Use of anthropometric and genetic data to study body fat mass and distribution with cancer risk in European-ancestry populations

By

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To my amazing daughters, Melody and Iris, wise beyond their years

and

To my beloved husband, Ding, and my parents, Hong and Shanqiao,

for being infinitely supportive through this journey

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LIST OF ABBREVIATIONS

BFP	Body Fat Percentage
BFPadjBMI	Body Fat Percentage adjusted for Body Mass Index
BMI	Body Mass Index
CI	Confidence Interval
CT	Computed Tomography
DXA/DEXA	Dual-Energy X-ray Absorptiometry
GCTA	Genome-Wide Complex Trait Analysis
GWAS	Genome-Wide Association Studies
HR	Hazard ratio
HRT	Hormone Replacement Therapy
LD	Linkage Disequilibrium
MAF	Minor Allele Frequency
MR	Mendelian Randomization
MRI	Magnetic Resonance Imaging
OR	Odds ratio
PCs	Principal Components
PRS	Polygenic Risk Score
SNP	Single Nucleotide Polymorphism
TFM	Trunk Fat Mass
TFMadjBMI	Trunk Fat Mass adjusted for Body Mass Index
TFP	Trunk Fat Percentage

TFPadjBMI	Trunk Fat Percentage adjusted for Body Mass Index
WBFM	Whole Body Fat Mass
WBFMadjBMI	Whole Body Fat Mass adjusted for Body Mass Index
WC	Waist Circumference
WHO	World Health Organization
WHR	Waist-to-Hip Ratio
WHtR	Waist-to-Height Ratio
WHRadjBMI	Waist-to-Hip Ratio adjusted for Body Mass Index
wPRS	Weighted Polygenic Risk Score

CHAPTER I

INTRODUCTION AND SPECIFIC AIMS

The prevalence of obesity is rapidly growing around the world (Afshin et al. 2017; Ng et al. 2014). This increase have important and adverse effects on public health (Lauby-Secretan et al. 2016; Afshin et al. 2017). Epidemiologic studies indicate higher adult body mass index (BMI) is associated with increased incidence of several cancer types (Bhaskaran et al. 2014; Lauby-Secretan et al. 2016), and mortality (Bhaskaran et al. 2018; Berrington de Gonzalez et al. 2010). However, using BMI as a method of identifying obesity is not an infallible approach to identify individuals with excess body fat percent (Donohoe, Doyle, and Reynolds 2011; Okorodudu et al. 2010). For example, BMI does not well differentiate very muscular individuals from overweight, and it does not reflect body composition change with age (Rothman 2008).

Waist-to-hip ratio (WHR), waist circumference (WC) and waist-to-height ratio (WHtR) are surrogate measures of visceral fat that has been hypothesized to confer greater risk of cancer and other chronic diseases than subcutaneous fat (Donohoe, Doyle, and Reynolds 2011; Guo, Key, and Reeves 2018; Ortega et al. 2017). However, investigations of the association of visceral adiposity and cancer risk are limited, and results are inconsistent. For instance, we found no association between WHR and overall cancer risk after adjusting for BMI among East Asians (Liu et al. 2016). Recent study has shown body fat is associated with postmenopausal breast cancer with normal BMI (Iyengar et al. 2019), but investigations on other body fat and cancer risk association are limited. In the UK Biobank cohort, body fat percentage (BFP), whole body fat mass

(WBFM), and trunk fat percentage (TFP) of approximately 492,000 participants were measured in addition to BMI and WHR, providing an exceptional opportunity to quantify the associations of body fat mass and distribution in relation to cancer risk.

Most epidemiologic studies find the association between BMI and breast cancer varies by menopausal status. For instance, a 2014 Lancet publication, found premenopausal breast cancer was inversely associated with BMI, whereas BMI was positively associated with postmenopausal breast cancer (Bhaskaran et al. 2014). Nonetheless, in our recent Mendelian Randomization analyses, we found genetically-predicted BMI and BMI adjusted WHR was inversely associated with both pre and postmenopausal breast cancer risk (Guo et al. 2016; Shu et al. 2019). We hypothesize that adult gain of body weight and body fat may be the principal factor accounting for the positive association between BMI and postmenopausal breast cancer risk observed in most traditional epidemiologic studies. Recent studies found that genetic predisposition increases early adulthood weight gain among women and has no significant effect on BMI change in middle or late adulthood (Song et al. 2018). Another study shows inversed relationship between BMI-associated risk-alleles numbers and weight gain during and after middle-age, while the association with weight gain in younger age was positive (Rukh et al. 2016). Additionally, we are interested in exploring the relationship between body fat mass and distribution-associated variants and changes in other body fat mass and distribution in the UK Biobank. In this dissertation project, I want to extend the research to evaluate effects of genetic predicted body fat mass and distribution in addition to BMI on the risk of breast cancer.

The following aims are developed to investigate the association between body fat mass and distribution and cancer risk among European population.

Specific Aim 1: To evaluate the associations of BMI, WHR, body fat mass and distribution including body fat percentage, whole body fat mass, and trunk fat percentage with mortality and cancer risk among European population. Although studies have studied the BMI and WHR with risk of cause-specific death and site-specific cancer risk, only a few studies have prospectively evaluated the association of other body fat mass and distribution on risk of deaths (Bigaard et al. 2004; Padwal et al. 2016) and postmenopausal breast cancer (Rohan et al. 2013), independent of BMI. To address these gaps, we analyze data from approximately 500,000 participants in the UK Biobank to prospectively examine the relationship of BMI, WHR, body fat mass and distribution including body fat percentage, whole body fat mass, and trunk fat percentage with total and cause-specific mortality and incidence of obesity-related cancers combined and site-specific cancers, and further evaluated whether body fat mass and distribution may be associated with health outcomes after accounting for BMI.

Hypothesis: I hypothesize that WHR, body fat percentage, whole body fat mass, and trunk fat percentage are positively associated with total and cause-specific mortality and incidence of obesity-related cancers combined and site-specific cancers, and these associations are independent of the effects of BMI.

Specific Aim 2: To determine the association of genetic predicted body fat mass and distribution with breast cancer risk among European population using Mendelian randomization (MR) analysis. MR has been used to evaluate potential causal relationships between exposures and disease outcomes by utilizing genetic variants as instrumental variables in the analysis (Burgess, Butterworth, and Thompson 2013; Burgess, Small, and Thompson 2017; Davies, Holmes, and Davey Smith 2018). Previous MR studies reported genetic predicted BMI and WHR with BMI adjustment (WHRadjBMI) were inversely associate with postmenopausal breast cancer risk, while the observational studies showed the opposite. We use the individual-level data from UK Biobank and summary statistics of the Breast Cancer Association Consortium (BCAC) to assess associations of body fat mass and distribution, including BMI, WHRadjBMI, body fat mass and distribution including body fat percentage, whole body fat mass, trunk fat percentage, and trunk fat mass and the measures with and without BMI adjustment with breast cancer risk.

Hypothesis: Genetic predicted BMI, WHRadjBMI and body fat mass and distribution are inversely associated with breast cancer risk in MR analyses among European population.

Specific Aim 3: To determine the association of genetic predicted body fat mass and distribution with measured body fat changes among different age groups in European population. Studies have shown genetic risk score comprising BMI-associated variants was not associated or inversely associated with middle or late adulthood weight increase (Rukh et al. 2016; Song et al. 2018). However, little is known about the influence of genetic predispositions on body fat mass and distribution and their change patterns of body fatness. We use the data from UK Biobank to investigate the associations and age-associated pattern of genetic predicted body fat mass and distribution, including BMI, WHR, body fat percentage, whole body fat mass, trunk fat percentage and trunk fat mass, on observed changes in body weight and body fat distribution at middle or late adulthood.

Hypothesis: Genetic predicted body fat mass and distribution are positively associated with body fat mass and distribution yet have different associations among different age groups in European population.

CHAPTER II

BACKGROUND

1. Epidemiology of Overweight and Obesity

1.1 Measurement of overweight and obesity

Although weight is the simplest anthropometric index of excess body fat, weight alone does not account for the fact that taller people have more tissue than shorter people, and so they tend to weigh more. Since the 1980s, indices of weight adjusted for height have gained favor because they provide a single and universal overall estimate of adiposity regardless of height (Calle and Thun 2004). According to WHO, overweight and obesity are defined as abnormal or excessive fat accumulation that may impair health (Table 1)(WHO 2016). Commonly in the scientific research arena, definitions for classifying and reporting healthy or normal weight, overweight, and obesity in populations have been based on measures of weight and height rather than clinical measures of adiposity (Kuczmarski and Flegal 2000). BMI, also called Quetelet's index), is defined as a person's weight in kilograms divided by the square of his height in meters (kg/m^2). It is widely used in defining overweight and obesity and is relatively comparable across studies and populations (Calle and Thun 2004). Large number of studies have shown that BMI is strongly correlated with body fat levels and BMI is a good predictor to higher risk of chronic diseases and early death (Di Angelantonio et al. ; Hu 2008b; Calle and Kaaks 2004; Bhaskaran et al. 2014; Renehan et al. 2008; Flegal et al. 2009). However, BMI is an indirect measurement of obesity that does not distinguish body fat and lean body fat (primarily consists of muscle, bone, and extracellular water) (Javed et al. 2015). In addition, BMI is age and sex dependent when used as an indicator of body fatness while the publicly available cutoff points do not take age and sex into consideration (Gallagher et al. 1996).

Table 1. Classification of adults according to BMI

Classification	BMI (kg/m^2)	Risk of comorbidities
Underweight	< 18.50	Low (but risk of other clinical problems increased)
Normal weight	18.50 – 24.99	Average
Overweight	≥ 25.00	
- Pre-obese	25.00 – 29.99	Increased
- Obese I	30.00 – 34.99	Moderate
- Obese II	35.00 – 39.99	Severe
- Obese III	≥ 40.00	Very severe

Note: Adapted from WHO Technical Report Series No. 894 Table 2.1(WHO 2000)

Central obesity, also known as abdominal obesity, or visceral adiposity, is excessive abdominal fat around the stomach and abdomen that has accumulated to the extent that it is likely to have a negative impact on health. WHO has recognized that the importance of abdominal fat mass, which varied considerably within a narrow range of total body fat and BMI, and it is an indispensable complement to BMI in assessing body fat distribution in order to assess cardiovascular risks of obesity (WHO 2008). Central obesity, usually classified by WHR or WC, is associated with cardiovascular risk factors (Despres and Lemieux 2006; Shuster et al. 2012). The WHO recommended measurement protocols are as follows: Measure the waist circumference at the end of several consecutive natural breaths, at a level parallel to the floor, midpoint between the top of the iliac crest and the lower margin of the last palpable rib in the mid axillary line. Measure the hip circumference at a level parallel to the floor, at the largest circumference of the buttocks (WHO 2008). Similar to BMI, sex, age and ethnic differences may lead to variations in WC and WHR measurements (WHO 2008).

Fat stores excess calories and releases hormones that control metabolism, while excess fat causes health problem. By definition, obesity is a medical condition in which excess body fat has accumulated to the extent that it may have an adverse effect on health, leading to reduced life expectancy and/or increased health problems (WHO 2016). In order to better measure body fat accumulation and distribution, a number of methods are available in addition to BMI and waist measures, such as measurement with calipers (skinfold), through the use of bioelectrical impedance analysis, and more precise measures including MRI/CT or DXA. Each method has its evident strengths and limitations (Table 2). Bio-impedance is defined as the opposition in biological tissues to the flow of alternating current, which is much greater in adipose tissue (which contains little water or electrolyte) than in lean tissue (which is essentially an electrolyte solution). As a result, the overall level of impedance in the body can be a good indicator of the absolute and relative amounts of adipose and lean tissue, when combined appropriately with other data (e.g. age, sex, weight and height)(Prentice and Jebb 2001). Magnetic resonance imaging (MRI) and computed tomography (CT) provide high-resolution scans of selected tissue or organs and are considered the most accurate methods for assessing body composition and regional fat distributions at as small as tissue-organ levels. Both methods accurately quantify percent body fat and visceral and subcutaneous fat. A major advantage of MRI over CT is that it does not bring much radiation exposure, which seems safer for subjects. The limitation of these two methods is that they are very expensive and not readily available. Further, they might not be able to accommodate morbidly obese people (Hu 2008a). DXA or DEXA, dual-energy-X-ray-absorptiometry-derived measure, is originally a means of measuring bone density, commonly in the lower spine and hips, using an enhanced form of X-ray technology in clinical setting. In addition to evaluating bone mineral density, DXA scan is also used to measure total body composition and fat mass with a high degree of accuracy (van der Kooy and Seidell 1993). However, high cost of DXA implementation makes it hard to use in large scale cohort studies.

