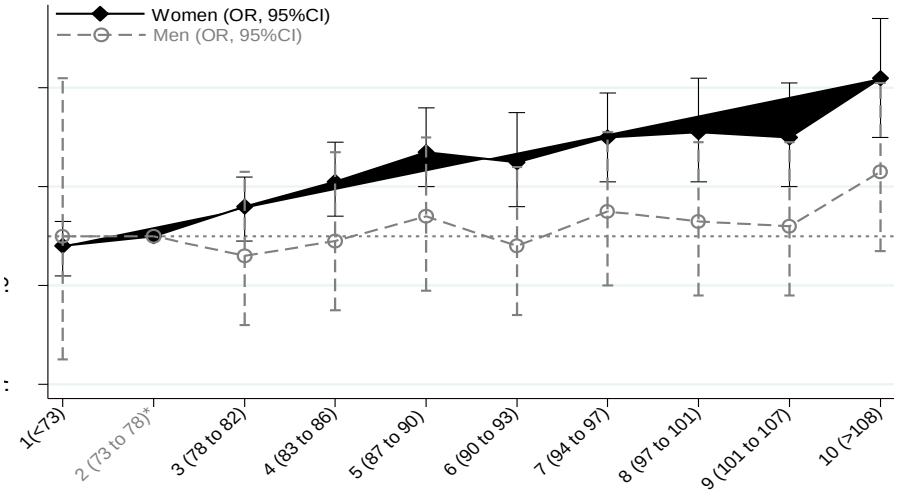
OR: Odds ratio; **CI:** Confidence Interval**; Model 1:** adjusted by age, sex, socio-economic status, and ethnicity; **Model 2 (**full adjusted): in addition to the variables in model-1 below variables were added: employment, alcohol consumption, smoking, comorbidity (CVD, diabetes, hypertension, cancer), and use of psychotropic medications.

Figure 8.3 Adjusted[¶] odds ratio of probable major depression by measures of adiposity and sex.

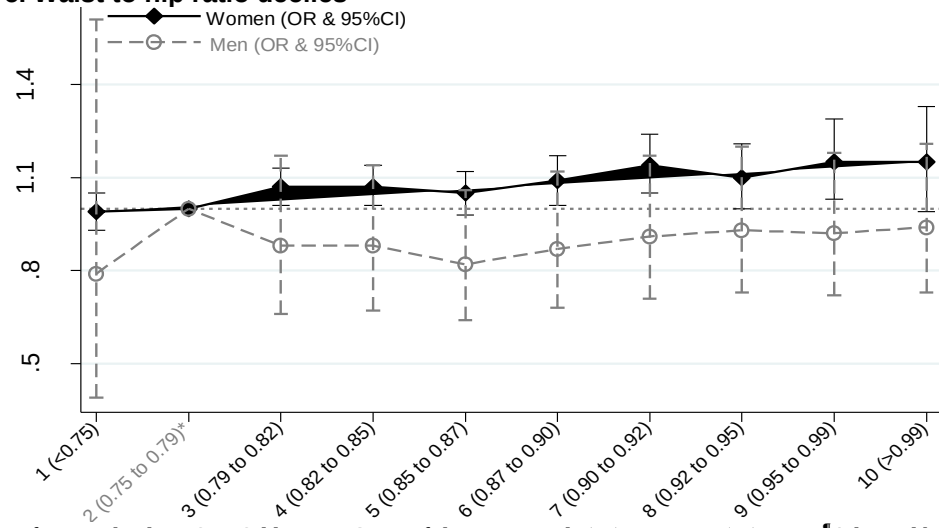
a. Body Mass Index deciles (kg/m^2)



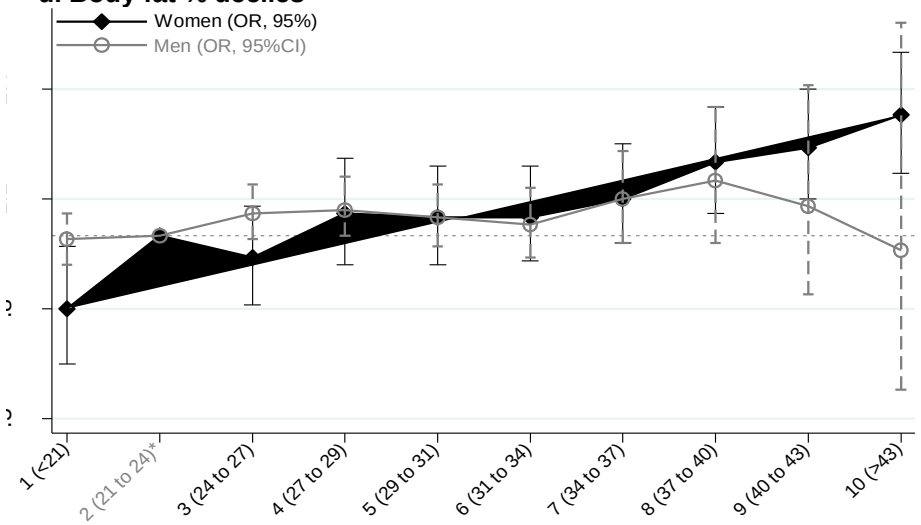
b. Waist Circumference deciles (cm)



c. Waist to hip ratio deciles



d. Body fat % deciles



Reference deciles, OR; Odds ratio, CI; confidence interval, (W) Women, (M) Men, [¶]Adjusted by age, socio-economic status, employment, ethnicity, alcohol consumption, smoking, comorbidity (CVD, hypertension, diabetes, cancer) and psychotropic medication

8.5 Discussion

Overall, both overweight and obese individuals were significantly more likely to have probable major depression than normal weight participants, irrespective of the anthropometric measurement used, and independent of potential confounding factors. There was evidence of a dose relationship with the risk of depression increasing with the level of adiposity, above normal weight. Being underweight was not associated with major depression. The relationship between adiposity and depression varied significantly by sex, such that the overall association was largely driven by women. In contrast, only men with class III obesity were at significantly increased risk of probable major depression.

In my meta-analyses, increased BMI was associated with significantly reduced physical HRQoL (Chapters 4 & 5; Ul-Haq, Z et al. 2013b; Ul-Haq, Z et al. 2013c). In contrast, psychological HRQoL was higher among overweight individuals and reduced significantly in only class III obese. Two previous meta-analyses have reported a significant association between obesity and depression with pooled OR of 1.38 for BMI (Luppino et al. 2010) and 1.26 for WC (Xu Q et al. 2011). Wiltink et al examined the association between obesity and depression and demonstrated a similar positive relationship using BMI, WC and WHR (Wiltink et al. 2013). In another study, Wyshak demonstrated a positive association between obesity, measured by BF%, and depression, relative to non-obese participants (adjusted OR 1.70, 95% CI 1.20, 2.39, p=0.002) (Wyshak 2011). These findings are consistent with those of Wiltink et al (Wiltink et al. 2013), in that the magnitude of the association between obesity and depression was comparable using a number of different measurements: 1.36, 1.34, 1.30, and 1.32 for BMI, WC, WHR and BF%, respectively and there was an overall dose response relationship across the categories from overweight to obese III.

I found that the relationship between adiposity and depression was stronger in women than men. Previous studies have reported that overweight individuals have better mental health than normal-weight individuals (Bentley et al. 2011), but I found that this was confined to men (Chapter 7; Ul-Haq, Z et al. 2013a). It is plausible that the association may be causal, and stronger in women. Adiposity can result in stigma, particularly in women, which is a known risk factor for depression (Puhl & Heuer 2010). Print and electronic media portray thin women

and larger, muscular men as ideals and may lead to a lower acceptance of increased body weight among women (Sheldon 2010). It is also plausible that reverse causation may play a role. Depression may lead to both less physical activity and over-eating, contributing to obesity (Pan et al. 2012). Physical attractiveness is known to be associated with depression, and depression may reduce an individual's general interest in maintaining their appearance (Noles et al. 1985). Depressed people are also reported to have more realism or even to underestimate their physical attractiveness (Lewinsohn et al. 1980). In contrast, feeling attractive may be protective against depression. Depression is also known to be associated with neuro-endocrine abnormalities, such as hypercortisolaemia, which can contribute to obesity (Bjorntorp 2001). In this cross-sectional study, I was unable to establish temporal relationships and, therefore, could not determine the most plausible direction of causation.

8.6 Strengths and limitations

Only a small number of previous studies have examined the association between level of adiposity and depression and, to my knowledge, this is the first study to explore the whole range of anthropometric measures (from underweight to class III obesity), not rely on self-reported measures and use four different anthropometric measurements. I used the recommended sex-specific deciles for adiposity (other than BMI). Use of UK Biobank data enabled me to analyze a very large number of participants recruited from the general population, and to adjust for a wide range of potential confounders. The importance of adjusting for medical comorbidity, use of psychotropic medications, ethnicity and socio-economic status has been highlighted previously (Luppino et al. 2010; Wiltink et al. 2013; Xu, Anderson et al. 2011), but this has rarely been carried out.

Inclusion in this study was limited to the participants who provided complete information on mood. Compared with participants who did not provide complete information, these individuals were more likely to be of normal-weight, male, younger and socioeconomically deprived, non smokers, in employment and consume alcohol and less likely to report medical comorbidity. UK Biobank recruited middle and old aged individuals (aged 40 to 69 years) from the general population and so young people or very old people are underrepresented. Less than 10% of invited individuals were recruited into UK Biobank.

One of the possible reasons of the very low response rate might be the concerns of the general public for participating in the genetic research. This is also noticed in the other genetic studies where respondents were less likely to agree for storing their blood sample for future research, compared to the non-genetically clinical data (McQuillan et al. 2003; Schwartz et al. 2001). A qualitative study revealed the findings of a focus group discussion among the patients and control of genetic study (McGuire et al. 2008). One of the participants shared his view about the consent for a genetic study is to, “Let them know up-front... keep it simple, keep it correct, and never lie”. Most of the participants were concerned about sharing of their genetic information on a public database, “I just keep thinking if the entire sequence is out there, one of these days the computers are going to catch up with us and they will be able to tack it back to us”. The other participant expresses his concern as, “I want to share everything ... my total history, whatever... but I want it to be in the medical community, not just some guy saying well I didn’t have anything else to do so I just went ahead and read this,... I want this information going to help people that I am here to help”. The genetic information, such as future risk of disease may have serious impact on individuals and their family lives (Baoqi & Darryl 2004).

The potential reasons of participating in the genetic research includes; the desire to help current and future generations, family member with a genetic condition, hope of development cure for disease through genetic research, ease of participating, trust and credibility of the responsible organization, how participants will benefit themselves such as receiving personal genetic test results, and clarity of information in the consent form (Lemke et al. 2010; Sterling et al. 2006; Ormond et al. 2011). Possible reasons of not participating includes; the lack of public education about genetic research, fear of the “unknown” associated with genetic research, fear of genetic discrimination by the insurance company, health department or employer, no direct or immediate benefit, fear of breach of confidentiality, or no belief in genetic research or genetic determinism (Ormond et al. 2011; Streicher et al. 2011; Schwartz et al. 2001).

This low response could introduce bias to the analysis of this study in terms of difference between people who did and did not respond to the study invitation. This may affect the generalisability of my results. However, the internal validity of mood disorder in the UK Biobank has previously described (Smith et al. 2013).

In Chapter 7, I reported an association between being underweight and poor mental health, particularly in women (Chapter 7; Ul-Haq, Z et al.2013c). The lack of an association with underweight in this study may reflect a lack of statistical power due to smaller numbers in this sub-group, or may be due to the previously I used the GHQ-12 which is a short screening instrument rather than a detailed assessment of mental health. The population of SHeS and UK Biobank differ considerably in age range which may perhaps explain differences in results.

The use of many psychotropic medications, such as mood stabilizers, anti-psychiatric and anti-depressants is associated with weight gain (exposure). These drugs may cause 2-17 kg of increase in the individuals' body weight over the period of a clinical treatment (Allison et al. 1999). It may be a potential confounder and therefore the analysis was adjusted for the use of psychotropic medications. However, the psychotropic drugs may be used by the participants with the probable major depression (outcome). Furthermore, adiposity may result in the non-compliance of psychotropic drugs and may be associated with the relapse of the depression and psychiatric hospitalization (Nihalani et al. 2011). Therefore, adjustment for it may be "over adjustment" and may underestimate or even change the direction of the association between adiposity (exposure) and probable major depression (outcome) (Schisterman et al. 2009).

8.7 Implications of this research

Overweight and obese women are significantly more likely to suffer from major depression, and the risk increases with increasing level of adiposity, even after adjusting for a range of potential confounders. Physicians managing overweight and obese women should be alert to this increased risk. Further research is required into whether the associations are causal, the direction of causality, and whether obesity interventions can reduce the risk of depression.

In the last five Chapters (Chapter 4 to 8, inclusive) I have explored the relationships between adiposity and HRQoL and mental health. In the next Chapter (Chapter 9), I explore whether the same relationships are present between adiposity and other two measures of subjective well-being: self-rated health and unhappiness.

9 Chapter 9: Adiposity, self-reported health and happiness.

Published in;

Ul-Haq Z, Mackay DF, Martin D, *et al*. *(*2014). Heaviness, Health and Happiness: A Cross-Sectional Study of 163,066 UK Biobank Participants. *J Epidemiol Community Health* **68**:340–348.

9.1 Chapter summary

Obesity is known to increase the risk of many diseases and reduce overall quality of life. This study examines the relationship with SRH and happiness.