Table 2. Capability of different body fat measurements to estimate total body fat amount, fat distribution, and applicability

Method	Capability measuring total body fat amount	Capability measuring fat distribution	Applicability in large population studies
CT	Moderate	Very high	Low
MRI	High	Very high	Low
DXA	Very high	High	Moderate
Bio-impedance	Moderate	Very low	High
Anthropometry			
- BMI	Moderate	Very low	Very high
- WC, WHR	Low	High	Very high
- Skinfolds	Moderate	Moderate	High

Note: Adapted from Table 1(Snijder et al. 2006).

1.2 The worldwide burden of obesity

Between 1980 and 2008, mean BMI worldwide increased by 0.4 kg/m^2 per decade (Finucane et al. 2011). According to the WHO estimates, worldwide obesity has more than doubled since 1980 (WHO 2016). Globally, an estimated 205 million men and 297 million women aged 20 years and older were obese by the year of 2008; and 1.46 billion adult men and women were overweight. Till the year of 2014, more than 1.9 billion (39%) adults over age 18 years, were overweight, 600 million (13%) of which were obese (WHO 2016). It is projected that there will be an estimated 18.1 million new cancer cases and 9.6 million cancer deaths in 2018. Obesity is related with female breast cancer, colorectal cancer, stomach cancer, liver cancer, and esophageal cancer are among the ten leading causes of incident cancer and cancer deaths, which accounts for 35.4% of estimated new cancer cases and 37.5% of estimated cancer deaths globally (Bray et al. 2018) (Figure 1).

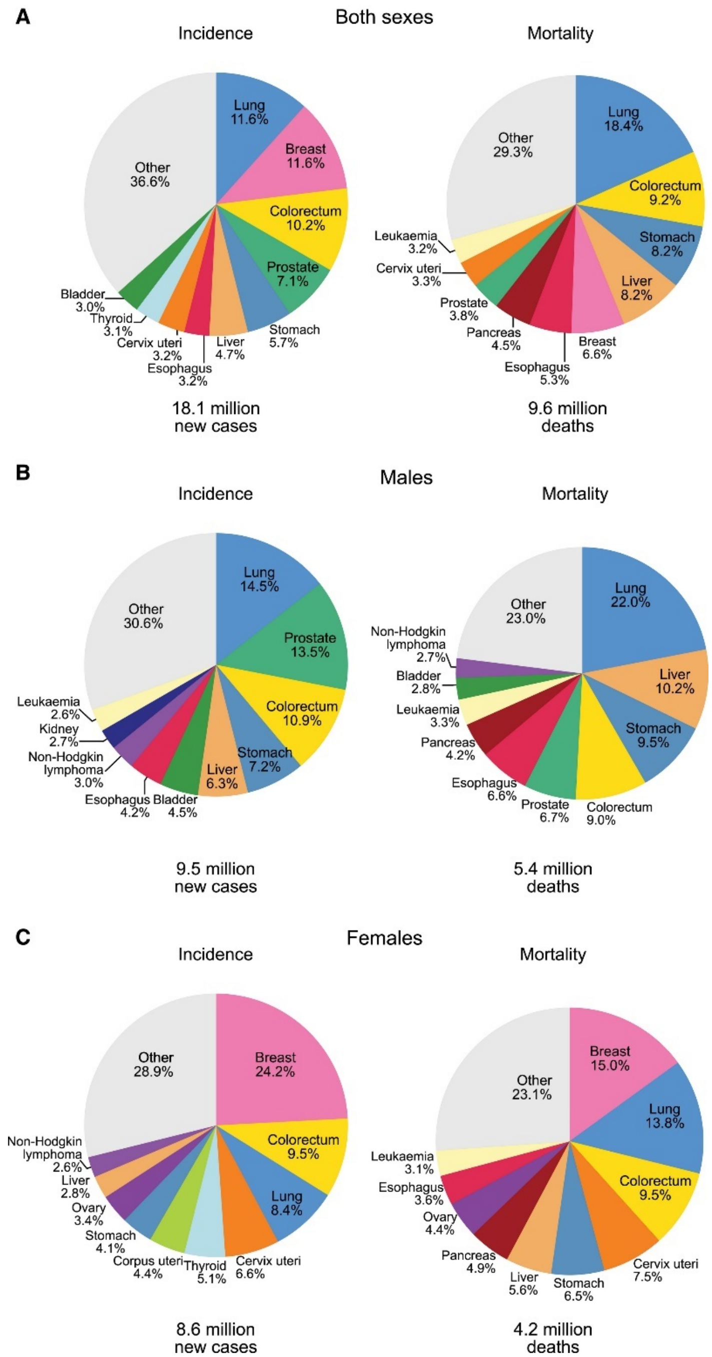


Figure 1. GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries

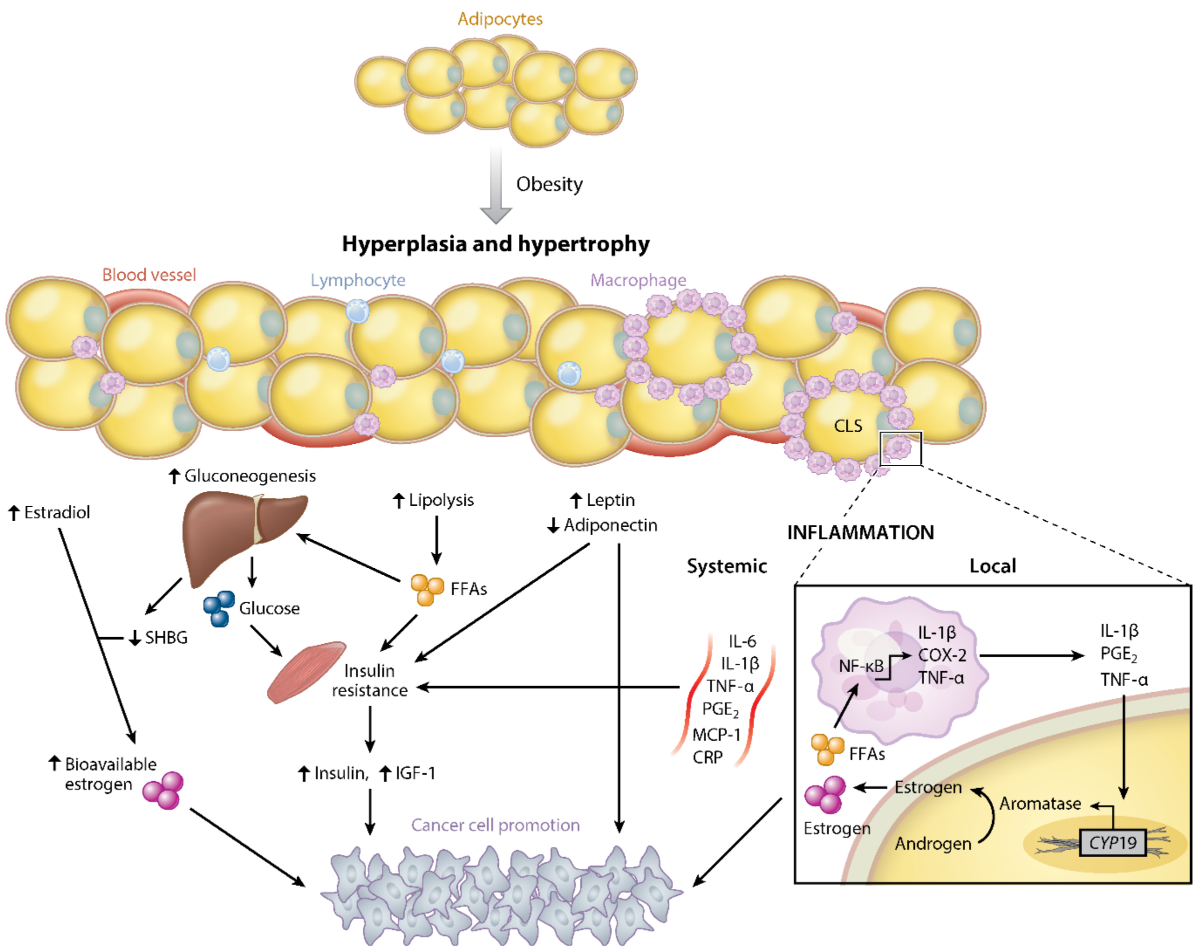
Figure adapted from Figure 4 of (Bray et al. 2018)

It is projected that there will be 65 million more obese adults in the US and 11 million more obese adults in the United Kingdom (UK) by 2030. Consequently, an additional 6-8.5 million cases of diabetes, 5.7-7.3 million cases of heart disease and stroke, and 5-6.7 million additional cases of cancer will occur in the US and UK combined (Wang et al. 2011). It is estimated that 3.6% of all new cancer cases in adults happened in 2012 were attributed to high BMI, and the population attributable fractions were greater in females than in males (5.4% vs 1.9%) (Arnold et al. 2015). Globally, excess body weight is the third (after smoking and infection) commonest attributable risk factor for cancer, while in UK, excess body weight is only second to tobacco smoking (Renehan and Soerjomataram 2016). Over the last 25 years, the obesity epidemic has been most extreme in the wealthy industrialized countries. However, with changing diets and lifestyle over time, obesity-related diseases are emerging, especially in low-middle and middle socio-demographic index countries (Collaborators 2018).

2. Epidemiology of obesity and cancer risk

2.1 Obesity and cancer mechanisms

Obesity is a risk factor for cancer development and poor cancer prognosis. Obesity is associated with systemic changes in levels of insulin, insulin-like growth factor-1 (IGF-1), leptin, adiponectin, steroid hormones, and cytokines, which creates an environment that favors tumor initiation and progression (Hopkins, Goncalves, and Cantley 2016; Iyengar, Hudis, and Dannenberg 2015). Specifically, excess adipose tissue is associated with increased levels of insulin and IGF-1, estrogen, leptin, and a decreased level of adiponectin. The obesity-related adipose tissue dysfunction, systematic inflammation, as well as local inflammation at tumor microenvironment has critical implications for tumor development, growth, and spread (Iyengar, Hudis, and Dannenberg 2015) (Figure 2).



AR Iyengar NM, et al. 2015.
Annu. Rev. Med. 66:297–309

Figure 2. Local and systemic consequences of adipose tissue dysfunction

Figure adapted from Figure 1 of (Iyengar, Hudis, and Dannenberg 2015).

2.2 Obesity and breast cancer risk

It is well established that obesity is associated with increased risk of postmenopausal breast cancer, while it is generally reported there is an inverse association of premenopausal breast cancer with obesity. The magnitude of the risk to develop postmenopausal breast cancer was found to be 20 to 50 percent increase in obese women compared to normal weight women ('Obesity and cancer outcome' 2012; Bhaskaran et al. 2014; Calle et al. 2003).

Studies have shown obesity is associated with a modest decreased breast cancer risk among premenopausal women (van den Brandt et al. 2000; Lahmann et al. 2004; Harris et al. 2011; Palmer et al. 2007; Key et al. 2003). This reduction in risk could be due to the increased tendency for young obese women to have anovulatory menstrual cycles and lower levels of circulating steroid hormones, notably of progesterone and estradiol. However, in our previous study, we found no association between BMI and premenopausal breast cancer among Chinese middle-aged and elderly females, which suggests the association or the mechanism may differ between populations (Liu et al. 2016).

Elevated postmenopausal breast cancer risk is also reported to be associated with WC, WHR, and weight gain (Harvie, Hooper, and Howell 2003; Huang et al. 1997). A recent study shows that relatively high body fat levels, DXA measured whole body fat and trunk fat mass, are associated with increased breast cancer risk among postmenopausal women with normal BMI (Iyengar et al. 2019).

The exact mechanism for this increased risk of breast cancer in obese women is not fully understood but it is thought that this is a function of lifetime exposure to estrogen, since the estrogen milieu is important in the initiation and progression of breast cancer lesions. Estrogen and perhaps, progesterone affect the rate of cell division which causes proliferation of breast epithelial cells. In postmenopausal women, the main source of estrogen is from the conversion of the androgen precursor androstenedione in the peripheral adipocytes to estrogen; the greater the amount of adipose tissue, the greater the conversion and hence the greater the exposure of breast cells to estrogen (Key et al. 2003). This could also explain the lower incidence of breast cancer in premenopausal obese women, as frequent anovulatory cycles in these women may reduce their overall exposure to estrogen and cumulative exposure should be more important than instant exposure. Obesity-related insulin resistance, and systematic inflammation might have a synergistic effect with estrogen in promoting mammary carcinogenesis (Calle and Kaaks 2004; Carmichael and Bates 2004). Body fat is positively associated with postmenopausal breast cancer among normal BMI females, which could be partly explained by enlarged adipocytes and inflammation found in the breast tissue of some women with normal BMI (Iyengar et al. 2019).

2.3 Obesity and other cancer risk

In addition to postmenopausal breast cancer, obesity is associated with multiple cancer sites, with diverse level of magnitude, including endometrial cancer, epithelial ovarian cancer, colorectal cancer, kidney cancer, esophageal adenocarcinoma, gastric cardia cancer (upper part of the stomach), liver cancer, pancreatic cancer, gallbladder cancer, and thyroid cancer (Bhaskaran et al. 2014; Calle 2007; Renehan et al. 2008; Lauby-Secretan et al. 2016). The significance of evidence differs by site and gender. However, most evidences are from studies using BMI as the measure of obesity. The findings of cancer risk with other body fat mass and distribution are limited.

Specifically, endometrial cancer is very strongly associated with obesity, which is associated with an around 5-fold increased risk of developing cancer (Reeves et al. 2007; Lauby-Secretan et al. 2016; Bhaskaran et al. 2014). The excess risk is believed to be associated with the endocrine and inflammatory effects of adipose tissue. Moreover, insulin and IGFs exert a proliferative effect on the endometrium because the level of insulin-binding globulins is reduced and free insulin levels are higher than normal (Schmandt et al. 2011). Some have argued that endometrial cancer is associated with the amount, but not the distribution of fat, because the association of endometrial cancer and WHR is attenuated or eliminated after adjusting for BMI

(Folsom et al. 2000; Folsom et al. 1989). We had similar findings in East Asian population (Liu et al. 2016).

Among several subtypes of ovarian cancer, epithelial ovarian cancer is reported to be most likely associated with obesity (Olsen et al. 2007; Lauby-Secretan et al. 2016; Bhaskaran et al. 2014). However, the association between epithelial ovarian cancer with obesity is not consistent (Kotsopoulos, Baer, and Tworoger 2010). In a recent report, central obesity, defined as trunk-to-peripheral fat ratio, has been associated with female genital organs cancers, including ovarian cancer, after BMI adjustment, which is thought to be associated with increased circulating sex hormones concentrations (Staunstrup et al. 2019). However, the study is undermined due to small number of cancers diagnoses to evaluate cancer risk of individual cancer site.

There is strong evidence that obesity play a critical role in colorectal carcinogenesis. The association with BMI is stronger for cancer of the colon than for that of the rectum, and the association of obesity, including abdominal obesity, is stronger in men than in women (Dai, Xu, and Niu 2007; Frezza, Wachtel, and Chiriva‐Internati 2006; Jochem and Leitzmann 2016; Bardou, Barkun, and Martel 2013; Larsson and Wolk 2007a). Some reported the positive association of WC or WHR with colon cancer remained after BMI adjustment, whereas the BMI colon cancer association was attenuated after WC, or WHR adjustment (Pischon, Lahmann, Boeing, Friedenreich, et al. 2006). Plausible biological mechanisms in obesity and colorectal cancer association include insulin resistance, chronic inflammation, altered levels of growth factors, adipocytokines and steroid hormones (Jochem and Leitzmann 2016).

Kidney cancer, or renal cell cancer risk, is consistently associated with 1.5- to 2.5-fold increase in BMI (Pischon, Lahmann, Boeing, Tjonneland, et al. 2006; Wang and Xu 2014; Bhaskaran et al. 2014). However, the positive association with WHR and renal cell cancer risk was observed in women but not in men (Adams et al. 2008a). The higher risk of kidney cancer could be attributed to many factors, including detection bias that obese people are more likely to seek medical attention and undergo abdominal imaging than the normal weight patients, obesity-induced renal damage due to a chronic hypoxic state in the kidney, obesity-induced inflammatory response, obesogenic metabolic environment and endocrine milieu (Klinghoffer et al. 2009).

There are reports of positive associations between risk of esophageal adenocarcinoma with general obesity and central obesity (Corley et al. 2007; Hoyo et al. 2012; Singh et al. 2013; Lauby-Secretan et al. 2016), and the effects are likely to be associated with chronic local inflammation induced by gastroesophageal reflux led by increasing body fatness. Excess body weight is positively associated with gastric cardia cancer among non-Asians but not non-cardia gastric cancer (Chow et al. 1998; Chen et al. 2013; Yang et al. 2009), whereas no association was found with central adiposity (Corley, Kubo, and Zhao 2008). Similar to increased risk in esophageal adenocarcinoma, the association of gastric cardia cancer might be associated with increased risk of gastroesophageal reflux, although the biological mechanism is still unclear. Dietary factors and diabetes might confound the study associations.

Liver cancer, or hepatocellular carcinoma (HCC), has been linked with obesity through the genesis of insulin resistance, development of non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), hepatic fibrosis, and cirrhosis, which might result in liver failure and liver cancer (Larsson and Wolk 2007b; Campbell et al. 2016; Sun and Karin 2012). Studies have studied abdominal obesity and HCC association, and found waist-to-height ratio is strongly associated with HCC, whereas WC and WHR are not associated with HCC in BMI adjustment (Schlesinger et al. 2013; Vongsuvanh et al. 2013).

Pancreatic cancer is one of the most fatal cancers and 75% die within one year of diagnosis (Bracci 2012). It is convincing from previous studies that BMI is associated with increased risk of pancreatic cancer while very limited studies showed a positive association of higher WHR and pancreatic cancer risk (Arslan et al. 2010; Genkinger et al. 2011; Bracci 2012). Hormonal and inflammatory effects of adipose tissue could partly explain the association, in addition to lifestyle factors including diet and physical inactivity.

Both overall and abdominal adiposity are positively associated with thyroid cancer, while the associations with BMI vary by histologic type (Schmid et al. 2015; Kabat et al. 2012; Rinaldi et al. 2012; Kitahara et al. 2016). Adiposity associated insulin resistance, chronic inflammation, oxidative stress and the nuclear factor κB are linked to thyroid-specific carcinogenesis (Schmid et al. 2015). In addition, the positive association between obesity and thyroid-stimulating hormone levels may result in greater risk of thyroid cancer (Schmid et al. 2015; Roef et al. 2012; Alevizaki et al. 2009).

3. Mendelian randomization (MR)

3.1 Introduction to MR

Traditional observational epidemiology attempts to measure an association between an exposure and an outcome, while adjusting for potential confounders. The ideal scenario is that all potential confounders are appropriately adjusted for, and this approach can infer a causal association between the outcome and exposure of interest. However, in practice, many confounders are unobserved, unmeasured, poorly measured, or not fully captured by current measurement, and thus cannot be fully adjusted for which results in residual confounding bias (Smith and Ebrahim 2002). Moreover, if we adjust for a mediator that lies on the causal pathway, we had the problem of over-adjustment and the association of interest would be attenuated.

In addition to confounding, reverse causation-in which the disease influences the exposure rather the exposure results in the disease outcome, is problematic and hard to avoid in traditional observational studies. The fact that overlook the presence of the outcome at baseline may affect the exposure and eventually result in the estimated associations to be biased from their true values.

Well conducted randomized trials are considered the gold standard to yield evidence of causal effects because it prevents the selection bias by eliminating the bias source in treatment assignments (Suresh 2011). Observational studies are potentially subject to selection bias in which participants' entry to a study is related to both their exposure level and disease risk, which undermines the association, which is very unlikely to occur with respect to genetic variants.

In attempt to address these issues, the MR techniques was introduced to mimic randomized clinical trials to use genetic variation as instrumental variable (IV) to examine the causal effect of an exposure on disease. An IV is a variable that is associated with the exposure, but not associated with any confounder of the interested exposure-outcome association, nor any causal pathway from the IV to the outcome other than via the exposure (Burgess, Small, and Thompson 2015). MR, using genetic variants as IV in the analysis, is based on the premise that alleles are assigned largely at random in the population at the time of gamete formation. As a result, genetic variants are typically not associated with the traditional confounders that may bias observational studies (Smith and Ebrahim 2003). Consequently, if there is a true causal relationship between the exposure and outcome of interest, the genetic variant or a series of variants that increases levels of the exposure should be associated with the outcome, provided the IV is strongly related and the study power is sufficient.

There are three fundamental assumptions in finding a valid IV in MR: 1) the relevance assumption, 2) the independence assumption, and 3) the exclusion restriction assumption.

Specifically, 1) the IV should be associated with the risk factor of interest, 2) the IV should share no common cause with the outcome, and 3) the IV do not affect the outcome except through the exposure of interest (Davies, Holmes, and Davey Smith 2018). The three core assumptions are illustrated in Figure 3.

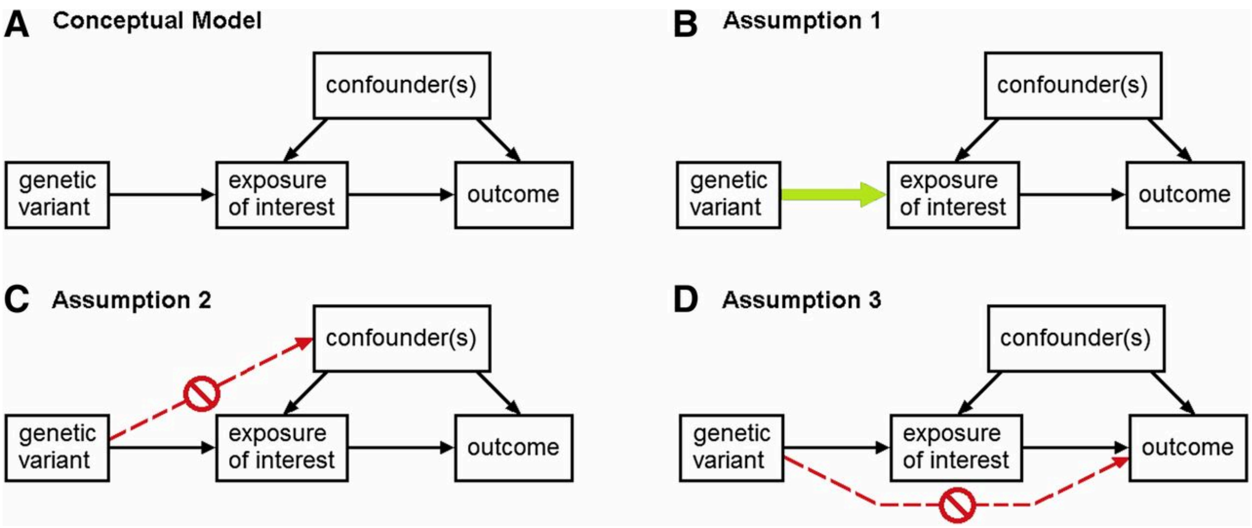


Figure 3. Conceptual illustration of the MR method and its three underlying core assumptions as directed acyclic graphs

Figure adapted from Figure 2 of (Sekula et al. 2016).