I conducted a cross-sectional study of the 163,066 UK Biobank participants who completed the happiness rating. The association between adiposity and SRH and happiness was examined using logistic regression. SRH was defined as good (excellent, good), or poor (fair, poor). Self-reported happiness was defined as happy (extremely, very, moderately) or unhappy (moderately, very, extremely).

Poor health was reported by 44,457 (27.3%) participants. The adjusted OR for poor health were 3.86, 2.92, 2.60 and 6.41 for the highest, compared with lowest, deciles of BMI, WC, WHR and BF%, respectively. The associations were stronger in men ($p<0.001$). Overall, 7,511 (4.6%) participants felt unhappy, and only class III obese participants were more likely to feel unhappy (adjusted OR 1.33, 95% CI 1.15, 1.53, $p<0.001$) than normal-weight but the associations differed by sex ($p<0.001$). Among women, there was a significant association between unhappiness and all levels of obesity. By contrast, only class III obese men had significantly increased risk and overweight and class I obese men were less likely to be unhappy.

Obesity impacts adversely on happiness as well as health, but the association with unhappiness disappeared after adjustment for SRH, indicating this may be mediated by health. Compared with obese men, obese women are less likely to report poor health but more likely to feel unhappy.

9.2 Introduction

Historically, the main focus of healthcare has been the avoidance of preventable mortality. As life-expectancy has increased, attention has focused on the need to improve health, as well as longevity. The WHO definition of health encompasses mental and social, as well as physical, well-being (World Health Organisation 1992) but, when self-reporting health, people give greater emphasis to physical well-being than psychological well-being (Smith et al. 1999). Poor SRH predicts mortality over 2-13 years follow-up overall (Idler and Benyamini 1997), but the association is significantly stronger in men (Benyamini et al. 2000). This has been attributed to women considering a wider range of health-related factors and non-health-related factors in the process of assessing their own health (Benyamini et al. 2000). Psychological well-being itself comprises several components, including happiness (hedonic well-being) and life satisfaction (eudaimonic well-being). In the United Kingdom, 38% of people who reported poor health had high levels of life satisfaction, and 20% of those who reported good health had low life satisfaction (Beaumont & Thomas 2012). Therefore, it is important that study results pertaining to one construct are not inappropriately generalised to another.

High levels of adiposity are associated with many diseases including hypertension (Narkiewicz 2006), stroke (Kurth et al. 2002), CHD (Silventoinen et al. 2009), diabetes (Hossain et al. 2007) and arthritis (Magliano 2008). Evidence is increasing that obesity may also impact adversely on psychosocial well-being. There are conflicting results regarding the association between obesity and poor SRH. Some studies have reported significant associations (Marques-Vidal et al. 2012; Trakas et al. 2001) while others have reported no (Kepka et al. 2007) or very weak associations (Macmillan et al. 2011). A recent study from the USA that found no association, hypothesised that a shift to the right in the BMI distribution of the general population had changed societal perspectives of what constituted normal weight (Macmillan et al. 2011). Previous studies on obesity have tended to use measures of HRQoL which encompass both physical and psychosocial well-being. In previous chapters, I demonstrated that obesity was associated with significantly reduced overall HRQoL, irrespective of the presence of comorbid conditions (Chapter 6; Ul-Haq, Z et al. 2012). The physical component of HRQoL was reduced in both overweight and obese adults with

evidence of a dose relationship (Chapter 4, 5; Ul-Haq, Z et al. 2013b; Ul-Haq,Z et al. 2013c). By contrast, the mental component of HRQoL was reduced only among class III obese individuals and was increased among overweight adults. On sub-group analyses it was also clear that the overall reduction in the mental component among class III obese was present in women only (Chapter 7 Ul-Haq, Z et al. 2013a).

While BMI remains the anthropometric measure of choice for most researchers, there is also growing evidence that favours other measures such as WC, WHR and BF% (Rothman 2008). Studies have reported associations between WC and WHR and perceived stress and higher levels of stress-dependent cortisol (Bjorntorp & Rosmond 2000). In some recent studies, abnormally high BF% was significantly associated with poor mental health and well-being (Saarni et al. 2009). Obesity can lead to stigma and discrimination (Cramer & Steznwert 1998). Compared with men, women are more likely to be judged based on physical appearance. Therefore, it is plausible that obesity will be associated with unhappiness, especially among women. The aim of this study was to explore the relationship between adiposity (objectively measured by BMI, WC, WHR and BF%), SRH and unhappiness among a large sample of the UK middle-aged population.

9.3 Material and methods

9.3.1 Data source

UK Biobank is a large, prospective cohort study of 502,682 residents of the United Kingdom, aged between 40 and 69 years (Allena et al. 2012; Collins 2012). The cohort provides one of the largest resources worldwide to study the genetic, environmental and lifestyle factors that cause or prevent disease in middle and older age (UK Biobank 2007). Recruitment was undertaken over a 4-year period from 2006 to 2010, but the rating on self-reported happiness was only included in the last two years of recruitment. In due course, follow-up information will be obtained via record linkage to routine health and administrative databases. This cross-sectional study was undertaken using the baseline data on those participants who completed the happiness rating.

9.3.2 Data collection

Participants attended one of 22 centres located across the United Kingdom (Chapter 8, Figure 8.1). Each person completed a touch screen questionnaire that collected information on demographics (including age, sex, ethnicity, employment status and postcode of residence), health-related behaviours (including smoking status and alcohol consumption), doctor-diagnosed comorbidity (CVD, hypertension, diabetes and cancer), overall health rating and happiness. Trained clinic staff used standard operating procedures to record physical measurements; including height, weight, waist and hip circumference and BF% (measured by bioimpedance). After removal of shoes and heavy outer clothing, weight and BF% were measured using the Tanita BC-418MA body composition analyser. Height, without shoes, was measured using the Seca 202 device. The Wessex non-stretchable sprung tape was used to measure WC at the level of the umbilicus and hip circumference at the widest point. WHR was derived by dividing WC by hip circumference and BMI was derived by dividing weight (measured in kilograms) by the square of height (measured in metres).

9.3.3 Definitions

BMI was categorised as WHO cut-off into underweight (<18.5 kg/m^2), normal weight (18.5-24.9 kg/m^2), overweight (25.0-29.9 kg/m^2), class I obese (30.0-34.9 kg/m^2), class II obese (35.0-39.9 kg/m^2) and class III obese (≥40 kg/m^2), using standard cut-point (World Health Organization 2013). Among men, WC was categorised into normal weight (<94 cm), overweight (94-101 cm), and obese (≥102 cm). The equivalent cut-off values for women were <80, 80-87 and ≥88 cm respectively.

Among men, WHR was categorised into normal weight (<0.90), overweight (0.90-0.99) and obese (≥1). Among women, the equivalent cut-off values were <0.80, 0.80-0.84 and ≥0.85 respectively (World Health Organization 2008) BF% was dichotomised into normal weight (defined as ≤25% for men and ≤32% for women) and obese (defined as >25% for men and >32% for women) (The American Council on Exercise 2013)

Smoking status, level of alcohol consumption, ethnic group and employment status were self-reported. Townsend deprivation index is an area-based measure of socioeconomic status and is derived from aggregated information collected in the census on: car ownership; overcrowding; owner-occupation and unemployment (Townsend 1987). The score includes both positive and negative values, with positive values indicating higher levels of deprivation. The presence of comorbidity was based on self-report of a physician diagnosis. Overall health was self-classified, and based on response to the question “In general, how would you rate your overall health; excellent, good, fair or poor? In this study, I collapsed these into two categories, one comprising excellent and good that I labelled good, and a second comprising fair and poor that I labelled poor. Overall happiness was self-reported, and based on response to the question: “In general, how happy are you; extremely happy, very happy, moderately happy, moderately unhappy, very unhappy or extremely unhappy?’ In this study, I collapsed these into two categories: happy (extremely happy, very happy, moderately happy) and unhappy (moderately unhappy, very unhappy or extremely unhappy). UK Biobank used validated questionnaires, particularly for lifestyle factors, socioeconomic status and general health (UK Biobank 2007).

This study was approved by the NHS National Research Ethics Service (17 June 2011, Ref 11/NW/0382). Written consent was obtained, including consent to collect baseline data, to obtain follow-up information via linkage to medical records, and to collect and analyse blood and urine samples. Participants agreed that, except for some measurements obtained during the visits, none of their results would be provided to them and they will not benefit from any future commercial developments.

9.3.4 Statistical analyses

Differences in the characteristics of participants by SRH and happiness were analysed using the x^2 test for categorical data, x^2 test for trend for ordinal data, and Wilcoxon rank-sum test for Townsend score (non-normally distributed). I examined the associations between anthropometric measurements (BMI, WC, WHR and BF%) and SRH and happiness using univariate and multivariate logistic regression models. Results are presented as OR and 95% CI. In the latter, I adjusted for the potential confounding effects of age, sex, socioeconomic and employment status, ethnic group, smoking status, frequency of alcohol consumption and presence of comorbidity. I tested whether there were statistically significant interactions by applying likelihood ratio test between anthropometric measurements and both sex; conducting subgroup analyses accordingly. All statistical analyses were performed using Stata version 12.1 (StataCorp, College Station, Texas). Statistical significance was defined as $p<0.05$.

9.4 Results

Of the 502,682 UK Biobank participants, 163,066 (32.4%) were recruited following inclusion of a happiness rating and were, therefore, eligible for inclusion in this study. Their mean BMI was 27.4 (SD 4.8) (men 27.8 (SD 4.2); women 27.1 (SD 5.2). Overall, the mean age was 57 years (SD 8 years), and 74,177 (45.5%) were men.

9.4.1 Self-reported health

Overall, 44,457 (27.3%) participants classified themselves as being in poor health. Compared to those with good SRH, those with poor SRH were more likely to be women, obese, deprived, unemployed, non-white, smoked and reported comorbidity, but consumed less alcohol and were not significantly different in terms of age (Table 9.1). There was a J-shaped relationship between several anthropometric measures and poor SRH in both men (Figure 9.1), and women (Figure 9.2). On both univariate and multivariate logistic regression analysis, there were significant associations between all anthropometric measures and SRH (all $p<0.001$) (Table 9.2). In relation to BMI category, those participants who were classified as underweight, overweight or obese (class I, II or III) had significantly increased odds of having poor SRH in comparison with normal weight participants with evidence of a dose relationship among participants with above-normal BMI (Table 9.2). Similarly, individuals classified as overweight or obese based on the other measures had significantly higher odds of poor SRH compared with individuals of normal-weight, with higher odds for obese than overweight. There was a significant interaction with gender ($p<0.001$). Sub-group analyses by sex demonstrated that the overall patterns of association were common to both men and women, but the OR associated with class II and III obesity tended to be higher in men (Table 9.2).

When the logistic regression analyses were re-run entering the anthropometric measures as sex-specific deciles, the adjusted OR in both sexes showed the same J shaped relationships (Figure 9.1 and 9.2) observed for the crude frequencies (Figures 9.3 and 9.4). Men and women in the highest deciles of BMI, WHR and WC had fourfold to sixfold higher odds of poor SRH. The magnitude of association with BF% was much greater in men than women. Being in the top decile of BF% increased the odds of poor SRH ninefold in men (adjusted OR 8.99, 95% CI 5.58, 14.49, $p<0.001$) (Figure 9.3) but only threefold in women (adjusted OR 3.33, 95% CI 3.09, 3.59, $p<0.001$) (Figure 9.4).

Table 9.1 Characteristics of the participants by self-reported health and happiness.

	Self-reported General Health			Self-reported overall Happiness		
	Good N=118609 N (%)	**Poor** N= 44457 N (%)	P-value	**Happy** N=155555 N (%)	**Unhappy** N=7511 N (%)	P-value
Sex						
Women	66600 (56.15)	22289 (50.14)	<0.001	85105 (54.71)	3784 (50.38)	<0.001
Men	52009 (43.85)	22168 (49.86)		70450 (45.29)	3727 (49.62)	
Age (years)						
39-49	26985 (22.75)	10167 (22.87)	0.134	34714 (22.32)	2438 (32.46)	<0.001
50-60	42930 (36.19)	16274 (36.61)		56076 (36.05)	3128 (41.65)	
61-72	48694 (41.05)	18016 (40.52)		64765 (41.63)	1945 (25.90)	
BMI category						
Underweight	555 (0.47)	241 (0.54)	<0.001	729 (0.47)	67 (0.89)	<0.001
Normal-weight	43995 (37.09)	9284 (20.88)		50873 (32.70)	2406 (32.03)	
Overweight	51983 (43.83)	17067 (38.39)		66216 (42.57)	2834 (37.73)	
Class I obese	17249 (14.54)	11432 (25.71)		27213 (17.49)	1468 (19.54)	
Class II obese	3837 (3.23)	4294 (9.66)		7665 (4.93)	466 (6.20)	
Class III obese	990 (0.83)	2139 (4.81)		2859 (1.84)	270 (3.59)	
WC category						
Normal-weight	53223 (44.87)	11257 (25.32)	<0.001	61636 (39.62)	2844 (37.86)	<0.001
Overweight	32791 (27.65)	10787 (24.26)		41781 (26.86)	1797 (23.92)	
Obese	32595 (27.48)	22413 (50.42)		52138 (33.52)	2870 (38.21)	
WHR category						
Normal-weight	47874 (40.36)	10293 (23.15)	<0.001	55681 (35.80)	2486 (33.10)	<0.001
Overweight	46689 (39.36)	18472 (41.55)		62219 (40.00)	2942 (39.17)	
Obese	24046 (20.27)	15692 (35.30)		37655 (24.21)	2083 (27.73)	
%BF category						
Normal-weight	45812 (38.62)	10479 (23.57)	<0.001	53582 (34.45)	2709 (36.07)	0.003
Obese	72797 (61.38)	33978 (76.43)		101973 (65.55)	4802 (63.93)	
[‡]**Townsend score median (IQR)**						
	-2.07 (3.85)	-1.08(4.78)	<0.001	-1.87 (4.08)	-0.64 (5.05)	<0.001
Employment status						
Employed	69946 (58.97)	22014 (49.52)	<0.001	87868 (56.49)	4092 (54.48)	<0.001
Retired	41330 (34.85)	15531 (34.93)		55225 (35.50)	1636 (21.78)	
Look after home	3517 (2.97)	1354 (3.05)		4589 (2.95)	282 (3.75)	
Unemployed	2761 (2.33)	1697 (3.82)		3953 (2.54)	505 (6.72)	
Not working	704 (0.59)	3740 (8.41)		3478 (2.24)	966 (12.86)	
Student	351 (0.30)	121 (0.27)		442 (0.28)	30 (0.40)	
Ethnicity						
White	110390 (93.07)	39330 (88.47)	<0.001	143128 (92.01)	6592 (87.76)	<0.001
Mixed	822 (0.69)	394 (0.89)		1137 (0.73)	79 (1.05)	
Asian	3111 (2.62)	2255 (2.62)		4991 (3.21)	375 (4.99)	
Black	2641 (2.23)	1562 (3.51)		3927 (2.52)	276 (3.67)	
Chinese	413 (0.35)	197 (0.44)		569 (0.37)	41 (0.55)	
Other	1232 (1.04)	719 (1.62)		1803 (1.16)	148 (1.97)	

Alcohol consumption						
Daily	25677 (21.65)	7563 (17.01)	<0.001	31720 (20.39)	1520 (20.24)	<0.001
3-4 times/week	28685 (24.18)	7880 (17.72)		35292 (22.69)	1273 (16.95)	
1-2 times/week	30600 (25.80)	10492 (23.60)		39502 (25.39)	1590 (21.17)	
1-2 times/month	13041 (10.99)	5517 (12.41)		17624 (11.33)	934 (12.44)	
Special occasions	12394 (10.45)	7321 (16.47)		18506 (11.90)	1209 (16.10)	
Never	8212 (6.92)	5684 (12.79)		12911 (8.30)	985 (13.11)	
Smoking status						
Never	68702 (57.92)	21696 (48.80)	<0.001	86586 (55.66)	3812 (50.75)	<0.001
Previous	40452 (34.11)	16039 (36.08)		54113 (34.79)	2378 (31.66)	
Current	9455 (7.97)	6722 (15.12)		14856 (9.55)	1321 (17.59)	
Comorbidity						
No	82923 (69.91)	20394 (45.87)	<0.001	98717 (63.46)	4600 (61.24)	<0.001
Yes	35686 (30.09)	24063 (54.13)		56838 (36.54)	2911 (38.76)	

‡ Townsend score, a measure of socio-economic status; a negative score represents greater affluence. P-value; χ^2 test for categorical data and χ^2 test for trend for ordinal data, Wilcoxon rank-sum test for Townsend score (non normally distributed).

Table 9.2 Logistic regression analysis of the participant characteristics associated with having poor self-reported health.

	Overall				Men				Women			
	Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate	
	Odds Ratio (95% CI)	P-value	Odds Ratio (95% CI)	P-value	Odds Ratio (95% CI)	P-value	Odds Ratio (95% CI)	P-value	Odds Ratio (95% CI)	P-value	Odds Ratio (95% CI)	P-value
BMI category												
Underweight	2.06 (1.77, 2.40)	<0.001	1.67 (1.41, 1.97)	<0.001	3.64 (2.67, 4.97)	<0.001	2.43 (1.72, 3.45)	<0.001	1.85 (1.54,2.21)	<0.001	1.49 (1.22, 1.81)	<0.001
Normal-weight	1	-	1	-	1	-	1	-	1	-	1	-
Overweight	1.56 (1.51, 1.60)	<0.001	1.40 (1.35, 1.44)	<0.001	1.34 (1.29, 1.40)	<0.001	1.29 (1.23, 1.35)	<0.001	1.63 (1.57, 1.70)	<0.001	1.47 (1.42, 1.54)	<0.001
Class I obese	3.14(3.04, 3.24)	<0.001	2.49 (2.40, 2.58)	<0.001	2.76 (2.63, 2.90)	<0.001	2.32 (2.20, 2.45)	<0.001	3.26 (3.12, 3.41)	<0.001	2.58 (2.46, 2.70)	<0.001
Class II obese	5.30 (5.05, 5.57)	<0.001	3.82 (3.63, 4.03)	<0.001	5.22 (4.83, 5.65)	<0.001	3.86 (3.55, 4.19)	<0.001	5.29 (4.97, 5.64)	<0.001	3.75 (3.50, 4.01)	<0.001
Class III obese	10.24 (9.47, 11.08)	<0.001	6.45 (5.94, 7.02)	<0.001	11.44 (9.86, 13.28)	<0.001	7.38 (6.31, 8.63)	<0.001	10.15 (9.25, 11.15)	<0.001	6.13 (5.55, 6.77)	<0.001
Waist circumference												
Normal-weight	1	-	1	-	1	-	1	-	1	-	1	-
Overweight	1.56 (1.51, 1.60)	<0.001	1.47 (1.42, 1.51)	<0.001	1.57 (1.51, 1.64)	<0.001	1.50 (1.43, 1.56)	<0.001	1.52 (1.46, 1.59)	<0.001	1.42 (1.35, 1.48)	<0.001
Obese	3.25 (3.17, 3.34)	<0.001	2.68 (2.60, 2.76)	<0.001	3.28 (3.16, 3.41)	<0.001	2.71 (2.60, 2.83)	<0.001	3.38 (3.26, 3.51)	<0.001	2.60 (2.49, 2.70)	<0.001
Waist to hip ratio												
Normal-weight	1	-	1	-	1	-	1	-	1	-	1	-
Overweight	1.84 (1.79, 1.89)	<0.001	1.51 (1.46, 1.55)	<0.001	2.01 (1.93, 2.10)	<0.001	1.79 (1.72, 1.87)	<0.001	1.52 (1.46, 1.58)	<0.001	1.34 (1.29, 1.40)	<0.001
Obese	3.04 (2.95, 3.13)	<0.001	2.34 (2.27, 2.42)	<0.001	4.77 (4.53, 5.02)	<0.001	3.48 (3.29, 3.68)	<0.001	2.54 (2.45, 2.64)	<0.001	1.90 (1.83, 1.98)	<0.001
Body fat Percent												
Normal-weight	1	-	1	-	1	-	1	-	1	-	1	-
Obese	2.04 (1.99, 2.09)	<0.001	1.98 (1.92, 2.03)	<0.001	2.30 (2.22, 2.37)	<0.001	2.0 (1.93, 2.07)	<0.001	2.24 (2.15, 2.33)	<0.001	1.93 (1.85, 2.02)	<0.001

9.4.2 Self-reported happiness

Overall, 7,511 (4.6%) participants reported feeling unhappy. Compared to those with good self-reported happiness, those with poor self-reported happiness were more likely to be women, obese, deprived, unemployed, non-white, smoked and reported comorbidity, but consumed less alcohol and were not significantly different in terms of age (Table 9.1). In both men (Figure 9.1) and women (Figure 9.2), the odds of being unhappy were higher in only the highest deciles of adiposity. There was a significant interaction with gender ($p<0.001$) but not with ethnicity ($p=0.366$). On logistic regression analysis, women who were obese, based on BMI, were more likely to be unhappy (Table 9.3). Adjustment for the potential confounding effects attenuated the associations but they remained statistically significant (class III obese adjusted OR 1.38, 95% CI 1.16, 1.65, $p<0.001$) (Table 9.3). BF% was less discriminatory. Men only had significantly higher odds of unhappiness if they were class III obese (adjusted OR 1.29, 95% CI 1.03, 1.63, $p=0.029$), and overweight and class I obese men were significantly less likely to be unhappy than men of normal weight (Table 9.3).

Overall, of the 44,457 participants with self-reported poor health, 39,869 (89.7%) were happy and, of the 7,511 participants who felt unhappy, 2,923 (38.9%) reported good health. After adjustment for SRH, obesity was no longer associated with a significantly increased risk of unhappiness (Table 9.4). In women, being underweight was associated with increased odds of being unhappy even after adjusting for potential confounders including comorbidity (Table 9.3). But when the analyses were stratified according to whether or not participants reported themselves as healthy, underweight women who reported themselves to be healthy were no longer significantly more likely to be unhappy (adjusted OR 1.39, 95% CI 0.86, 2.24, $p=0.181$) (Table 9.5a) whereas unhealthy underweight women were still more likely to feel unhappy (adjusted OR 1.70, 95% CI 1.14, 2.53, $p=0.009$) (Table 9.5b). Among men, there was a significant univariate association between being underweight and unhappy but this was no longer significant following adjustment for potential confounders (Table 9.3).

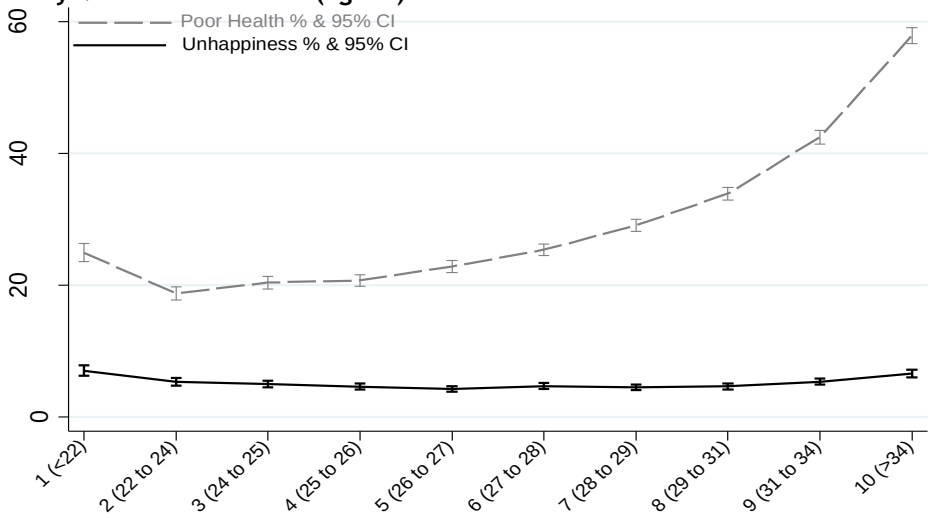
Table 9.3 Logistic regression analysis of the participant characteristics associated with self-reported Unhappiness.

	Overall				Men				Women			
	Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate	
	Odds Ratio (95% CI)	P-value	Odds Ratio (95% CI)	P-value	Odds Ratio (95% CI)	P-value	Odds Ratio (95% CI)	P-value	Odds Ratio (95% CI)	P-value	Odds Ratio (95% CI)	P-value
BMI category												
Underweight	1.94 (1.51, 2.50)	<0.001	1.44 (1.11, 1.88)	0.006	1.74 (1.02, 2.97)	0.043	0.93 (0.53, 1.63)	0.798	2.16 (1.62, 2.89)	<0.001	1.73 (1.28, 2.33)	<0.001
Normal-weight	1	-	1	-	1	-	1	-	1	-	1	-
Overweight	0.90 (0.86, 0.96)	<0.001	0.89 (0.84, 0.94)	<0.001	0.79 (0.73, 0.86)	<0.001	0.83 (0.77, 0.90)	<0.001	0.94 (0.87, 1.01)	0.105	0.94 (0.87, 1.02)	0.137
Class I obese	1.14 (1.07, 1.22)	<0.001	1.02 (0.95, 1.09)	0.576	0.94 (0.85, 1.04)	0.21	0.89 (0.81, 0.99)	0.029	1.27 (1.16, 1.40)	<0.001	1.15 (1.05, 1.27)	0.004
Class II obese	1.29 (1.16, 1.42)	<0.001	1.03 (0.93, 1.15)	0.536	1.10 (0.94, 1.29)	0.221	0.91 (0.77, 1.07)	0.245	1.41 (1.23, 1.61)	<0.001	1.15 (1.00, 1.32)	0.057
Class III obese	2.0 (1.75, 2.28)	<0.001	1.33 (1.15, 1.53)	<0.001	1.88 (1.51, 2.34)	<0.001	1.29 (1.03, 1.63)	0.029	2.11 (1.79, 2.49)	<0.001	1.38 (1.16, 1.65)	<0.001
Waist circumference												
Normal-weight	1	-	1	-	1	-	1	-	1	-	1	-
Overweight	0.93 (0.88, 0.99)	0.022	0.96 (0.90, 1.02)	0.218	0.92 (0.84, 0.99)	0.036	0.96 (0.88, 1.05)	0.366	0.94 (0.86, 1.03)	0.193	0.96 (0.88, 1.05)	0.381
Obese	1.19 (1.13, 1.26)	<0.001	1.11 (1.05, 1.17)	<0.001	1.15 (1.07, 1.24)	<0.001	1.09 (1.01, 1.19)	0.037	1.26 (1.17, 1.36)	<0.001	1.12 (1.04, 1.22)	0.004
Waist to hip ratio												
Normal-weight	1	-	1	-	1	-	1	-			1	-
Overweight	1.06 (1.0, 1.12)	0.039	0.99 (0.93, 1.05)	0.732	1.0 (0.92, 1.07)	0.9	1.01 (0.93, 1.10)	0.791	1.0 (0.92, 1.09)	0.958	0.97 (0.89, 1.06)	0.507
Obese	1.24 (1.17, 1.32)	<0.001	1.14 (1.07, 1.21)	<0.001	1.29 (1.17, 1.43)	<0.001	1.16 (1.04, 1.29)	0.008	1.25 (1.16, 1.35)	<0.001	1.12 (1.03, 1.21)	0.006
Body fat Percent												
Normal-weight	1	-	1	-	1	-	1	-	1	-	1	-
Obese	0.93 (0.89, 0.97)	0.004	0.98 (0.93, 1.04)	0.535	0.98 (0.92, 1.05)	0.541	0.98 (0.91, 1.05)	0.505	0.96 (0.89, 1.03)	0.26	0.96 (0.89, 1.04)	0.298