3.2 MR analytic methods

A typical MR analysis consists of two main steps, which are examining whether the three assumptions are held and evaluating the association between exposure and outcome of interest. The first assumption of IV and exposure association (Figure 3B) could be tested using regression of study individual data or summary statistics from prior GWAS. Some studies demonstrate the association by explaining the fact that the variant is in the gene that encode the exposure biomarker (Swanson and Hernan 2013). The second and third assumption (Figure 3C, Figure 3D) could not be empirically verified. In practice, researchers present associations of IV with observed variables known to confound the exposure-disease association of interest or explain the biologic reasons on why the IV is unlikely to be associated with the confounders in the study association and why the IV is unlikely to affect the outcome except through the exposure of interest (Sekula et al. 2016).

The causal effect could be estimated using individual-level data and summarized data. When MR using individual-level data is conducted, the effect could be estimated using Wald method, two-stage methods, likelihood-based methods, and semi-parametric methods (Burgess, Small, and Thompson 2017). The Wald method could also be called ratio of coefficients method, which is used when only one instrument is implemented in the analysis, the method is to divide the IV-outcome association by the IV-exposure association (Boef, Dekkers, and le Cessie 2015; Burgess and Thompson 2013). One instrument could be a single SNP or an allele score (Dudbridge 2016). Two-stage methods are often implemented in one single step by two separate regression models. The first stage model uses a regression of the exposure of interest on the IV and the second stage model uses a regression of the outcome of interest on the exposure, while the exposure is represented by the IV using the results from the first stage. Likelihood-based methods were developed to provide maximum likelihood estimates, which have the desirable properties of asymptotic unbiasedness, normality, and efficiency. For example, limited information maximum likelihood method is a maximum likelihood counterpart of two-stage least squares method. A semi-parametric model has both parametric and non-parametric components. To use semi-parametric estimators with IV, researchers usually assume a parametric model relating the outcome and exposure but make no additional assumption on the distribution of the errors. The generalized method of moments is a semi-parametric estimator designed as a more flexible form of two-stage least squares method to deal with problems of heteroscedasticity of error distributions and non-linearity (Burgess, Small, and Thompson 2017).

One limitation MR has is that for many complex exposures, genetic variants only explain a tiny fraction of the variation, which requires extremely large sample size to obtain sufficient power to detect the association, if any. Weak instrument bias may be resulted in such situation. Multiple genetic variants are used to partially address the problem, in which combine all causal variants available assuming each variant explains additional variation in the exposure of interest. Large quantity of genome-wide association studies (GWAS) provide such data source (Burgess, Butterworth, and Thompson 2013).

A common method used in MR with summarized data is inverse-variance weighted method, which is essentially the weighted mean of the ratio estimates from multiple genetic variants and it is equivalent to a two-stage least squares analyses when an allele score is used. A more robust method, Egger regression, is developed to allow genetic variants to have pleiotropic effects on the outcome that do not operate via the exposure (Bowden, Davey Smith, and Burgess 2015). The conventional inverse-variance weighted method only provides consistent estimates when all the genetic variants in the analysis are valid IV. Median-based estimation is developed to provide consistent estimates even if up to 50% of the genetic variants are not valid IV (Bowden et al. 2016). Both median-based and MR-Egger regression methods are recommended to be considered as sensitivity analyses for MR investigations with multiple genetic variants.

Some issues could undermine the MR analysis (VanderWeele et al. 2014). In order to generate unbiased and unconfounded MR estimates, the IV genetic variants should not be in linkage disequilibrium (LD) and not correlated. When the variation explained by IV on the exposure of interest, it leads to weak instrument bias and the relative bias of the IV estimator to the observational estimator is 1/F, where F is the F-statistic in the regression of exposure on IV. When F is less than 10, the bias of the IV estimator is more than 10% of the bias of the observational estimator, leading to the “rule of thumb” that the F-statistic should be at least 10 to avoid bias, which does not guarantee that with an F-statistic greater than 10 weak instrument bias could be avoided in IV analysis (Burgess and Thompson 2011). The major limitation of MR is pleiotropy. Pleiotropy, more precisely biological or horizontal pleiotropy, is a phenomenon that the same genetic variant affects multiple outcomes through different biological pathways (Solovieff et al. 2013). In response to the pleiotropic effect problem, many approaches have been suggested. For instance, MR-Egger method is able to assess whether genetic variants have average pleiotropic effects that differ from zero using the intercept from MR-Egger method, and provide a consistent estimate of the causal effect, under a weaker assumption, which would be violated if the pleiotropic effects act via a confounder of the association of interest (Bowden, Davey Smith, and Burgess 2015). Some have argued that the use of multiple genetic variants is favorable because it is very unlikely that all those different genetic variants yield the same estimate of the causal effect, or have the same pleiotropic effect on the studies’ associations (Davey Smith and Hemani 2014).

4. Changes in body weight and fat distribution over the life course

Adult weight gain has been associated with several cancers, including postmenopausal endometrial cancer, postmenopausal breast and ovarian cancer among no- or low-HRT users, kidney cancer, and colon cancer in men (Keum et al. 2015; Ahn et al. 2007). Study had suggested that weight gain since menopause increases the risk of postmenopausal breast cancer, whereas weight loss after menopause is associated with a decreased breast cancer risk (Eliassen et al. 2006; Huang et al. 1997).

Excess body weight arises as the result of an energy imbalance when calories consumed is higher than calories expended. Genetic predisposition may lead to better appetite, lower metabolism in calories consumed or increased fat deposit. However, combining all identified obesity related genes only explain a small portion of variation in body weight or anthropometric measures (Yengo et al. 2018; Pulit et al. 2018; Rask-Andersen et al. 2019). Moreover, it is difficult to identify genetic variants associated with individual's timings of gaining weight or body weight pattern, which could be associated with life expectancy and risk of chronic diseases. In addition to genetic variants, dietary factor, sedentary, physical inactivity, psychological factors, certain disease or treatment, socioeconomic status, and environmental factors (obese social ties or microbiota) are playing roles in body weight changes at different ages of a life time (Hruby and Hu 2015).

Age is associated with changes in body weight and body fat composition and distribution. Body weight tends to increase during life up till the age of 70-80 years, and after that body weight is observed to decline (Reinders, Visser, and Schaap 2017). Studies show that changes in body weight and BMI strongly influence fat-free mass change (Forbes 1999). Loss of muscle mass and increase in fat mass occurs while aging. From late middle age to the older age, volume of subcutaneous fat tends to decline and there is a redistribution of fat from subcutaneous to visceral depots, and the fat mass accumulates in muscle, liver and bone marrow (Organization 2011; Cartwright, Tchkonia, and Kirkland 2007). Existing studies have attempted to use BMI-associated genes to predict body weight change, and found a paradoxical inverse relationship between a high number of BMI-associated risk-alleles and less weight gain during and after middle-age, in contrast to the expected increased weight gain seen in younger age (Rukh et al. 2016; Song et al. 2018).

It is established that childhood obesity and adulthood obesity increase risks for developing chronic disease and mortality. In addition, studies suggest that different body fatness change trajectories might predict risks for chronic diseases and mortality (Song, Hu, et al. 2016; Zheng et al. 2017; Song, Willett, et al. 2016). For example, for people who were lean at younger age but gain substantial weight and become obese, compare to people who were obese at younger age and lose some weight and become normal weight at adulthood, the risk of developing chronic disease might be different. I am interested to explore the genetic determinants for the change patterns of body fatness. Recent study has investigated the question on BMI or weight change using GWAS identified SNPs for BMI, and found that individuals with more genetic variants for adulthood BMI tend to have high BMI and gain weight throughout life (Song et al. 2017). No reports have been seen in the associations of study weight and body size change patterns with SNPs for other body fat measure.

CHAPTER III

RESEARCH GAP

BMI and WHR have been linked to cancer risk and mortality. However, BMI does not account for body composition and could not differentiate between muscle mass and fat. In addition, for people with normal BMI, categorized as 18.5 kg/m^2 – 24.9 kg/m^2, excess body fat might exert additional risk for cancer development and death. Large prospective cohort study is lacking for investigating the association of body fat mass and distribution including body fat percentage, whole body fat mass, and trunk fat percentage in addition to BMI and WHR with disease mortality and cancer incidence.

General and central obesity have been associated with increased risk of obesity related cancer, such as breast cancer in previous studies, while causality is difficult to draw due to potential confounding bias due to non-randomized study design. Mendelian randomization (MR)studies using genetic instruments on exposure and test association of the instruments on the outcome was introduced to study the association. Existing MR suggested an inverse association on BMI and WHRadjBMI with breast cancer, which was opposite to the findings from observational studies conducted among postmenopausal women. Observational studies also suggested increased breast cancer risk with body fat percentage, independent from BMI. MR on other body fat mass and distribution with cancer risk is difficult to perform due to the lack of powerful genetic instruments for body fat mass and distribution. I performed GWAS on these measures to identify instruments and then study the association of body fat measure in addition to BMI and WHRadjBMI with breast cancer risk to fill the gap.

Most epidemiologic studies have focused mainly on BMI during midlife; weight gain over the life course is an additional risk factor that might contribute to the association between adiposity and chronic disease risk. The prevalence of overweight worldwide can be partly attributed to environmental factors, but the extent of the influence of genetic determinants is still far from clear. In addition to body weight and weight change, timing of weight change and patterns of the changes might be relevant to increased risk of developing chronic diseases. Studies have attempted to investigate GWAS identified BMI associated SNPs on the variations in BMI, but no studies have been conducted on the associations on other body fat measure traits. With the expansion of SNPs identified in GWAS described before on body fat mass and distribution, I explore the association of genetic predicted WHR and body fat mass and distribution with body weight change and change patterns.

CHAPTER IV

METHODS

1. Methods for Specific Aim 1: To evaluate the associations of BMI, WHR, body fat mass and distribution including body fat percentage, whole body fat mass, and trunk fat percentage with mortality and cancer risk among European population.

Hypothesis: In addition to BMI, WHR, body fat mass and distribution including body fat percentage, whole body fat mass, and trunk fat percentage are positively associated with total and cause-specific mortality and incidence of obesity-related cancers combined and site-specific cancers, and these associations are independent of the effects of BMI.

Study design and participants

Data from the UK Biobank were analyzed in the present study (Application number 24487, approved in February 2017). The UK Biobank is a population-based cohort study that recruited over 500,000 adults aged 37-73 from the general population. Study participants were recruited between March 2006 and October 2010 from one of 22 assessment centers across England, Scotland, and Wales (Sudlow et al. 2015). The design and methods for the UK Biobank study have been previously described elsewhere (Sudlow et al. 2015). In brief, each participant completed a detailed baseline assessment consisting of an electronic signed consent form, a brief computer-assisted interview, physical and functional measures, including anthropometric measures, and biomarker collection. Follow-up was conducted through linkages to the National Health Service (NHS) Central Register, which provides information on new cancer diagnosis and cause of deaths.

Participants were excluded from the analyses if they were pregnant at baseline (n = 150) or had an existing diagnosis at baseline of any cancer except for non-melanoma skin cancer (n = 26,872), heart attack (n = 11,609), or stroke (n = 7,669). In addition, we excluded the first two years of follow-up after baseline to minimize possible of reverse causation. These exclusions were not mutually exclusive.

Exposure assessment

At the baseline recruitment, after obtaining consent, anthropometric measures were taken from all participants following the standard protocols. Specifically, body weight, body fat percentage, whole body fat mass, and trunk fat percentage were measured using Tanita BC-418 MA body composition analyzer. Waist circumference and hip circumference were measured using a Wessex non-stretchable sprung tape (Biobank 2007). BMI was computed by dividing weight by the square of standing height. WHR was derived by dividing measured waist circumference by hip circumference. Body fat percentage, whole body fat mass, and trunk fat percentage were obtained using the bio-impedance analysis (BIA) method, which uses the difference of impedance to the alternating current, which is greater in adipose tissue and smaller in lean tissue (Bohm and Heitmann 2013). Body fat percentage, whole body fat mass, and trunk fat percentage were directly read on the body composition analyzer.