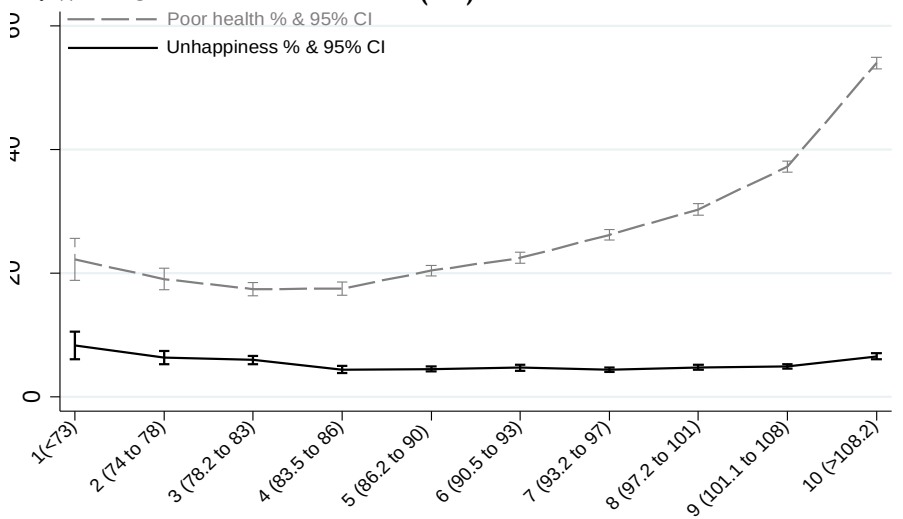
CI; Confidence Interval, adjusted by age, sex, socio-economic status, employment, ethnicity, alcohol consumption, smoking and comorbidity (CVD, hypertension, diabetes and cancer)

Figure 9.1 Frequency (%) of self-reported poor health and unhappiness by measures of adiposity in Men

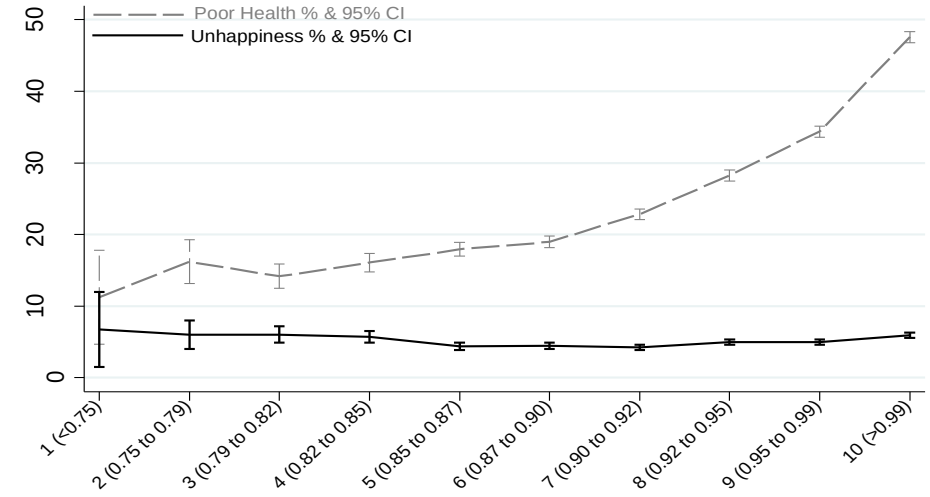
a. Body Mass Index deciles (kg/m^2)



b. Waist Circumference deciles (cm)



c. Waist to hip ratio deciles



d. Body fat % deciles

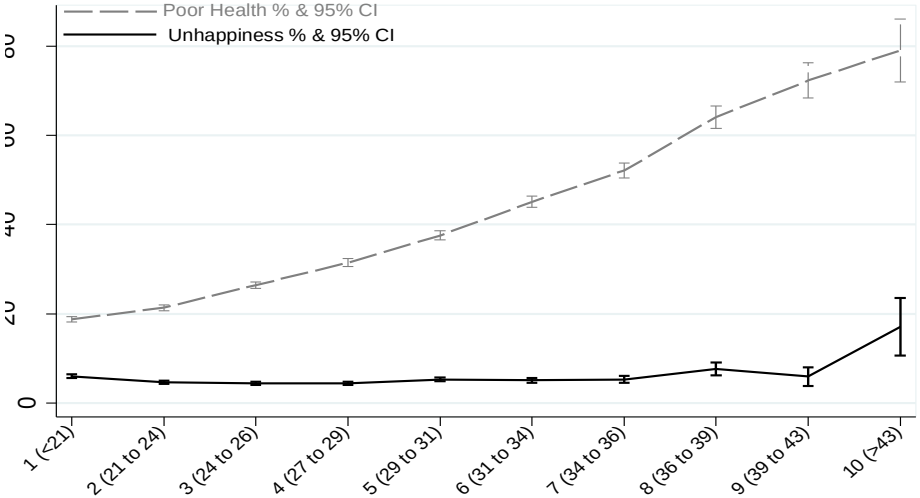
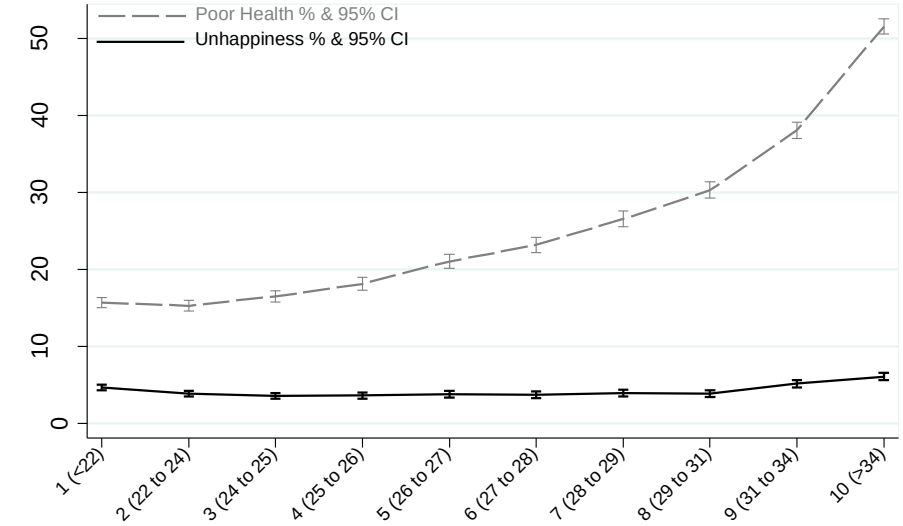
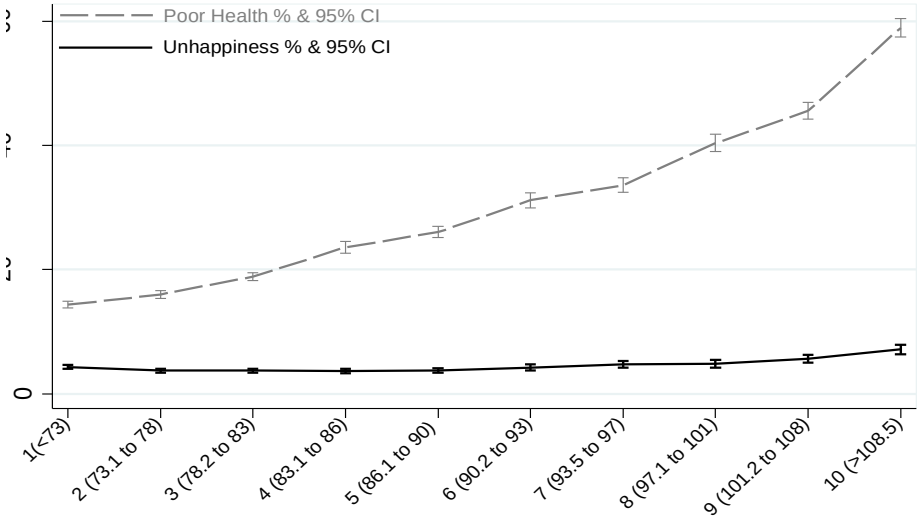


Figure 9.2 Frequency (%) of self-reported poor health and unhappiness by measures of adiposity in Women.

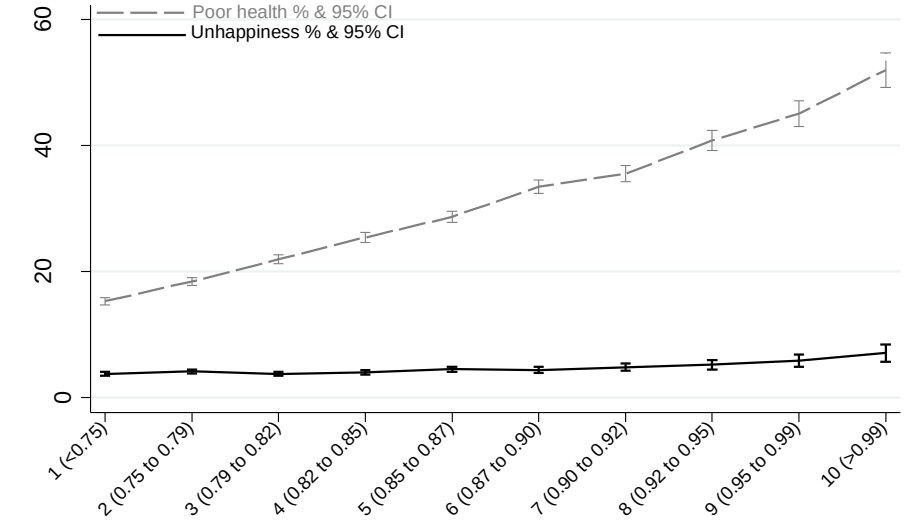
a. Body Mass Index deciles (kg/m^2)



b. Waist Circumference deciles (cm)



c. Waist-to-hip ratio deciles



d. Body fat% deciles

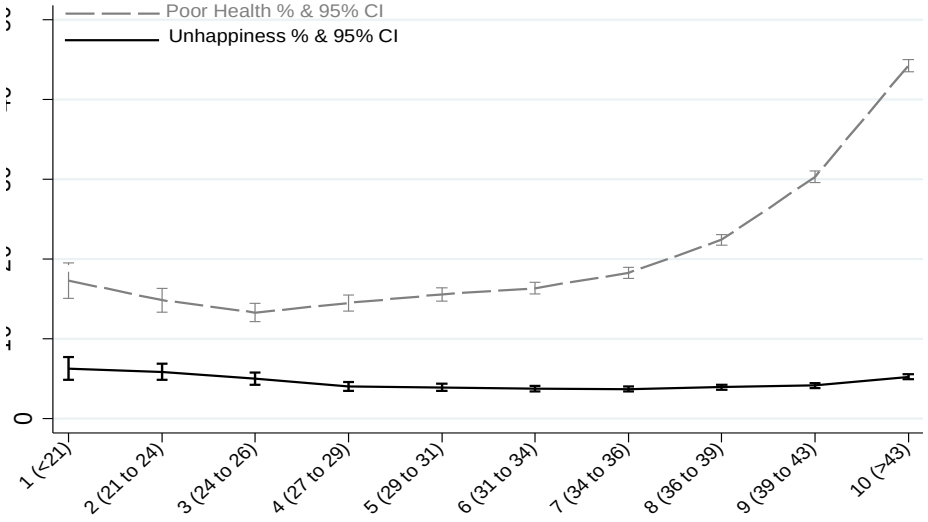
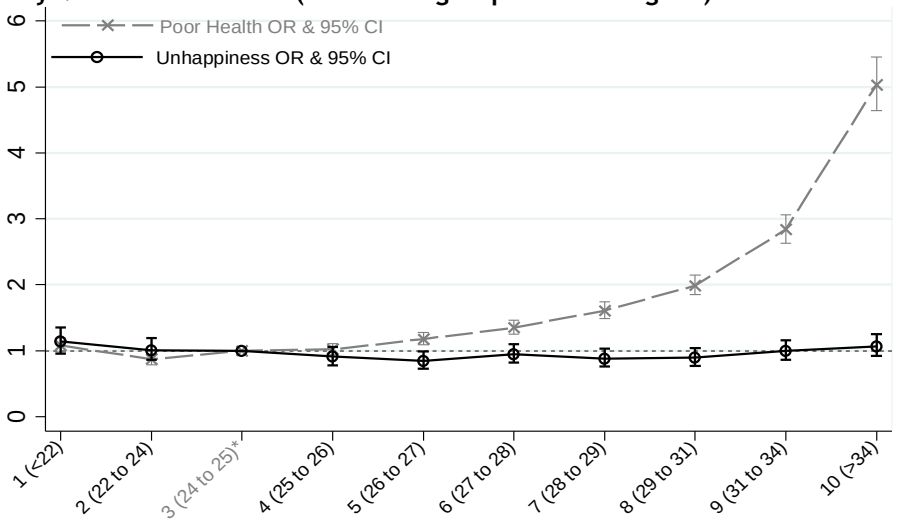
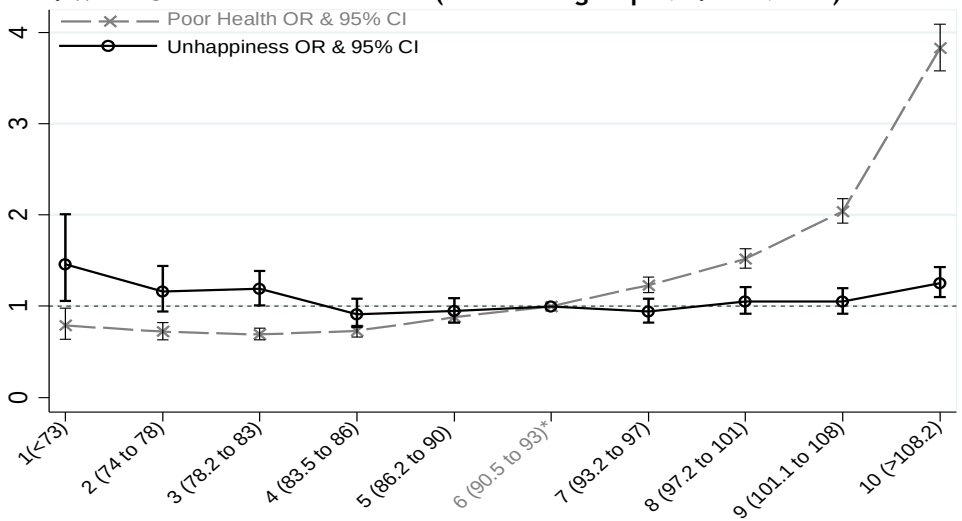


Figure 9.3 Adjusted odds ratio of self-reported poor health and unhappiness by measures of adiposity in Men.

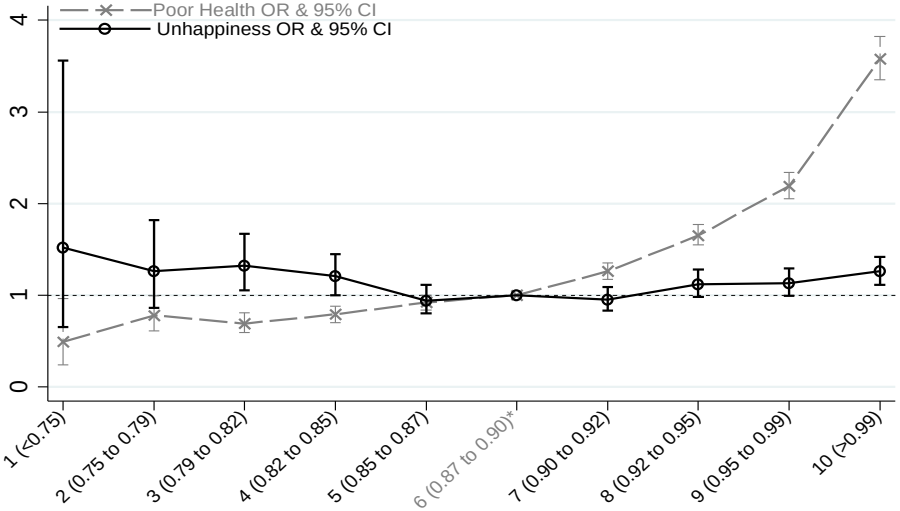
a. Body Mass Index deciles (reference group* 24 to 25kg/m^2)



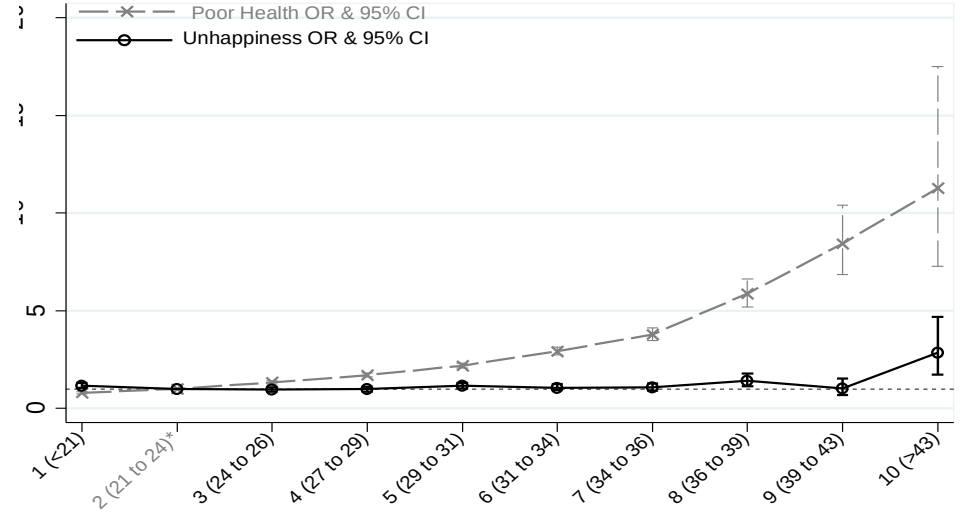
b. Waist Circumference deciles (reference group* 90.5 to 93cm)



c. Waist to hip ratio deciles (reference group* 0.87 to 0.90)



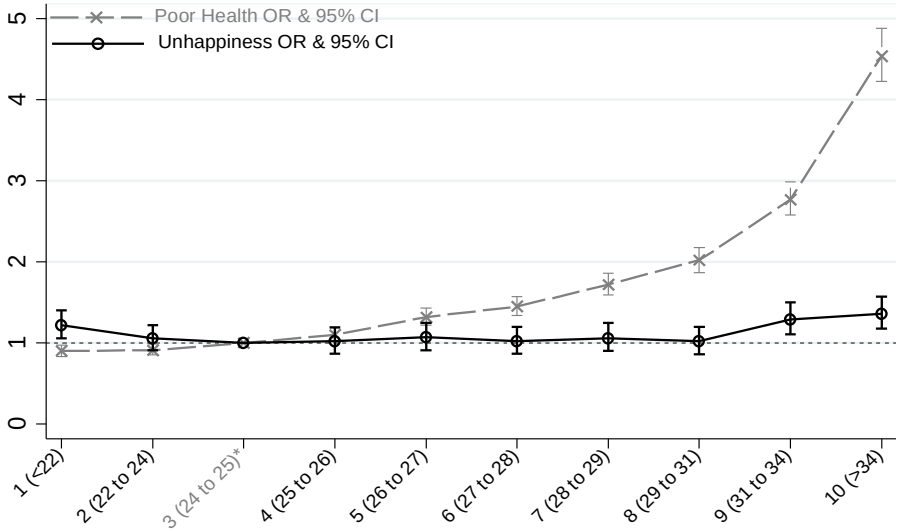
d. Body fat % deciles (reference group* 21 to 24%)



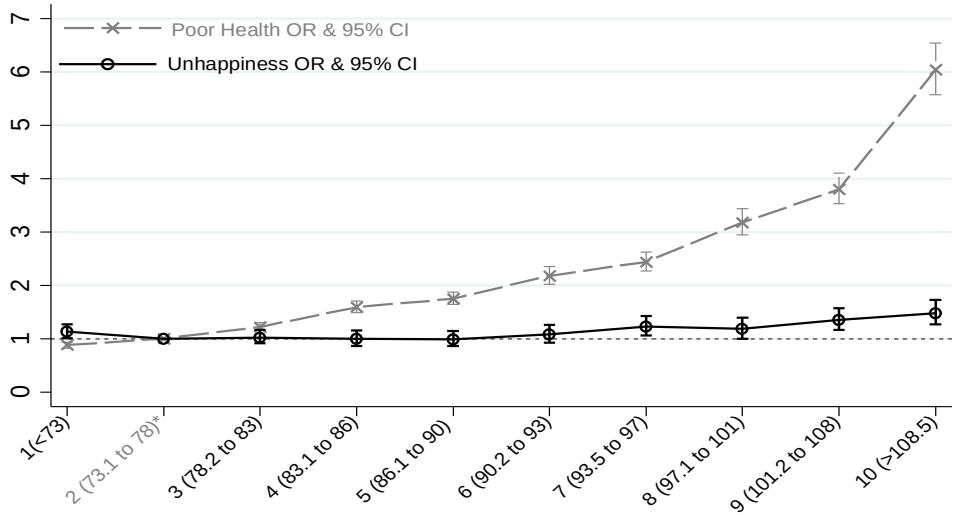
OR; Odds ratio, CI; confidence interval, Adjusted by age, socio-economic status, employment, ethnicity, alcohol consumption, smoking, and comorbidity

Figure 9.4 Adjusted odds ratio of self-reported poor health and unhappiness by measures of adiposity in Women

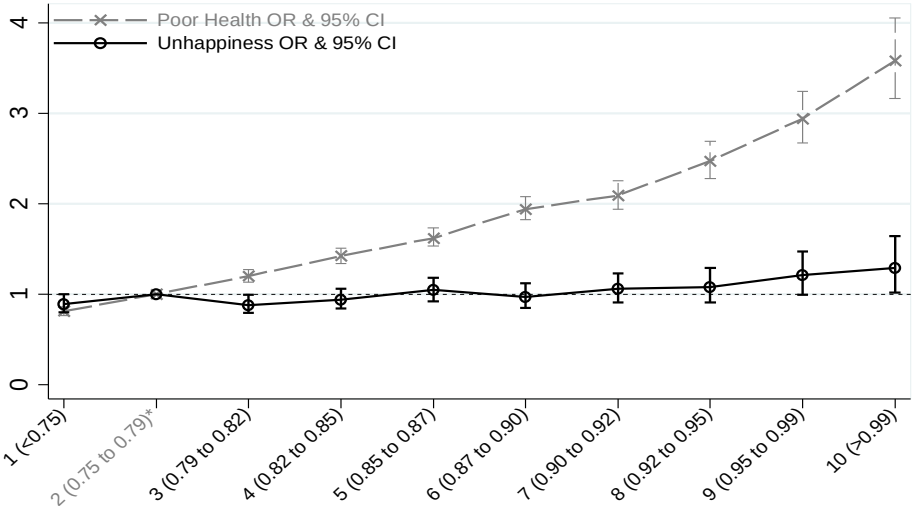
a. Body Mass Index deciles (reference group* 24 to 25kg/m^2)



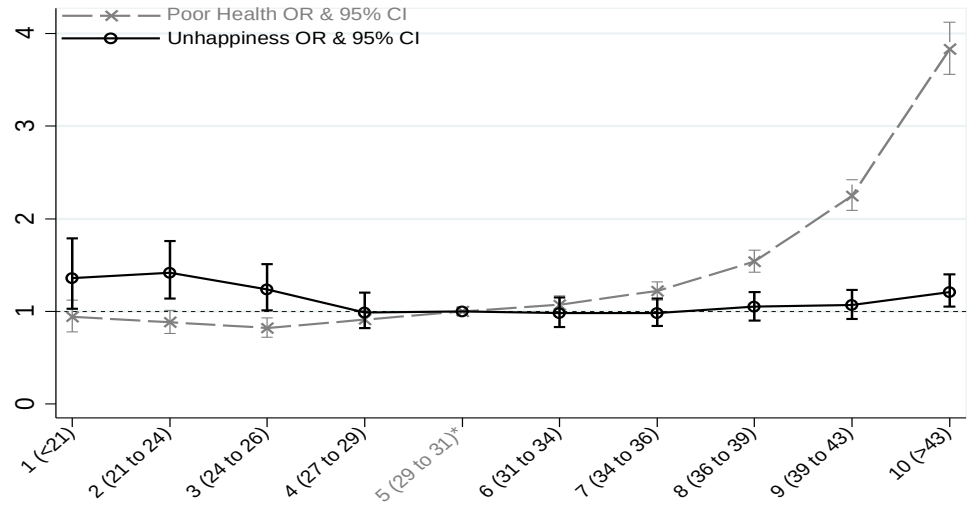
b. Waist Circumference deciles (reference group* 73 to 78cm)



c. Waist to hip ratio deciles (reference group* 0.75 to 0.79)



d. Body fat % deciles (reference group* 29 to 31%)



OR; Odds ratio, CI; confidence interval, Adjusted by age, socio-economic status, employment, ethnicity, alcohol consumption, smoking, and comorbidity

Table 9.4 Logistic multivariate regression analysis of the body mass index associated with self-reported unhappiness after adjustment for self-reported health, in addition to the other potential confounding factors.

	Odds Ratio (95% CI)	P-value
BMI category		
Underweight	1.24 (0.94, 1.62)	0.123
Normal-weight	1	-
Overweight	0.81 (0.77, 0.86)	<0.001
Class I obese	0.78 (0.73, 0.84)	<0.001
Class II obese	0.71 (0.64, 0.79)	<0.001
Class III obese	0.84 (0.73, 0.97)	0.015

CI; Confidence Interval, adjusted by age, sex, socio-economic status, employment, ethnicity, alcohol consumption, smoking, comorbidity and self-reported health.