BMI were categorized by WHO suggested cut off points. Per five units increase in BMI and per standard deviation (SD) increase in WHR, Body fat percentage, whole body fat mass, and trunk fat percentage were additionally examined for their associations with total and cause-specific mortality and incidence of site-specific cancers. Individuals missing exposures of interest were excluded. Further, participants with an extreme value of these body fat mass and distribution, typically accounting for <0.5% of the overall participants, were excluded to minimize measurement error. Finally, 448,826 individuals were included in our analysis of BMI and outcomes, 448,930 in WHR analyses, 441,736 in whole body fat mass analyses, 442,304 in body fat percentage, and 442,401 in trunk fat percentage analyses.

Cohort follow-up and outcomes ascertainment

Data and diagnoses on site-specific incident cancer were provided by NHS. Dates and primary causes of death were obtained from death certificates held by the same centers. At the time of analysis, mortality data were available up to January 31, 2016 for England and Wales and up to November 30, 2015 for Scotland. Therefore, for analyses of mortality outcomes, we censored follow-up at these dates, or at the date of death if it occurred earlier. Cancer registry data were available up to November 30, 2014 for England and Wales and up to December 31, 2014 for Scotland. Therefore, the censoring date of incident cancer was defined as the dates mentioned above or date of cancer diagnosis, or death, whichever occurred first.

Information regarding the primary cause of death and types of cancer diagnosis was coded by the International Classification of Diseases, Tenth Revision (ICD-10), in the UK Biobank cohort data. For cause-specific mortality analyses, we evaluated deaths from CVD (I00-I78), cancer (C00-C99) and other causes, excluding external causes (other codes except for V01-Y89). For incident cancer, all cancer combined was defined as C00-C99, excluding non-melanoma skin cancers (C44). For site-specific cancers, we included obesity-related cancers combined (including esophageal adenocarcinoma, cardio stomach, colorectal, liver, gallbladder, pancreas, kidney, thyroid, multiple myeloma, and female cancers of breast, corpus uteri, and epithelial ovary) and major cancers found in this cohort (with more than 100 incident cases). Specifically, we included cancer of esophageal adenocarcinoma (C15, morphology codes: 8140, 8144, 8145, 8260, 8480, 8481, and 8490)(Reeves et al. 2007), cardia stomach (C16.0), colon (C18), rectum (C20), liver (C22), pancreas (C25), lung (C34), female breast (C50), corpus uteri (C54), epithelial ovarian (C56, morphology codes: 8441, 8460, 8462, 8380, 8381, 8470, 8471, 8472, 8473, 8480, 8310, 8140, 8260, 8440, 8450, 9000, 8000, 8010)(Ma et al. 2013), prostate (C61), kidney (C64), thyroid (C73) and multiple myeloma (C90.0). Female breast cancer was further divided into pre- and post-menopausal breast cancer based on Data and diagnoses on site-specific incident cancer were provided by NHS. Dates and primary causes of death were obtained from death certificates held by the same centers. At the time of analysis, mortality data were available up to January 31, 2016 for England and Wales and up to November 30, 2015 for Scotland. Therefore, for analyses of mortality outcomes, we censored follow-up at these dates, or at the date of death if it occurred earlier. Cancer registry data were available up to November 30, 2014 for England and Wales and up to December 31, 2014 for Scotland. Therefore, the censoring date of incident cancer was defined as the dates mentioned above or date of cancer diagnosis, or death, whichever occurred first.

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Statistical analysis

A marginal Cox model approach was utilized to analyze the associations because nearly a third of the UK Biobank participants were inferred to be related (third degree or closer) to one or more person in the cohort (Bycroft et al. 2018). We treated each "family" formed by any participants who are third degree or closer to any other participants in the cohort as one cluster and a robust variance estimator was applied to account for the clustering of subjects (Austin 2017). Those without any relatives in the cohort, were each treated as independent of all others. The proportional hazards assumption was tested by the correlation of scaled Schoenfeld residuals with time. Since the proportional hazards assumption held, Cox proportional hazards regression models, with age (after excluded first two years' observations) as the time scale, were used to estimate hazard ratios (HR) and 95% confidence intervals (CI) for the associations of BMI, WHR, WBFM, BFP, and TFP with the risk of death and cancer, after adjusting for potential confounders. The models were adjusted for age, sex, race, deprivation score, education, processed and red meat intake, smoking status and pack-years of smoking, alcohol consumption frequency, and family history of cancer. We further adjust for menopausal status, hormone therapy use, and parity in the analyses for female cancers of breast, corpus uteri and epithelial ovarian. The sex-stratified associations of obesity measures and cancers were presented because the obesity-cancer association was sex and site specific (Bhaskaran et al. 2014). We used a residual method (Willett, Howe, and Kushi 1997) to adjust for BMI when examining the association of WHR and other body fat mass and distribution with mortality and risk of cancer. This residual method was applied to address the correlations between the anthropometric measures. For instance, WHR was regressed on subject's BMI; the residuals from the regression represent the differences between individual's actual WHR and the WHR predicted by BMI. The Cox model assessing the association of WHR and cancer risk included the WHR residual plus BMI, with other covariates.

For sensitivity analyses, associations of body fat measurements with mortality were further examined among non-smoking whites only to eliminate potential residual confounding due to race and cigarette smoking. Likelihood ratio tests comparing models with and without the interaction terms were utilized to assess the interaction of obesity measures with sex and age group (stratified into < 60 years and ≥ 60 years old group for evenly distribution) on their associations with all-cause mortality.

Additional analyses were conducted within normal weight participants (18.5 kg/m^2 <=BMI<25.0 kg/m^2). Quintiles of different body fat mass and distribution were calculated on the overall normal weight participants and white never smoking participants in normal weight. WHR and other body fat mass and distribution, including body fat percentage, whole body fat mass, and trunk fat percentage were also assessed as continuous variables (per SD increase) for their associations with total and cause-specific mortality and incidence of all cancers combined and obesity-related cancers.

Statistical analyses were performed using the SAS Enterprise Guide (version 7.1; SAS Institute, Cary, NC). All statistical tests were based on two-sided probability.

2. Methods for Specific Aim 2: To determine the association of genetic predicted body fat mass and distribution with breast cancer risk among European population using MR analysis

Hypothesis: Genetic predicted BMI, WHRadjBMI and body fat mass and distribution are inversely associated with breast cancer risk in MR analyses among European population.

Many studies have demonstrated increased breast cancer risk with overall and central obesity and body fat, especially among postmenopausal female who never used HRT. However, the causation of these observed associations is not established because traditional observational epidemiology is limited in appropriately adjusting for unmeasured or poor-measured confounding and addressing reverse causality. Our group reported previously that genetically predicted BMI and WHR adjusted for BMI were inversely associated with breast cancer risk in both pre- and postmenopausal women (Shu et al. 2019; Guo et al. 2016). Here I examine genetically predicted body fat mass and distribution and breast cancer risk, in addition to BMI and WHRadjBMI, using MR method. UK Biobank cohort with genotyping data passed quality control for sample and genetic variants were used in the MR individual-level analyses. Summary statistics from BCAC were used in the MR summarized data analyses.

Individual-level data from UK Biobank and polygenic risk scores derivation

Study population

Data from the UK Biobank were analyzed in the present study (Application number 24487, approved in February 2017). The UK Biobank is a population-based cohort study that recruited over 500,000 adults aged 37-73 from the general population. Study participants were recruited between March 2006 and October 2010 from one of 22 assessment centers across England, Scotland, and Wales (Sudlow et al. 2015). The design and methods for the UK Biobank study have been previously described elsewhere (Sudlow et al. 2015). Imputed genotype data from the third UK Biobank genotype data release were used in the analyses. To reduce confounding by race ancestry, analysis was restricted to the cohort of individuals of White-British descent (more than 80% of the participants). White-British descent was identified by self-reported white British in baseline survey and genetically confirmed as "Caucasian" using principal components analyses. Closely related individuals (third-degree relatives or closer) were excluded. After further sample quality control (QC, describe below), 337,151 individuals remained for analysis.

Anthropometric measures and body fat mass and distribution were obtained at the baseline recruitment as described in Aim 1 Methods section. For individual body fat measure analysis, only those with complete measurement of the specific measure were included. Female breast cancer cases were ascertained ICD-10 code of C50 by NHS cancer registry data available up to the year of 2016. Female breast cancer was further divided into pre- and post-menopausal breast cancer based on the age of diagnosis and the participant's age of menopause. In total, 9,386 breast cancer cases were included for analysis.

SNP selection

In June 2019, I identified SNPs associated with BMI and WHRadjBMI from the NHGRI-EBI Catalog of Published Genome-Wide Association Studies and latest findings from GIANT consortium (Locke et al. 2015; Shungin et al. 2015; Justice et al. 2019). SNPs associated with any of the two traits at the genome-wide significance levels ($P < 5 \times 10^{-8}$) in populations of European ancestry were selected. I included independent SNPs defined as $r^2 < 0.01$ based on International HapMap Project phase 3 CEU data. For each GWAS-identified locus, the SNP with the lowest *P*-value was selected.

For other body fat mass and distribution, provided limited number of SNPs were identified and small variations of these measures were explained by previous GWAS (Lu et al. 2016; Shungin et al. 2015), I performed a GWAS using UK Biobank data to identify independent SNPs associated with body fat mass and distribution traits (body fat percentage, whole body fat mass, trunk fat percentage, and trunk fat mass) with and without BMI adjustment at the genome-wide significance levels.

Genotyping

Blood samples were collected from participants when they attended one of the UK Biobank assessment centers. Then DNA was extracted for each retrieved sample when amount is sufficient. Aliquots were then shipped to Affymetrix Research Services Laboratory for genotyping. Full details of the UK Biobank sample retrieval and DNA extraction process are described elsewhere (Welsh et al. 2017; Welsh). Specifically, UK Biobank features an automated sample retrieval process to guarantee extraction did not relate to the time and location of sample collection or the phenotypes.

Two closely related arrays from Affymetrix were used to genotype all the samples in UK Biobank. Around 50,000 samples used the UK BiLEVE Axiom array, which covers 807,411 markers. The UK Biobank Axiom array was then used to genotype the rest 450,000 samples, which covers 825,927 markers and shares 95% of marker content with the previous array. Both arrays were designed specifically for the UK Biobank genotyping project and had good genome-wide coverage. Details of the design of the arrays were described elsewhere (Wain et al. 2015; Biobank).

Phasing and imputation

SHAPEIT3 was used to phase the dataset after filtering out any low quality and outlier markers and samples, with the 1000 Genomes Phase 3 dataset as a reference panel in UK Biobank (O'Connell et al. 2016; Auton et al. 2015). Imputation had been implemented using UK10K + 1000 genomes phase 3 panels (Walter et al. 2015; Auton et al. 2015). The imputation process yielded a dataset with over 92,000,000 autosomal SNPs, short indels and large structural variants in more than 487,000 individuals.

Quality control

In addition to stringent QC performed in UK Biobank (Clare Bycroft), I further filtered out any autosomal SNPs with low call rate (< 95%), deviating from Hardy-Weinberg equilibrium (HWE) in the controls at P-value $< 1 \times 10^{-6}$, rare variants with MAF < 0.05 and low imputation quality (info score < 0.8), which left more than 4 million SNPs in the analysis.

In addition to restricting study sample within white British unrelated participants (not in third degree or closer relatedness), I excluded all poor-quality samples flagged in UK Biobank data, which included missingness and extreme heterozygosity not due to mixed ancestry, flagged identical samples with extremely high concordance, and any mismatch on genetically determined sex with self-reported sex. The positions are in GRCh37 human genome assembly coordinates.

Phenotype

The measured body fat percentage, whole body fat mass, trunk fat percentage and trunk fat mass were derived from bio-impedance measures described in Aim 1 Methods section. Prior to performing GWAS, each body fat measure was adjusted for age, age squared, array, recruiting center, and first eight principal components. For BMI adjusted body fat mass and distribution, additional BMI adjustment was implemented. Residuals were calculated separately for men and women, and then transformed by the rank based inverse normal transformation. These normalized residuals were used as the tested phenotype in the downstream genome-wide association testing. Same steps were applied to these traits: 1) body fat percentage; 2) BMI adjusted body fat percentage; 3) whole body fat mass; 4) BMI adjusted whole body fat mass; 5) trunk fat percentage; 6) BMI adjusted trunk fat percentage; 7) trunk fat mass; 8) BMI adjusted trunk fat mass.