Table 9.5 Logistic regression analysis of the women body mass index associated with self-reported unhappiness after stratification by self-reported health.

a. Self-reported good health women

	Odds ratio (95% CI)	P-value
BMI category		
Underweight	1.39 (0.86,2.25)	0.181
Normal-weight	1	-
Overweight	0.82 (0.72, 0.91)	<0.001
Class I obese	0.87 (0.74, 1.03)	0.100
Class II obese	0.77 (0.58, 1.03)	0.075
Class III obese	0.75 (0.46, 1.23)	0.254

b. Self-reported poor health women

	Odds ratio(95% CI)	P-value
BMI category		
Underweight	1.70 (1.14,2.53)	0.009
Normal-weight	1	-
Overweight	0.85 (0.75, 0.95)	0.005
Class I obese	0.84 (0.74, 0.95)	0.007
Class II obese	0.75 (0.63, 0.89)	0.001
Class III obese	0.85 (0.70, 1.03)	0.098

CI; Confidence Interval, adjusted by age, socio-economic status, employment, ethnicity, alcohol consumption, smoking, comorbidity

9.5 Discussion

In this study I sought to investigate the relationship between obesity, health and happiness using a large cross-sectional study of the UK general population. I found that there was no association between happiness and self-reported good health which suggests that the general population may primarily define their health in terms of physical, rather than psychosocial, well-being. Overweight and obese individuals were significantly more likely to report poor overall health than individuals of normal weight, even after adjustment for potential confounders, and irrespective of the anthropometric measure used. The association varied by sex such that obesity increased the odds of poor self-rated health in men more than in women. In contrast, obesity increased the odds of unhappiness in women more than men. Overweight and class I obese men were more likely to report being happy than men of normal weight, and men only reported feeling unhappy if they were severely obese. Conversely, women reported unhappiness at lower levels of obesity. The significant association between obesity and unhappiness was lost following adjustment for SRH suggesting that the association may be mediated by health. Being underweight may occur as a result of ill-health, and underweight women were only at increased risk of unhappiness if they also reported themselves as unhealthy.

Self-reported poor health is a stronger predictor of mortality among men (Idler & Benyamini 1997). My findings suggested that the association between poor SRH and obesity was also stronger in men. Both may be due to sex differences in the range of factors considered when self-reporting health (Benyamini et al. 2000). Previous study findings have been inconsistent as to whether SRH is poorer in overweight and obese individuals. Studies have reported different results across countries (Gray et al. 2012; Macmillan et al. 2011; Marques-Vidal et al. 2012). Poor SRH was more prevalent in the UK than other European countries, particularly in men (Gray et al. 2012). In contrast, poor mental health was more prevalent in women than men, in all the European countries studied (Gray et al. 2012). There is a paucity of UK studies on the association between body weight and SRH, but my findings of higher poor SRH among overweight and obese individuals are in line with published international studies (Okosun et al. 2001; Trakas et al. 2001).

The sex differences I observed in the relationship between adiposity and happiness are consistent with the previous studies that have examined overall quality of life; as is the finding of greater happiness among overweight men. In Chapter 7, I reported sex differences in the relationship between BMI and mental health in a cross-sectional study of more than 37,000 Scottish adults (Chapter 7; Ul-Haq,Z 2013a). Being overweight was associated with better mental health in men only and obesity was associated with significantly worse mental health in women only. Greeno et al reported an association between obesity and reduced life satisfaction in women only (Greeno et al. 1998). Obese men had significantly higher life satisfaction (Greeno at al. 1998). In a recent meta-analysis, HRQoL was significantly reduced in class III obese adults and improved in overweight adults (chapter 4; Ul-Haq, Z et al. 2013b).

Health is an important determinant of well-being and happiness; but it is not the only determinant. Electronic and print media invariably use thin and muscular models and are becoming increasingly unrepresentative of the general population in which more than 65% of individuals are either overweight or obese. Portrayal of these models as the ideal can promote negative body image and disordered eating (Diedrichs et al. 2011). Several studies have reported more discriminatory societal attitudes towards obesity in women than men (Fabricatore & Wadden 2003). Obesity-related stigma begins very early in life, as young as three years of age, and persists through childhood and adolescence into adult and later life (Cramer & Steznwert 1998). There is evidence of discrimination in recruitment, education, news and the media (Roehling 1999). Recurrent stigma, prejudice and discrimination could result in chronic psychological stress, reduced mental health and overall happiness.

9.6 Strengths and limitations

A small number of previous studies have examined the association between level of adiposity and SRH and happiness. To my knowledge, this is the first study to examine the relationship across the full spectrum from underweight to class III obese, and use multiple anthropometric measurements. Use of UK Biobank provided a large sample of middle-aged and old-aged individuals recruited from the general population. I was able to adjust for a series of potential confounders, but as with any observational study, residual confounding is always

possible. Many studies have used only BMI which is a poor measure of adiposity in muscular individuals. Having access to three other measures of adiposity (WC, WHR and BF%) enabled me to corroborate my findings using BMI. I was able to demonstrate interactions by sex and to undertake subgroup analyses accordingly. As with any cross-sectional study, it was not possible to establish a temporal relationship and exclude reverse causation. Obesity may predispose to unhappiness. Conversely, unhappiness may lead to over-eating. A longitudinal study reported that after 5 years of follow-up, obesity, predicted unhappiness (OR 1.70) and depression (OR 2.16), but depression did not predict obesity (Roberts et al. 2002; Roberts et al. 2003). Conversely, another study reported that baseline depressive symptoms influenced future adiposity but initial adiposity did not influence future depressive symptoms (Richardson et al. 2003).

One weakness of this study is that it used a condensed rating scale for happiness that has been rarely used. However, some previous studies have used a similar happiness question using the full range of categories from extremely happy to extremely unhappy (Charness & Grosskopf 2001; Lee et al. 2000). Less than 10% of invited people participated in UK Biobank. It is representative of the UK population in terms of breakdown for age, sex, ethnicity and socioeconomic status, but may not be representative in terms of other parameters, such as lifestyle. However, my finding of an overall prevalence of 66% for overweight or obese (42% and 24% respectively) corresponds closely with national statistics (Health and Social Care Information Centre 2013; Keenan at al. 2011). The 27% prevalence for poor SRH observed in my study and mean score of 2.177 are higher than the UK figures (9.1% and 1.196 respectively) reported in WHO's "2002 World Health Survey" (Subramanian et al. 2010) but this difference is likely to be due, in part, to WHO survey participants being younger (mean age of 45 years compared with 57 years in UK Biobank) since my figures are commensurate with UK national figures (Young et al. 2010). Inclusion was restricted to participants who had completed the happiness question. They were more likely to be older ($p<0.001$), and deprived ($p<0.001$) than participants who did not complete the happiness question, but were not significantly different in terms of sex ($p=0.855$). The association between BMI and happiness is highly significant ($p<0.001$) but the odds ratios are small. Clinical significance as well

as statistical significant should be considered when interpreting the outputs, particularly in the high-powered studies.

9.7 Implications of this research

High levels of adiposity are associated with unhappiness as well as poor health. Compared with obese men, obese women are less likely to report poor health but more likely to report unhappiness. However, after adjustment for SRH the association between adiposity and unhappiness is lost, suggesting that this association may be mediated by health. This study further supports the existing evidence that there is an association between adiposity and subjective well-being, particularly perceived health, regardless of the anthropometric measurements used, and independent of various potential confounders, including comorbidity. These findings emphasise the need for individual and community-level interventions to reverse the higher prevalence of obesity because it is a risk to mental, as well as physical, well-being.

10 Chapter 10: Conclusion

This chapter describes the inter-linkages between the thesis chapters, summarises the key findings, discusses the strengths and limitations of the methodology used, and proposes recommendations based on the findings of the research included in this thesis.

10.1 Inter-linkages between thesis chapters

The terms subjective well-being, life satisfaction and happiness are frequently used interchangeably. Correspondingly, the terms quality of life are occasionally used as synonym with health status, well-being, life-satisfaction and happiness. These are all broad ranging concepts but in simple, these are the scientific term relating to how individuals evaluate their own lives. Health is an important element of subjective well-being; but there are many other domains, such as income, jobs, socio-economic status, education, housing, leisure time, neighbourhood, marital status, heredity characters and social belonging (Wilson et al. 2003; Subramanian et al. 2005). Findings from the Framingham Heart Study social network showed that the people's happiness depends on the other people's happiness related to them to a 3 degree of separation i.e., to one's friends' friends' friends (Fowler & Christakis 2008). The concept of HRQoL, SRH or self-perceived health corresponds to those aspects of subjective well-being that are closely related to health, either physical or mental. According to the WHO, worldwide the life-expectancy at birth for both men and women has reached to 70 years, ranges from 62 years in developing countries to 79 years in the developed countries. There is a 6 years of gain, since 1990. Women are living longer by 5 years (more than 6 years in developed country) and this gap is consistent since 1990. The developed countries have achieved an adequate level of affluence that survival is no more a fundamental factors in individuals' lives but how good is their quality of life. The increasing trend of individualism has also enhanced the importance of individual's well-being and happiness (Ogihara & Uchida 2014). Furthermore, the development of valid and more reliable measure of well-being, such as the generic measure of SF-36 (Ware Jr. 2000), SF-12 (Wee et al. 2008), PedsQL (Varni et al. 2003), SRH (Bowling 2005), and GHQ (Goldberg et al. 1997) are the reasons of flourishing the research of well-being over the recent past. Self-reported physical and mental health and HRQoL are independent predictors of all-

cause mortality (Nielsen et al. 2008; Haring et al. 2011), but whether they are also independent predictors of incident diseases such as cancer, CHD and psychiatric hospitalisation is not well-documented.

Adiposity is a significant higher risk factor for the development of many physical conditions than other avoidable factors such as smoking, alcohol and poverty (Sturm & Wells 2001). The annually direct and indirect health care costs due to obesity is in billions of pounds (Vlad 2003). The higher prevalence of obesity is a threat to halt and possibly reverse the steady increase in the life expectancy (Lavie et al. 2009). Obesity can also spread to three degrees of separation (Christakis & Fowler 2007), just like the spread of happiness (Fowler & Christakis 2008) and smoking behaviour (Christakis & Fowler 2008). The impact of this highly prevalent avoidable risk factor on all the aspects of public health is of greater importance, not only in terms of objective measurements of health; morbidity and mortality but perhaps also in relation to self-perceived health.

The research on the association between adiposity and subjective well-being is in an early phase. There is a paucity of existing studies and those conducted, have suggested a complex relationship between adiposity and different measures of subjective well-being. The aim of this thesis was to first investigate whether self-reported physical and mental health and HRQoL are independent predictors of incident diseases such as cancer, CHD and psychiatric hospitalisation in the general population, and then to determine relationships between adiposity and self-perceived health, and whether any associations varied by sex, and comorbidity. The thesis comprises eight complementary studies (Chapters 2 to 9, inclusive) to achieve these aims.

Chapters 2 and 3 looked at subjective well-being (exposure) and clinical outcomes, whereas the other chapters looked at adiposity (exposure) and subjective well-being (outcome) (Figure 10-1). This thesis is focused on adiposity and health. Health can be defined in many ways. In chapters 2 and 3 I demonstrated that subjective well-being (measured in terms of both HRQoL and Self-reported physical and mental health) was associated with clinical adverse outcomes, such as cancer,

CHD, psychiatric admissions and deaths, thereby demonstrating the importance of subjective well-being as a health outcome measure. Therefore, the subsequent chapters focus on the association between adiposity (exposure) and subjective well-being (outcome).

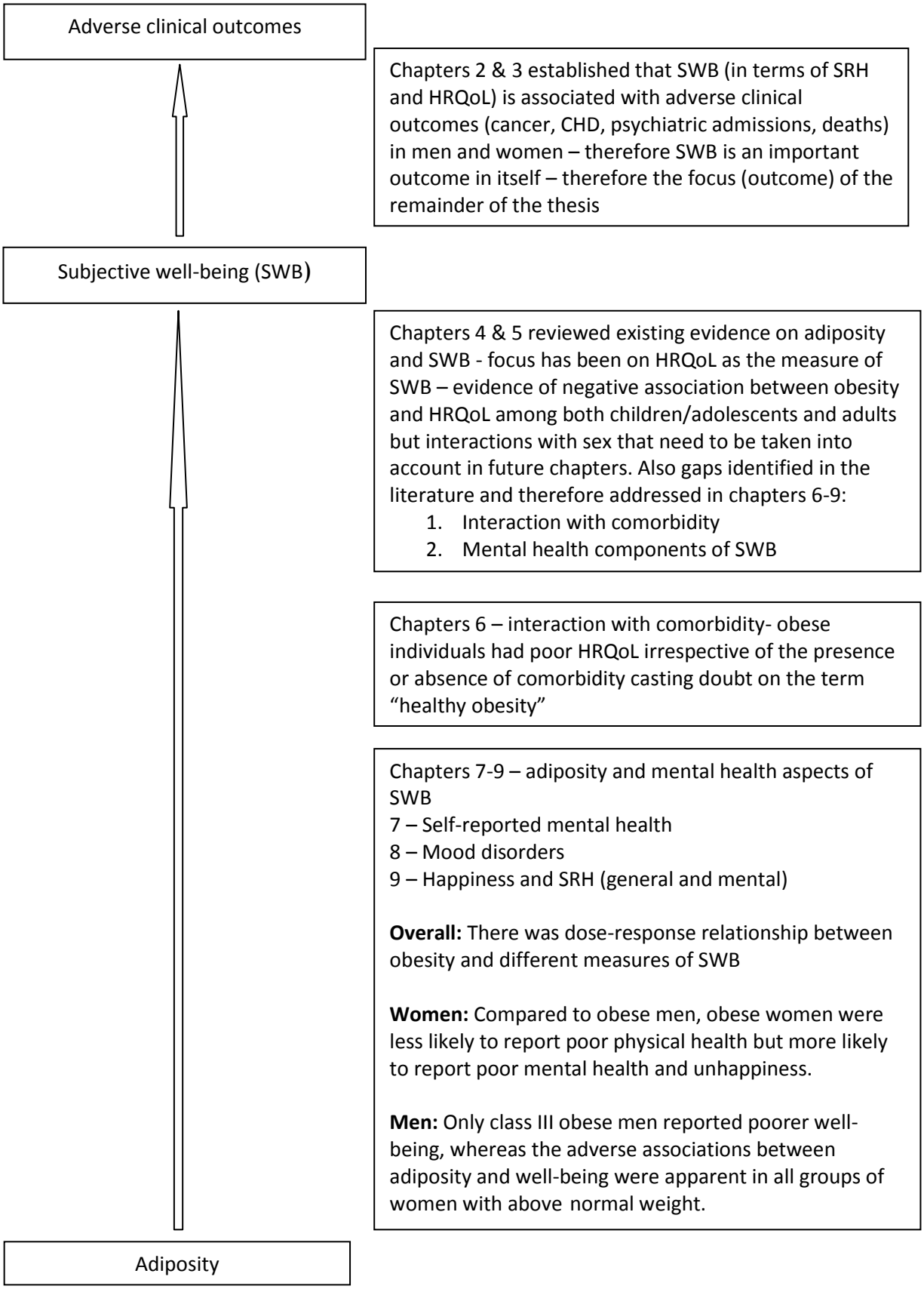
I initially reviewed the existing literature in both adults and children (chapters 4&5). I found that previous studies have focused on HRQoL as the measure of subjective well-being. Studies of both adults and children, have demonstrated negative associations between obesity and HRQoL but highlighted differences between men and women. Therefore, it was important that my subsequent chapters included exploration of differences by sex.