Association testing

GWAS of the eight body fat traits were performed in PLINK v2.00 using additive linear regression models with the rank inverse normal transformed residuals with adjustment for sex. After association testing, LD score regression intercepts (implemented in the ldsc software package (Bulik-Sullivan et al. 2015)) to adjust for genomic inflation.

The PLINK clumping algorithm was used to select top-associated SNPs ($P < 5 \times 10^{-8}$) and identify all SNPs in LD ($r^2 > 0.01$) with the top associated SNP within one million base pairs away. Then conditional analyses were performed in each locus to identify the lead independent SNPs using joint and conditional analysis (cojo-slct model) as implemented in the Genome-wide Complex Trait Analysis (GCTA) software (Yang et al. 2011). But no further signals were identified. For all identified top SNPs, I conducted association test among females and select top ones with p-value < 10^{-7} as our final set of instrumental SNPs.

Instrumental variables

After identifying independent body fat mass and distribution associated SNPs from previous GWAS and GWAS from UK Biobank I performed, the F-statistic was taken to demonstrate whether the instrumental variables were adequate for MR analysis (assess MR Assumption 1). The percentage of variation explained (R^2) by used SNPs for each genetic predicted trait by including all the selected SNPs into a linear regression model and calculated the adjusted R^2. F statistics for each specific trait was calculated using formula $F\ statistic = R^2 * (n - 1 - k)/[(1 - R^2) * k]$, where R^2 is the percentage of variance explained computed from regression models mentioned above; n is the sample size of UK Biobank female cohort I used for MR analysis; and k is the number of SNPs used in the instrument (Pierce, Ahsan, and VanderWeele 2010; Burgess and Thompson 2011).

Weighted polygenic risk scores for each trait were constructed using the formula ($wPRS = \sum_{i=1}^{k} \beta_i * SNP_i$,). In brief, the allele that is associated with increased levels of the body weight or fat measures was considered the effect allele. The β_i in the formula is the effect of the *i*th SNP for the exposure of interest, and SNP_i is the number of the effect allele (0, 1 or 2) of the *i*th SNP. Specifically, for BMI and WHRadjBMI, the β_i was according to the previous published associations, whereas for body fat traits with or without BMI adjustment I applied the effect estimates from the GWAS using UK Biobank data as previously described.

Summary level data from Breast Cancer Association Consortium (BCAC)

To further assess the association between genetically predicted BMI, WHRadjBMI, and body fat mass and distribution with breast cancer risk, I further analyzed data from BCAC (Appendix A), which provided summary-level statistics of breast cancer cases and controls of European ancestry, specifically from 56,762 cases and 43,207 controls from OncoArray and

42,080 cases and 40,257 controls from iCOGS array (Michailidou et al. 2015; Michailidou et al. 2013; Michailidou et al. 2017). Details of genotyping protocols for the two arrays are described elsewhere (iCOGS: http://ccge.medschl.cam.ac.uk/research/consortia/icogs/; OncoArray: https://epi.grants.cancer.gov/oncoarray/). Summary association statistics are available for overall, ER-positive and ER-negative breast cancer, and summary level MR were conducted for overall, ER-positive and ER-negative breast cancer.

Statistical analysis

For summary-level data, inverse-variance weighted method (described in Introduction) was applied to examine the associations between each body fat trait and breast cancer using BCAC data. The MR-Egger method, weighted median method, and maximum likelihood method were used for sensitivity analysis as described in Introduction. In brief, MR-Egger method was used to detect potential pleiotropy of the IVs, while weighted median approach could provide valid estimates if more than 50% of SNPs are valid IVs. Maximum likelihood method allows for uncertainty in the genetic associations with the exposure, which is ignored in the IVW method using simple weights.

The polygenic risk scores were generated using method described above in Instrumental Variables. For ease of interpretation, I rescale the weighted BMI, BFP, WBFM, TFP and TFM genetic risk score to the one unit or the 5 units of each trait. Specifically, I performed a linear regression among all controls to regress observed BMI on wPRS-BMI using this regression model ($observed\ BMI \sim wPRS - BMI + error$). Then I calculated the genetically predicted BMI (kg/m^2) as the formula: $Genetically\ predicted\ BMI = \beta_0 + \beta_1 * (\mathrm{wPRS} - \mathrm{BMI})$, where β_0 and β_1 are the parameters from the above linear regression model. Similarly, wPRS-BFP, wPRS-WBFM, wPRS-TFP, and wPRS-TFM were rescaled to genetically predicted BFP (%), genetically predicted WBFM (kg), genetically predicted TFP (%), and genetically predicted TFM (kg). For wPRS-WHRadjBMI, the polygenic risk score was rescaled to 1-SD standardized WHRadjBMI. Specifically, I performed linear regression among all controls to regress inverse normal transformed body fat measure with BMI adjustment on the weighted PRSs using $transformed\, WHRadjBMI \sim wPRS - WHRadjBMI + error$), and calculated the genetically predicted WHRadjBMI as the formula: $Genetically\, predicted\, WHRadjBMI = \beta_0 + \beta_1 * (\mathrm{wPRS} - \mathrm{WHRadjBMI})$, where β_0 and β_1 are the parameters from the above linear regression model. Similar methods applied for genetically predicted BFPadjBMI, WBFMadjBMI, TFPadjBMI, and TFMadjBMI.

For individual-level data from UK Biobank, iterative reweighted least square logistic regression was used to determine the association of each polygenic risk score and breast cancer outcome. I calculated Pearson's correlations between each pair of wPRSs in the control data. In order to assess the associations of genetically predicted body fat mass and distribution with breast cancer risk, logistic regression models were adjusted for age, age-squared, first eight principal components, and an indicator of genotyping array. I examined the associations of the genetically predicted body fat mass and distribution with potential breast cancer risk factors among controls. Linear regression was utilized for continuous variables and logistic regression used for binary variables. Models were further adjusted for breast cancer risk factors, and mutually adjusted for other body fat measure traits. The analysis was further stratified to show associations among pre- and post-menopausal women. Among postmenopausal women, I further assessed heterogeneity by hormone replacement therapy use (ever vs never), smoking status (ever vs never), and family history of breast cancer (yes vs no).

Analyses were performed using PLINKv2.00 (https://www.cog-genomics.org/plink/2.0/), R version 3.5.2 (R Project for Statistical Computing), and SAS Enterprise Guide (version 7.1; SAS Institute, Cary, NC). A two-sided P-value < 0.005 was considered statistically significant considering multiple comparison (10 body fat measure traits were studied, 0.05/10 = 0.005).

3. Methods for Specific Aim 3: To determine the association of genetic predicted body fat mass and distribution with measured body fat mass and distribution and changes of body fatness among different age groups in European population.

Hypothesis: Genetic predicted body fat mass and distribution are positively associated with body fat mass and distribution yet have different associations among different age groups in European population.

Study population

Data from the UK Biobank were analyzed for this aim. As discussed in Aim 2 Methods section, 337,151 unrelated white British ancestry individuals (aged 40 to 69) remained for analysis. In UK Biobank cohort, a repeat assessment of 20,000 participants was carried out between August 2012 and June 2013 at the coordinating center at Stockport. Participants who lived within a 35 km radius of the assessment center were invited for the repeated assessment (Bycroft et al. 2018; Biobank 2013). During the repeated assessment, a repeat of the baseline assessment was performed, including a range of physical measurements. BMI, waist and hip circumference, bio-impedance measured body fat percentage, whole body fat mass, trunk fat percentage and trunk fat mass were ascertained at the repeated assessment.

Genotyping, SNP selection and polygenic risk scores

See Aim 2 Methods section. In brief, DNA was extracted from blood sample collected at baseline assessment. The UK BiLEVE Axiom array and the UK Biobank Axiom array were used to genotype the samples. Stringent quality control was performed to address quality problem caused by ethnically diverse, two arrays and many batches were used. Imputation had been implemented using UK10K + 1000 genomes phase 3 panels (Walter et al. 2015; Auton et al. 2015).

In addition to stringent QC performed in UK Biobank (Clare Bycroft), I further filtered out any autosomal SNPs with low call rate (< 95%), deviating from Hardy-Weinberg equilibrium (HWE) in the controls at P-value < 1×10^{-6}, rare variants with MAF < 0.05 and low imputation quality (info score < 0.8), which left more than 4 million SNPs in the analysis. In addition to restricting study sample within white British unrelated participants, I excluded all poor-quality samples flagged in UK Biobank data as described in Aim 2 Methods. The positions are in GRCh37 human genome assembly coordinates.

Weighted polygenic risk scores for each trait were constructed using the formula ($wPRS = \sum_{i=1}^{k} \beta_i * SNP_i$,) and then rescaled to genetically predicted body fat mass and distribution as described in Aim 2 Methods section.

Phenotype

After QC, a total of 7463 female subjects with baseline and follow-up body fat mass and distribution were included in body weight and body fat measure changes analysis. Percent body weight change (%) was calculated as the weight difference (kg) from baseline measurement to the repeated assessment, then divided by the baseline body weight measurement and multiply by 100. Absolute body weight change (kg) and body weight percent change (%) were used as the outcome of interest in body weight and genetically predicted body fat measure traits associations. Similarly, absolute change and percent changes of BMI, WHR, body fat percentage, whole body fat mass, trunk fat percentage, and trunk fat mass were calculated for any participant with both baseline and repeated assessment.

Subjects with baseline and repeated measurements were categorized into different age group based on their age at recruitment (40-49, 50-59, and 60-70) to investigate age pattern at associations of body fat change with genetically predicted body fatness traits. All female subjects with body fat mass and distribution (N=181034) were included to study the relationship of genetically predicted body fat traits with measured body fatness at baseline in different age groups (40-44, 45-49, 50-54, 55-59, 60-64, and 65-70).

With the purpose of assessing associations of weight change patterns with genetically predicted body fat mass and distribution, I categorized subjects into 2 sets of six groups based on self-reported comparative body size at age 10 and baseline BMI (N=177982). Specifically, the first set of six groups are 1) self-reported thinner than average at age 10 and BMI < 25kg/m^2 at baseline, 2) self-reported body size was about average at age 10 and BMI < 25kg/m^2 at baseline, 3) self-reported plumper than average at age 10 and BMI < 25kg/m^2 at baseline, 4) self-reported thinner than average at age 10 and BMI ≥ 25kg/m^2 at baseline, 5) self-reported body size was about average at age 10 and BMI ≥ 25kg/m^2 at baseline, and 6) self-reported plumper than average at age 10 and BMI ≥ 25kg/m^2 at baseline. The second set of six groups are 1) self-reported thinner than average at age 10 and BMI < 30kg/m^2 at baseline, 2) self-reported body size was about average at age 10 and BMI < 30kg/m^2 at baseline, 3) self-reported plumper than average at age 10 and BMI < 30kg/m^2 at baseline, 4) self-reported thinner than average at age 10 and BMI ≥ 30kg/m^2 at baseline, 5) self-reported body size was about average at age 10 and BMI ≥ 30kg/m^2 at baseline, and 6) self-reported plumper than average at age 10 and BMI ≥ 30kg/m^2 at baseline. For each category, mean body fat mass and distribution ascertained at baseline and mean genetically predicted body fat mass and distribution were computed. In addition, the associations of weight change patterns with genetically predicted body fat mass and distribution were examined.

Statistical analysis

Linear regression models were used to estimate the effect size of genetically predicted BMI, WHRadjBMI, BFP, BFPadjBMI, WBFM, WBFMadjBMI, TFP, TFPadjBMI, TFM, and TFMadjBMI on the absolute and percent body weight change, as well as their corresponding body fat measure changes. Genetically predicted body fat mass and distribution were linear transformation of weighted PRSs of body fat measure as described in Aim 2 Methods. Further, analyses were performed separately in different age groups then pooled together to assess potential interaction of age groups with the genetically predicted body fatness trait using likelihood ratio test by comparing models with and without the product terms of age and age-squared with genetically predicted body fatness at 2 degrees of freedom (Song et al. 2018). Multinomial logistic regression model was applied to study the associations of body fatness change patterns from age 10 to baseline for each trait with the group of thinner to normal weight or non-obese as referent.

For each model, age, age-squared, first eight genetic principal components, an indicator of genotyping array was adjusted. For outcomes are body fat measure changes, baseline body fatness measure and years of follow-up were further adjusted. In associations of genetically predicted body fatness adjusted for BMI (WHRadjBMI, BFPadjBMI, WBFMadjBMI, TFPadjBMI, and TFMadjBMI) with baseline body fat mass and distribution, baseline BMI was included in the model.

Analyses were performed using R version 3.5.2 (R Project for Statistical Computing), and SAS Enterprise Guide (version 7.1; SAS Institute, Cary, NC). A two-sided P-value < 0.005 was considered statistically significant considering multiple comparison (10 body fat measure traits were studied, 0.05/10 = 0.005).

CHAPTER V

FINDINGS FOR SPECIFIC AIM 1: TO EVALUATE THE ASSOCIATIONS OF BMI, WHR, BODY FAT MASS AND DISTRIBUTION WITH MORTALITY AND CANCER RISK AMONG EUROPEAN POPULATION.

1. Results

In the entire cohort of over 500,000 subjects, 14,421 subjects died during a median follow-up time of 7.0 years and 23,058 incident cancer cases were diagnosed during a median follow-up time of 5.8 years. After exclusion due to the above-mentioned criteria, more than 7,500 deaths and 15,000 incident cancers remained in our analyses. Subjects included in our analyses were 45.6% males and 94% whites. The age and race distribution were similar among male and female participants (Table 3). Comparing to females, males were more likely to have a higher educational attainment, to ever smoke cigarettes and drink alcoholic beverage, to be heavier smokers and alcohol consumers, to more frequently exercise vigorously, and to have eaten processed and red meat more often. While males were more likely than females to have had a diagnosis of heart attack, stroke, hypertension, and diabetes, a higher percentage of females than males had a history of cancer diagnosis at baseline. There were modest correlations between BMI and WHR, but strong correlations between BMI and other body fat mass and distribution (WBFM, BFP, and TFP) (Table 4).

Table 3. Baseline characteristics of study participants by sex, the UK Biobank cohort, 2006-2010

Characteristics	Male	Female	P value
No. of participants (%)	229,138 (45.6)	273,405 (54.4)	--
Age (years, median (25^{th}, 75^{th}))	58 (50, 64)	57 (50, 63)	< 0.001
Race (%)			< 0.001
White	94.0	94.2	
Black	1.5	1.7	
Asian	2.6	2.0	
Mixed and other	1.3	1.6	
Unknown	0.7	0.5	
Townsend deprivation score, fifths (%)			< 0.001
1 Most deprived	20.1	19.9	
2	19.9	20.0	
3	19.7	20.2	
4	19.7	20.3	
5 Least deprived	20.6	19.5	
Unknown	0.1	0.1	
Education (%)			< 0.001
College or university degree	33.5	30.9	
Some professional qualifications	28.9	25.3	
Secondary education	18.5	25.0	
None of the above	17.2	16.8	
Unknown	2.1	2.0	
Smoking (%)			< 0.001
Never	48.7	59.3	
Former	38.2	31.3	
Current <20 pack-years	2.8	3.0	
Current 20 - <40 pack-years	3.5	3.2	
Current ≥40 pack-years	2.4	1.2	
Unknown	4.4	2.1	
Alcohol consumption (%)			< 0.001
Never	6.4	9.5	
Occasionally	16.2	28.0	
1 – 2 times/week	25.8	25.7	
3 – 4 times/week	26.0	20.5	
Almost daily	25.3	16.0	
Unknown	0.3	0.3	
Moderate physical activity (days/week, %)			< 0.001
0	12.6	11.8	
1 – 2	22.0	21.1	
3 – 5	38.0	37.7	
6 – 7	23.0	23.1	
Unknown	4.4	6.9	
Vigorous physical activity (days/week, %)			< 0.001
0	32.5	38.0	
1 – 2	27.9	28.6	
3 – 5	28.2	23.4	
6 – 7	6.7	4.1	
Unknown	4.7	5.9	

Intake of processed and red meat (times/week, %)			< 0.001
0 – <2	19.8	37.0	
2 – <4	33.1	36.4	
≥4	46.8	26.5	
Unknown	0.3	0.2	
Family history of cancer (yes, %)	34.5	35.4	< 0.001
Personal history of major diseases (yes, %)			
Cancer	6.1	9.1	< 0.001
Heart attack	4.1	0.9	< 0.001
Stroke	2.0	1.2	< 0.001
Diabetes	7.0	3.8	< 0.001
Hypertension	30.5	24.1	< 0.001
Anthropometric			
Body mass index (kg/m^2, median (25^{th}, 75^{th}))	27.3 (25.0, 30.1)	26.1 (23.5, 29.7)	< 0.001
Waist-to-hip ratio (median (25^{th}, 75^{th}))	0.93 (0.89, 0.98)	0.81 (0.77, 0.86)	< 0.001
Whole body fat mass (kg, median (25^{th}, 75^{th}))	21.3 (16.8, 26.6)	25.3 (19.9, 32.2)	< 0.001
Body fat percentage (%, median (25^{th}, 75^{th}))	25.4 (21.6, 29.1)	36.8 (32.0, 41.4)	< 0.001
Trunk fat percentage (%, median (25^{th}, 75^{th}))	28.0 (23.6, 32.1)	34.5 (29.1, 39.6)	< 0.001

Note: Percentages do not sum to 100% due to rounding.

Table 4. Pairwise correlations between body mass index, waist-to-hip ratio, whole body fat mass, body fat percentage, and trunk fat percentage by sex, the UK Biobank cohort, 2006-2010

	BMI	WHR	WBFM	BFP	TFP
			Male		
BMI	1.00				
WHR	0.59	1.00			
WBFM	0.92	0.61 (0.20)	1.00		
BFP	0.80	0.62 (0.31)	0.92 (0.78)	1.00	
TFP	0.76	0.60 (0.29)	0.89 (0.75)	0.99 (0.97)	1.00
			Female		
BMI	1.00				
WHR	0.46	1.00			
WBFM	0.94	0.44 (0.03)	1.00		
BFP	0.85	0.46 (0.14)	0.93 (0.71)	1.00	
TFP	0.76	0.41 (0.11)	0.89 (0.77)	0.98 (0.97)	1.00

Note: BMI, body mass index; WHR, waist-to-hip ratio; WBFM, whole body fat mass; BFP, body fat percentage; TFP, trunk fat percentage.
BMI adjusted correlation coefficients shown in parentheses.

All assessed body fat mass and distribution were positively associated with total and cause-specific mortality, where CVD mortality had a stronger association compared with cancer mortality (Table 5). However, the associations for mortality outcomes with body fat mass and distribution diminished after adjustment of BMI, except for WHR and WBFM. After BMI adjustment, WHR (per SD increment) remained significantly associated with all-cause mortality (HR = 1.14, 95% CI = 1.11-1.17), mortality due to CVD (1.15, 1.09-1.22), cancer (1.10, 1.06-1.14), and other causes (excluding external causes) (1.25, 1.19-1.31). WBFM, independent of BMI, also was associated with total mortality (1.05, 1.03-1.08) and cancer mortality (1.09, 1.06-1.14). Similar associations were seen in white never smokers.

There was no significant interaction of sex with BMI, WHR, and WBFM on all-cause mortality in the analysis including all subjects (Figure 4). In the sub-analysis restricted to white never smokers, however, the magnitude of these associations was stronger among males than females, and tests for interactions were all statistically significant. BMI and WBFM showed a stronger positive association with total mortality among younger (<60 years) than older subjects in analyses that included all subjects or only white never smokers (p for interactions <0.001). A similar pattern of association was observed for WHR, although the interaction test was statistically significant only in the analysis including all subjects. When further adjusted for BMI, no interactions were shown in the sex or age categories with WHR or WBFM in association with all-cause mortality (data not shown).

Due to multiple comparison, we reported significant findings only when the p-value is smaller than 0.005. Obesity (BMI>=30.0-34.9 kg/m^2) and extreme obesity (BMI>=35.0 kg/m^2) was significantly associated with total and cause-specific mortality, and incident cancer of all cancers combined and obesity related cancer (Table 6). Among men, BMI and WBFM were not

Table 5. Hazard ratios (HR) and 95% confidence intervals (CI) for total and cause-specific mortality associated with body fat mass and distribution, among all participants and white never smokers, the UK Biobank cohort, 2006-2016

Cause of deaths	Body fat mass and distribution	Number of events	Non-BMI adjusted*		BMI adjusted	
			HR (95% CI) **	p	HR (95% CI)	p
			All participants ***			
All causes	BMI	7241	1.13 (1.10-1.16)	< 0.001		
	WHR	7385	1.18 (1.15-1.21)	< 0.001	1.14 (1.11-1.17)	< 0.001
	WBFM	7087	1.12 (1.09-1.15)	< 0.001	1.05 (1.03-1.08)	< 0.001
	BFP	7106	1.09 (1.06-1.12)	< 0.001	1.00 (0.97-1.03)	0.90
	TFP	7117	1.08 (1.05-1.11)	< 0.001	1.01 (0.98-1.04)	0.48
CVD	BMI	1562	1.31 (1.24-1.38)	< 0.001		
	WHR	1586	1.29 (1.23-1.35)	< 0.001	1.15 (1.09-1.21)	< 0.001
	WBFM	1505	1.25 (1.19-1.32)	< 0.001	1.02 (0.96-1.07)	0.55
	BFP	1510	1.22 (1.15-1.30)	< 0.001	0.98 (0.93-1.04)	0.55
	TFP	1511	1.21 (1.14-1.29)	< 0.001	0.99 (0.94-1.06)	0.84
Cancer	BMI	3694	1.08 (1.04-1.12)	< 0.001		
	WHR	3730	1.12 (1.09-1.16)	< 0.001	1.10 (1.06-1.14)	< 0.001
	WBFM	3632	1.10 (1.07-1.14)	< 0.001	1.09 (1.06-1.13)	< 0.001
	BFP	3637	1.08 (1.04-1.12)	< 0.001	1.03 (0.99-1.06)	0.12
	TFP	3642	1.07 (1.04-1.11)	< 0.001	1.03 (0.99-1.06)	0.14
Other ****	BMI	1683	1.13 (1.07-1.20)	< 0.001		
	WHR	1758	1.25 (1.19-1.31)	< 0.001	1.25 (1.19-1.31)	< 0.001
	WBFM	1651	1.07 (1.02-1.14)	0.01	1.01 (0.96-1.06)	0.76
	BFP	1660	1.04 (0.98-1.11)	0.18	0.98 (0.92-1.04)	0.40
	TFP	1664	1.05 (0.99-1.11)	0.14	1.01 (0.95-1.07)	0.79
			White never smokers *****			
All causes	BMI	2636	1.21 (1.16-1.26)	< 0.001		
	WHR	2680	1.20 (1.15-1.24)	< 0.001	1.11 (1.06-1.15)	< 0.001
	WBFM	2569	1.20 (1.15-1.24)	< 0.001	1.04 (1.00-1.08)	0.06
	BFP	2570	1.16 (1.11-1.21)	< 0.001	0.98 (0.94-1.03)	0.43
	TFP	2570	1.15 (1.10-1.20)	< 0.001	1.00 (0.96-1.04)	0.93
CVD	BMI	523	1.39 (1.27-1.52)	< 0.001		
	WHR	531	1.30 (1.21-1.40)	< 0.001	1.12 (1.02-1.24)	0.02
	WBFM	502	1.34 (1.23-1.45)	< 0.001	1.00 (0.91-1.09)	0.92
	BFP	503	1.29 (1.16-1.43)	< 0.001	0.94 (0.85-1.03)	0.20
	TFP	504	1.25 (1.12-1.39)	< 0.001	0.94 (0.86-1.03)	0.20
Cancer	BMI	1360	1.15 (1.09-1.22)	< 0.001		
	WHR	1366	1.14 (1.08-1.20)	< 0.001	1.07 (1.01-1.13)	0.02
	WBFM	1339	1.19 (1.13-1.26)	< 0.001	1.12 (1.06-1.18)	< 0.001
	BFP	1339	1.17 (1.10-1.24)	< 0.001	1.05 (0.99-1.11)	0.10
	TFP	1338	1.17 (1.10-1.24)	< 0.001	1.06 (1.01-1.12)	0.03

Other ****	BMI	635	1.20 (1.10-1.32)	< 0.001		
	WHR	660	1.24 (1.16-1.33)	< 0.001	1.19 (1.10-1.29)	< 0.001
	WBFM	611	1.13 (1.03-1.24)	0.01	0.95 (0.87-1.03)	0.22
	BFP	611	1.08 (0.98-1.19)	0.13	0.91 (0.83-1.00)	0.05
	TFP	611	1.07 (0.97-1.18)	0.19	0.94 (0.85-1.03)	0.18

Note: BMI, body mass index; WHR, waist-to-hip ratio; WBFM, whole body fat mass; BFP, body fat percentage; TFP, trunk fat percentage.