My reviews in chapters 4&5 demonstrated that there were two main gaps in the existing literature. Firstly, it was unclear whether the findings of the previous studies were true for the relatively new phenomenon of “healthy” obesity. I explored this in chapter 6 and found that the findings were consistent irrespective of whether obesity occurred in isolation or with comorbidity.

Secondly, the existing literature had tended to overlook the mental health aspects of subjective well-being. Therefore I explored this in chapters 7, 8 and 9 looking at a number of measures: mood disorder, happiness and mental, as well as general, SRH. Overall, there was dose relationship between obesity and poor mental health, mood disorder, poor SRH and unhappiness, and the associations differed by sex.

The highly prevalent rate of adiposity has significantly adverse impact on the objective measurements of health in terms of morbidity and mortality. The findings of these individual chapters and this thesis as whole may extend our existing knowledge about its association with self-perceived health.

Figure 10.1 Schematic of thesis chapters



10.2 Review of key findings

This thesis established the importance of subjective well-being as a predictor of adverse outcomes and then explored the relationship between adiposity and subjective well-being.

In two long-term, retrospective cohort studies I demonstrated that both SRH and HRQoL were significant predictors of a range of fatal and non-fatal adverse outcomes in the Scottish adult general population: incident cancer and CHD, psychiatric hospitalisations and all-cause mortality. The associations were independent of potential confounders and there was evidence of dose relationships. These findings demonstrated the importance of subjective well-being as an indicator of overall health and further strengthened the notion that health extends beyond physical well-being, to encompass psychological well-being.

I undertook meta-analyses of studies in both adults and children/adolescents to collate the existing evidence and then undertook four, complementary cross-sectional studies to explore the relationship between adiposity and subjective well-being in more detail and address some of the limitations of previous studies. I was able to study the whole range of anthropometric measurements. I also explored whether the relationship was consistent across a variety of measures of adiposity (BMI, WC, WHR and BF%) and a variety of measures of subjective well-being (SRH, HRQoL [overall, physical and mental/psychosocial]), mental health and mood disorder, and whether it varied by sex and the presence of comorbidity.

Overall, obesity was associated with reduced HRQoL, irrespective of the presence of comorbidity, suggesting that “healthy obesity” (obesity without metabolic comorbidity) is a misnomer. The association differed by sex, such that being overweight was associated with significantly better overall HRQoL in men only. In contrast, being underweight and obese was associated with significantly poor overall HRQoL in women only.

However, overall HRQoL covers physical and mental domains. On further research, I found that both overweight and obesity were significantly associated

with reduced physical HRQoL in adults, as well as children/adolescents, compared with normal weight with evidence of a dose relationship. In contrast, mental HRQoL was reduced only in class III obese, and overweight individuals had better mental HRQoL than normal-weight individuals. In adults, a between-groups difference of 5 points in individual SF-36 domains, or 2-3 points in the summary scores (PCS, MCS) is generally considered clinically significant (Ware 1994). The reductions in physical HRQoL among overweight and obese were both clinically and statistically significant. In contrast, the reduction in mental HRQoL was only clinically and statistically significant in class III obese.

The adverse impact of adiposity on physical HRQoL I demonstrated is consistent with previous research. In contrast, there were inconsistencies in the existing literature regarding the relationship between adiposity and mental health, and whether the association varied by sex. To address this question, I used data from two large population based surveys which enabled me to analyze multiple measurements of adiposity (BMI, WC, WHR and BF%) and mental health (GHQ-12 and mood disorder). I found consistent results, such that overweight participants reported better mental health than the normal-weight group, and obese individuals had poorer mental health. However, the adverse associations between adiposity and mental health were specific to women. In contrast, the findings of better mental health in overweight individuals were specific to men, and only class III obese men were at significantly increased risk of poor mental health.

In the cohort studies I conducted in Chapters 2 and 3, SRH was a strong predictor of adverse clinical outcomes and mortality. Therefore, I explored the relationship between four measurements of adiposity (BMI, WC, WHR and BF%) and self-reported poor health and unhappiness among the large number of adults recruited to UK Biobank from the general population. I found that obesity was associated with both unhappiness and poor SRH.

In summary, the previous literature provided ample evidence that adiposity has an adverse impact on physical health conditions and life-expectancy. In comparison, there was a relative paucity of studies on the association between adiposity and subjective well-being. There had been some previous systematic reviews but no meta-analysis had been conducted. The existing literature had

some limitations and reported contradictory results. Many of the studies only relied on self-reported BMI as a measure of adiposity, and only HRQoL as a measure of subjective well-being.

My thesis demonstrated that poor subjective well-being was a significant independent predictor of a range of adverse clinical outcomes and mortality. Overall, obesity was consistently associated with a variety of measures of poor subjective well-being (overall HRQoL, physical HRQoL, mental/psychosocial HRQoL, SRH, mental health and mood disorder) across a series of studies. The findings were consistent using different measures of obesity and were apparent in all of the subgroups studied: both adults and children/adolescents, men and women, and people with and without comorbidity. However, there were sex differences, such that both overweight and obesity were associated with poor mental health and major depression in women only. In contrast, the better mental health in overweight individuals was confined to men. Compared with obese men, obese women were less likely to report poor health but more likely to feel unhappy.

10.3 Strengths and limitations

This thesis comprises eight, complementary studies using three study designs: meta-analyses, retrospective cohort studies and cross-sectional studies. The meta-analyses were conducted in accordance with PRISMA guidelines. However, they have a number of limitations. The adult meta-analysis was limited to the use of SF-36, and similarly the children and adolescents meta-analysis used only PedsQL as a measure of HRQoL. I did not have access to individual-level data and therefore could not adjust for potential confounders consistently across the studies. However, there was no evidence of significant publication bias as assessed by both funnel plots. The included studies were conducted on both clinical and community based samples. The former might be expected to over-estimate the association, but previous studies have demonstrated no significant differences in HRQoL between the two groups (Pinhas-Hamiel et al. 2006).

Cross-sectional studies are inferior to cohort studies in that they cannot establish a temporal relationship between the risk factor/exposure and outcome. Possible reverse causation is a particular concern among underweight

women. Cross-sectional studies are also more prone to survival bias. Therefore, ideally, the cross-sectional studies examining the relationship between adiposity and subjective well-being would have been undertaken as cohort studies but this was not possible.

Both the cohort studies and cross-sectional studies comprised secondary analyses of existing data. Whilst such an approach provides rapid, low cost access to large amounts of data on a large number of participants, a limitation is the inability to determine what data are collected and how. For example, the four cross-sectional studies were undertaken using two existing studies: the Scottish Health Survey and baseline data from UK Biobank. An advantage is that I was able to demonstrate consistency of the findings across two studies conducted on different study populations: Scottish adults aged ≥16 years and UK adults aged 40 to 69 years. However, a limitation was the inability to ensure that the same data were available from both studies. For example, UK Biobank had a very large sample size and had certain measurements that SHeS did not have it, such as BF% but SHeS did not have any age limits and is linked with Scottish Morbidity Record, cancer registry and death records. At the moment UK Biobank linked data is not available. Therefore, it was not possible to undertake all of the analyses using a single resource. In particular, some studies were limited to BMI, which is a poor measure of adiposity in individuals with a high muscle mass.

UK Biobank recruited individuals, aged 40 to 69 years, from the general population and so young people or very old people were excluded. Less than 10% of invited individuals were recruited into UK Biobank. UK Biobank is representative of the UK population in terms of demographics, but may not be representative in terms of other parameters, such as lifestyle. However, whilst this might impact on the generalizability of some types of results such as overall prevalence it does not, necessarily impact on the generalisability of measures of effect size.

I chose the studies used in this thesis (SHeS and UK Biobank) because they provided very large numbers of participants recruited from the general population, and multiple measures of both adiposity and subjective well-being. I had sufficient power to test for interactions with sex and comorbidity and undertake sub-group analyses where appropriate. Other strengths of the thesis

include being able to study the whole range of anthropometric measurements (from underweight to class III obesity), having access to actual measurements rather than having to rely on self-reported adiposity, and using four different measurements of adiposity (BMI, WC, WHR and BF%) and several standardized measures of subjective well-being. Many previous studies have used binary variables for SRH, GHQ, PCS and MCS. By using ordinal data, I was able to examine whether there was evidence of a dose relationship. The analyses were adjusted for a series of potential confounding factors. However, residual confounding is always possible in any observational study.

In Chapters 2 and 3, I used the measures of subjective well-being; self-reported physical and mental health and HRQoL as the exposure variables and the cancer incidence, CHD events, psychiatric admissions and overall mortality as the outcome variables. In the subsequent chapters (4 to 9), I used the measures of adiposity as the exposure variables and that of subjective well-being as the outcome variables by using the SHeS and the UK Biobank. The technique of data linkage has been used since the second half of the nineteenth century, mostly in the health-related research (Karmel & Rosman 2008). In this technique the individual's information from two or more datasets/sources are merged together using the personal identifier (name, address, date of birth or a unique ID number) into a single source of information (Taylor & Lynch 2010). However, worldwide not many population based linked data is available, including the Scottish Record Linkage system, Oxford Record Linkage Study and Work & Pensions Longitudinal Study in the UK. The other such datasets are; the Rochester Epidemiology Project in the USA, British Columbia Linked Health Database and Manitoba Population Health Information System in Canada, and Western Australia Data Linkage System and NSW Centre for Health record Linkage in Australia (Holman et al. 2008).

Once the data linkages are established then there are many advantages of using it including the reduced cost (Flowers & Ferguson 2010) and length of time (Gissler & Haukka 2004), compared to the primary study. The linkages of data make the better use of the existing data by re-using it for a range of new research and can also improve its quality by removing the duplicates and other errors (Christen & Goiser 2007; Holman et al. 2008). Data linkage provides

researchers the opportunity of the cost-effective alternative to the individual prospective studies (Sibthorpe et al. 1995; Brook et al. 2008). It also allows the monitoring and evaluation of the community health over time and the outcomes of the projects could be used to inform the existing or new health policies (Kelman et al. 2002; Bass & Carfield 2002).

There are some limitations/disadvantages of linking data, including the need of good working relationship between the technical and management staff of different institutions (Taylor & Lynch 2010). It is argued that the data linkage may be vulnerable for breaching the privacy and confidentiality of the participants (Flowers & Ferguson 2010). In contrary, research has shown that it actually enhances the privacy of the participants by not relying on the name, sex or date of birth but a unique identifying number, compared to the primary research (Holman et al. 2008). Initially the data linkage project demands high technical expertise, cost and time but once it is established then little of these are required for the subsequent research (Gissler & Haukka 2004). Sometimes the linked dataset is of good quality but the required individual variables may not be of good quality or not available (Taylor & Lynch 2010).

The linkage of three large representative SHeS (1995, 1998 & 2003) with follow-up of cancer registry, death record, CHD events and psychiatric admission has produced a large cohort study that allowed me to explore the association between the measure of subjective well-being and adverse outcomes. The participants' information has been linked from 1981 to the data of interview which provides the opportunity to know and exclude the existing health conditions (Gray et al. 2010). However, this information may be incomplete for those who immigrated to Scotland after 1981. The SHeS only interviewed those individuals who were living in private households and exclude others which may have introduced bias to the original survey and subsequently to the linked data. In case of no trace of the mortality record, the linked data assumed the individuals to be alive, but in actual may have moved from Scotland and died there or had an event.

One of the limitations of using the linked data is that the outcome variables are those which are recorded routinely with complete information and coded in correct way. There were age limitations in the SHeS 1995 and 1998 and at the

moment the follow-up is relatively short, due to which the number of outcome is currently not very high. Therefore, I have to limit my outcome to the CHD events, cancer incidence, psychiatric admissions and overall death. Furthermore, I could not explore which particular cancer, CHD event, psychiatric disease or disease specific mortality is associated with poor subjective well-being. I have used only the hospitalization records which underestimate the actual number of outcome, particularly in case of mental health. The possible means of collecting data on the other health outcomes could be the General Practitioner (GP) consultations. I used the population based cancer registry which records the incidence of all cancer in the Scottish population. I did not have the periodic information about the status of subjective well-being over time. This may have introduced a potential bias as I had no information whether the baseline exposure was valid over the time period of follow-up.

In Chapter 9, I used the "unhappiness" as the outcome variable but there was no standardized questionnaire for it. This may affect its comparability with the other relevant studies. Ideally, the exposure information should be recorded before the occurrence of the outcome but in Chapters 4 to 9, the exposure (adiposity) and the outcome (subjective well-being) was recorded at the same time. However, these descriptive epidemiological studies are useful by generating hypotheses rather than testing it and further analytical studies may confirm their findings.

10.4 Recommendations

10.4.1 Future Directions

Research on adiposity and subjective well-being is still developing. It is anticipated that the studies included in this thesis will provide a foundation for future research, both in terms of corroborating the findings and investigating new questions which have now emerged from these studies.

Further research is required into whether the associations between adiposity and subjective well-being, particularly with the psychosocial aspect are causal, the direction of causality, and whether obesity interventions can reduce the risk of poor subjective well-being. This requires that the associations are corroborated

with cohort studies, to establish temporality, and that intervention studies are then used to demonstrate reversibility. Being overweight is linked with poor physical well-being but not with mental health or unhappiness in men. The apparently protective role of overweight among men for the association with poor mental health and unhappiness, and the findings that psychosocial sequelae of increased BMI are greater in children than in adults warrant further investigation using qualitative as well as quantitative research.

The findings of the research included in this thesis strongly recommend the use of the full-spectrum of BMI (from underweight to class III obese), as merging or excluding the underweight or overweight category might not only increase the risk of weakening the association between measures of adiposity and subjective well-being, but also the risk of missing valuable information associated with being in these adiposity groups.

BMI is a proxy measure of adiposity and is reported to have some important limitations (Mei Z et al. 2002). The research included in this thesis used three other measures of adiposity (WC, WHR and BF%) along with BMI. Overall, the association of BMI with subjective well-being was corroborated by these other measure of adiposity. It shows that BMI is a valid measure of adiposity in studies of the association with subjective well-being.

Adiposity increased the odds of poor SRH in men more than in women. In contrast, adiposity increased the odds of unhappiness and poor mental health in women more than men. This thesis did not explore the underlying mechanism but supports the need to consider sex variations in future studies of adiposity and subjective well-being and to ensure that interactions are always tested before analyses are undertaken as overall results may mask important differences and provide misleading results.

Subjective well-being was a strong independent predictor of adverse outcomes, including a range of adverse clinical outcomes and all-cause death. But the underlying mechanism is not fully understood, and further studies in different population are required to fully elucidate the mechanism.

The recent published studies in different countries on the topic of “healthy obesity” suggest that weight loss will not be beneficial in this particular group or may even increase their risk of cardio-metabolic outcomes. This thesis revealed that even if there are obese individuals who do not develop metabolic comorbidity, they still have the higher risk of poor subjective well-being, which is a strong independent predictor of future adverse health outcomes. This needs to be replicated, ideally in a different population. There may be merit in designing a cohort study of obese individual with and without comorbidity and following them up to understand the risk of developing poor subjective well-being.

I linked base-line subjective well-being with few of the adverse outcomes and found that it was a strong independent predictor of CHD events, cancer incidence, psychiatric admission and overall morality in general population. It should be further studied to know what type of particular cancers, CHD, and disease-specific death is linked with poor subjective well-being. I only included the psychiatric hospitalization which underestimates the mental health cases and exploration of GP consultation data or similar might give more information. Poor subjective well-being should also be studied with other health outcomes such as diabetes, arthritis, pulmonary diseases, stroke and functional ability in general population.

Subjective well-being was a strong independent predictor of adverse outcomes, including a range of adverse clinical outcomes and all-cause death. But the underlying mechanism is not fully understood, and further studies in different population are required to fully elucidate the mechanism. There may be merit in conducting a longitudinal study of both quantitative and qualitative data with frequent measurements of subjective well-being. Integrating the findings of the qualitative and quantitative analysis could be very helpful in explaining the underlying mechanism.

This thesis includes one of the very initial analyses of the UK Biobank. The dataset is now linked with the hospital records and the findings from this thesis may be useful for the upcoming studies as a baseline. For example I have used for the first time the diagnosis of probable major depression and prescription

information with the help of UK Biobank mental health group. The baseline information should be corroborated with the longitudinal studies.

10.4.2 Public health and clinical implications

Worldwide, the prevalence of adiposity has reached an epidemic level, and is expected to further rise (World Health Organization 2013). About 62% of Scottish adults are either overweight or obese and 27% are obese (NHS Scotland 2013). The Foresight report predicted that in the UK alone, 60% of men and 40% of women could be clinically obese (BMI > 30kg/m^2) by 2050 (Foresight 2007). As such, it is critical to understand the experiences and quality of life of the individuals and community who have abnormally low or high body fat. Similarly, life expectancy at birth has significantly increased, particularly in developed countries. Therefore, in the recent past a paradigm shift in the measurement of health outcomes has been observed, as subjective well-being has become an important part of it (Bowling 2014).The interest in measuring subjective well-being has also substantially increased in the UK in the last few years (Waldron 2010). Measures of subjective well-being are now included in major health, social and economic surveys. It is anticipated that the findings of several studies included in this thesis will inform new or existing policy, clinicians, public health physicians and others who are dealing with the subjective well-being of individuals or the community in general and in particular those who are overweight and obese.

Overweight children are more likely to develop into overweight adults (Whitaker et al.1997), and are at increased risk of many physical conditions (Ebbeling et al. 2002). Similarly, adiposity is related to many physical conditions in adults (Calle et al. 1999). This thesis suggests that they also suffer from impaired subjective well-being. Therefore, adiposity is an important public health problem and effective interventions are needed urgently to stem the higher prevalence. These findings will facilitate clinicians, public health physicians and others to educate individuals and the community about the potential adverse effects of obesity on their quality of life.

The sex specific findings could help in targeting or focusing on particular subgroups, for example, BMI well above or below normal values is associated

with significantly poorer mental health in women only, the psychosocial sequelae of increased BMI is greater in children than in adults, and the association between being overweight and having poor mental health was confined to women. These findings suggest that health care providers should be aware that underweight and obese women and children are predisposed to poorer mental health and may be in particular need of intervention. The risk increases with increasing level of adiposity even after adjusting for a range of potential confounders.

Overall, this thesis provides further evidences to support the injurious effects of adiposity on all aspects of health, and supports the need to take action to reverse the higher prevalence of obesity. Commonly, population health is measured in terms of disease and mortality. This thesis may strengthen the growing evidence that subjective well-being provides additional information and is predictive of future morbidity and mortality. Individuals with poor subjective well-being are a higher risk group who may merit closer surveillance and earlier intervention. Subjective well-being is as important as objective measures of both health and health risk, and should be considered in identifying how best to target public health and health care interventions.

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Appendix 1: PRISMA checklist

Section/topic	#	Checklist item	Chapter 4 Reported on page #	Chapter 5 Reported on page #
TITLE				
Title	1	Identify the report as a systematic review, meta-analysis, or both.	90	112
ABSTRACT				
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	91	113
INTRODUCTION				
Rationale	3	Describe the rationale for the review in the context of what is already known.	92	114
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	92	114
METHODS				
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	None	None
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	93	115
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	93	115
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	93	115
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	93	115
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	93	115
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	94	116

Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	93-94	116
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	94	116
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	93-94	116
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	94-97	116
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	None	None
RESULTS				
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	97, Figure 4.1	116-117, Figure 5.1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	97-98, Table 4.1	120, Table 5.1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	102, Figure 4.3,4.4	121, Figure 5.3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	102-103, Figure 4.5, 4.6	124-127, Figure 5.4 & 5.5
Synthesis of results	21	Present the main results of the review. If meta-analyses are done, include for each, confidence intervals and measures of consistency"	102, Table 4.2, Figure 4.5, 4.6	123, Table 5.2, 124-127, Figure 5.4, 5.5
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	100, Figure 4.2	119, Figure 5.2
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	None	None
DISCUSSION				

Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	109	128
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	110-11	129-131
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	111	131
FUNDING				
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	None	None

Appendix 2: Permission to use UK Biobank data

From: UK Biobank Access Team [access@ukbiobank.ac.uk]
Sent: 21 March 2013 15:19
To: Jill Pell
Cc: Zia Ul Haq
Subject: [SPAM?] UK Biobank Application 774 - Researcher successfully registered

Dear Professor Pell

I am emailing to confirm that Dr Zia Ul Haq has successfully registered with UK Biobank. UK Biobank now authorise the secure sharing of data for Application 774 with this approved researcher.

Yours sincerely,

Erin Scobie

Access Administrator

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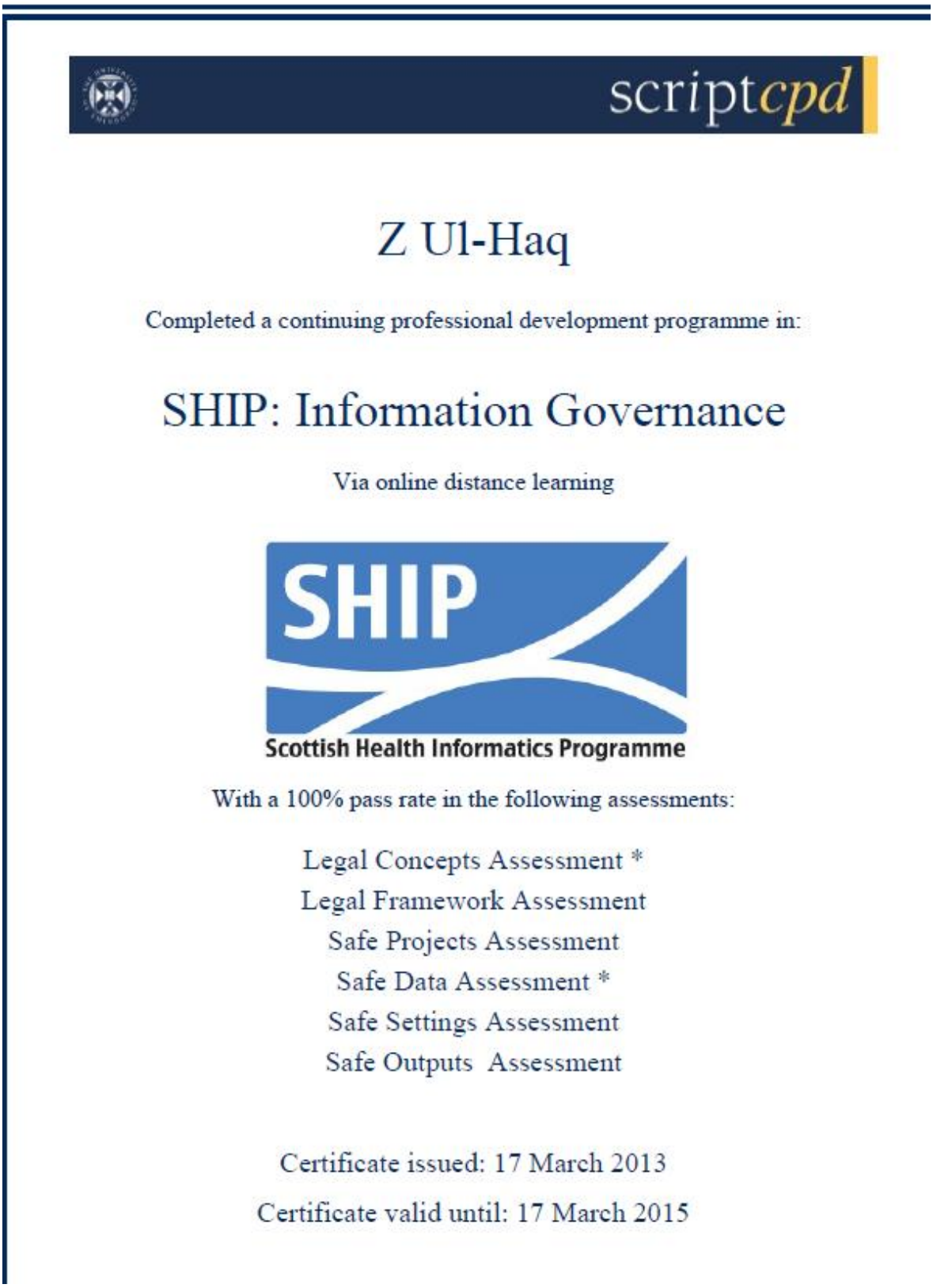
Appendix 3: Certificate of completion of Scottish Health Informatic Programme to use the SMR linked data



scriptcpd

Z Ul-Haq

Completed a continuing professional development programme in:

SHIP: Information Governance

Via online distance learning

SHIP

Scottish Health Informatics Programme

With a 100% pass rate in the following assessments:

Legal Concepts Assessment *
Legal Framework Assessment
Safe Projects Assessment
Safe Data Assessment *
Safe Settings Assessment
Safe Outputs Assessment

Certificate issued: 17 March 2013

Certificate valid until: 17 March 2015