* For body mass index, per 5 units (kg/m^2) increase estimates were presented; for body fat mass and distribution, per SD increase estimates were presented

** Adjusted for age, Townsend deprivation score, sex, smoking status, pack-year of smoking, alcohol consumption, race, education, family history of cancer, intake of processed and red meat

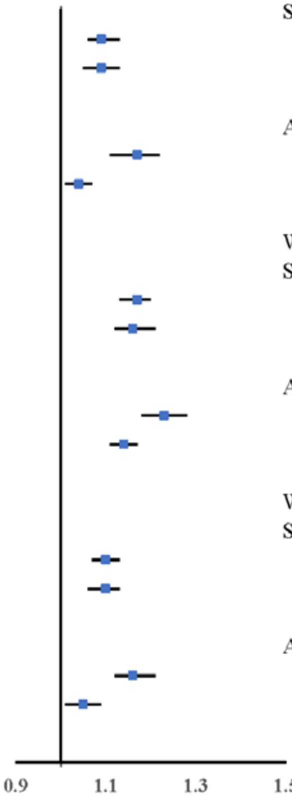
*** Number of participants in each analysis: 445,755 for body mass index, 448,861 for waist-to-hip ratio, 441,820 for whole body fat mass, 442,280 for body fat percentage, and 442,343 for trunk fat percentage

**** Excluding external causes

***** Number of participants in each analysis: 229,845 for body mass index, 231,364 for waist-to-hip ratio, 227,904 for whole body fat mass, 228,123 for body fat percentage, and 228,158 for trunk fat percentage

All participants

Body mass index		
Sex	HR (95% CI)	*p* value
Male	1.09 (1.06, 1.13)	< 0.001
Female	1.09 (1.05, 1.13)	< 0.001
	P for interaction = 0.84	
Age		
< 60	1.17 (1.13, 1.22)	< 0.001
≥ 60	1.04 (1.01, 1.07)	0.016
	P for interaction < 0.001	
Waist-to-hip ratio		
Sex	HR (95% CI)	*p* value
Male	1.17 (1.13, 1.20)	< 0.001
Female	1.16 (1.12, 1.21)	< 0.001
	P for interaction = 0.78	
Age		
< 60	1.23 (1.18, 1.28)	< 0.001
≥ 60	1.14 (1.11, 1.17)	< 0.001
	P for interaction = 0.03	
Whole body fat mass		
Sex	HR (95% CI)	*p* value
Male	1.10 (1.07, 1.13)	< 0.001
Female	1.10 (1.06, 1.14)	< 0.001
	P for interaction = 0.90	
Age		
< 60	1.16 (1.12, 1.21)	< 0.001
≥ 60	1.05 (1.01, 1.09)	< 0.001
	P for interaction < 0.001	



Never smokers, white

Body mass index		
Sex	HR (95% CI)	*p* value
Male	1.25 (1.18, 1.33)	< 0.001
Female	1.15 (1.09, 1.21)	< 0.001
	P for interaction = 0.003	
Age		
< 60	1.32 (1.25, 1.40)	< 0.001
≥ 60	1.09 (1.04, 1.15)	< 0.001
	P for interaction < 0.001	
Waist-to-hip ratio		
Sex	HR (95% CI)	*p* value
Male	1.25 (1.19, 1.32)	< 0.001
Female	1.14 (1.08, 1.21)	< 0.001
	P for interaction = 0.002	
Age		
< 60	1.25 (1.18, 1.33)	< 0.001
≥ 60	1.18 (1.12, 1.23)	< 0.001
	P for interaction= 0.59	
Whole body fat mass		
Sex	HR (95% CI)	*p* value
Male	1.21 (1.15, 1.27)	< 0.001
Female	1.15 (1.09, 1.22)	< 0.001
	P for interaction = 0.06	
Age		
< 60	1.30 (1.23, 1.37)	< 0.001
≥ 60	1.10 (1.05, 1.16)	< 0.001
	P for interaction < 0.001	

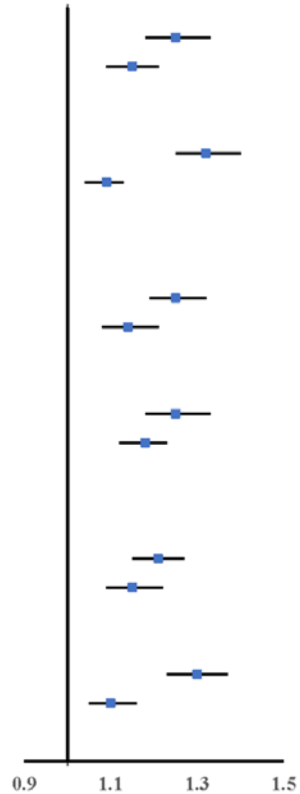


Figure 4. Association of BMI, WHR, and WBFM and all-cause mortality by sex, age, the UK Biobank cohort, 2006-2016

Note: BMI, body mass index; WHR, waist-to-hip ratio; WBFM, whole body fat mass.
The calculations of hazard ratios were adjusted for age (when appropriate), Townsend deprivation score, sex (when appropriate), smoking status and pack-year (when appropriate), alcohol consumption, race, education, family history of cancer, intake of processed and red meat.

Table 6. Hazard ratios (HRs) and 95% confidence intervals (CIs) for total and cause-specific mortality and cancer risk associated with Body Mass Index, among all participants and white never smokers, the UK Biobank cohort, 2006-2016

	Body mass index (BMI) categories at baseline (kg/m^2)										Per 5 kg/m^2 increase	
	15.0-<18.5		18.5-<25.0		25.0-<30.0		30.0-<35.0		35.0-<60.0			
	No. of cases	HR (95% CI)	No. of cases	HR	No. of cases	HR (95% CI)	No. of cases	HR (95% CI)	No. of cases	HR (95% CI)	HR (95% CI)	P value
	All participants *											
	N = 2,312		N = 148,305		N = 190,373		N = 76,935		N = 30,142			
Mortality												
All causes	88	2.46 (1.99-3.04)	2,054	1.00	2,976	0.92 (0.87, 0.97)	1,482	1.09 (1.02-1.17)	729	1.50 (1.37, 1.64)	1.11 (1.08-1.14)	< 0.001
CVD	12	1.85 (1.04-3.29)	390	1.00	631	0.96 (0.85, 1.09)	334	1.22 (1.05, 1.42)	207	2.23 (1.88, 2.65)	1.29 (1.22-1.37)	< 0.001
Cancer	27	1.48 (1.01-2.17)	1,046	1.00	1,584	0.99 (0.92, 1.08)	762	1.16 (1.05, 1.27)	302	1.27 (1.12, 1.45)	1.07 (1.04-1.11)	< 0.001
Other causes **	45	4.85 (3.56-6.62)	512	1.00	636	0.77 (0.69, 0.87)	336	0.95 (0.82, 1.09)	199	1.52 (1.28, 1.80)	1.07 (1.01-1.14)	0.03
Cancer incidence												
All combined	66	0.97 (0.77-1.24)	4,374	1.00	6,673	1.08 (1.04-1.12)	2,789	1.12 (1.06-1.17)	1,099	1.21 (1.13-1.29)	1.06 (1.04-1.08)	< 0.001
Obesity related ***	30	0.82 (0.57-1.17)	2,115	1.00	2,806	1.13 (1.07-1.20)	1,350	1.33 (1.24 (1.43)	661	1.57 (1.44-1.72)	1.15 (1.13-1.18)	< 0.001
	White never smokers ****											
	N = 1,234		N = 83,048		N = 36,398		N = 14,470		N = 6,234			
Mortality												
All causes	20	1.93 (1.24-3.01)	787	1.00	1,060	0.97 (0.88, 1.07)	518	1.26 (1.13-1.41)	271	1.79 (1.56, 2.07)	1.19 (1.14-1.24)	< 0.001
CVD	4	2.40 (0.89-6.51)	142	1.00	206	0.96 (0.77, 1.19)	104	1.29 (1.00, 1.67)	71	2.51 (1.88, 3.36)	1.38 (1.26-1.51)	< 0.001
Cancer	4	0.74 (0.28-1.97)	408	1.00	573	1.06 (0.93, 1.21)	262	1.33 (1.13, 1.56)	117	1.64 (1.32, 2.02)	1.15 (1.09-1.22)	< 0.001
Other causes **	10	3.50 (1.84-6.65)	202	1.00	229	0.79 (0.65, 0.96)	128	1.11 (0.88, 1.39)	76	1.70 (1.29, 2.22)	1.17 (1.06-1.28)	0.001
Cancer incidence												
All combined	24	0.77 (0.52-1.16)	2,223	1.00	3,029	1.11 (1.05-1.17)	1,129	1.13 (1.05-1.21)	458	1.23 (1.11-1.36)	1.08 (1.05-1.11)	< 0.001
Obesity related ***	13	0.67 (0.39-1.15)	1,174	1.00	1,389	1.14 (1.05-1.23)	616	1.30 (1.18-1.43)	317	1.57 (1.38-1.78)	1.16 (1.12-1.20)	< 0.001

* Adjusted for age, Townsend deprivation score, sex, smoking status, pack-year of smoking, alcohol consumption, race, education, family history of cancer, intake of processed and red meat

** Excluding external causes

*** Including esophageal adenocarcinoma, cardia stomach cancer, colorectal cancer, liver cancer, gallbladder cancer, pancreatic cancer, kidney cancer, thyroid cancer, multiple myeloma, female breast cancer, cancer of corpus uteri, and epithelial ovarian cancer

**** Adjusted for age, Townsend deprivation score, sex, alcohol consumption, education, family history of cancer, intake of processed and red meat significantly associated with risk of all cancers combined, whereas WHR was positively associated with all cancer risk (1.04, 1.01-1.06), obesity related cancers (1.12, 1.07-1.17) and colorectal cancer (1.14, 1.07-1.22) (Table 7).

Among women, high BMI, WHR, and WBFM (both before and after BMI adjustment) were associated with an elevated risk of all cancers combined (Table 8). After BMI adjustment, WHR was positively associated with a risk of cancers of the colon/rectum (1.14, 1.06-1.22), while greater WBFM was associated with an increased risk of obesity related cancer (1.06, 1.03-1.09), postmenopausal breast cancer (1.08, 1.03-1.13), and epithelial ovarian cancer (1.20, 1.07-1.34). The associations with BFP and TFP were similar and we did not any significant associations after BMI adjustment.

The quintiles of each body fat mass and distribution were categorized for the whole study population. Therefore, we observed fewer normal weight participants in higher quintile groups for each body fat measure. Among normal BMI participants, higher WHR was associated with mortality and incident cancer risk, and the independent associations were observed after BMI adjustment (Table 9). Risks of all-cancers combined and obesity-related cancers were positively associated with increased whole body fat mass (Table 10). Compared to the lowest fifth, participants in the highest quintile groups in body fat and trunk fat percentage show approximately 2 folds risk of overall death and death due to CVD and other causes (Table 11, Table 12).

Table 7. Hazard ratios (HR) and 95% confidence intervals (CI) of risk of cancer associated with body fat mass and distribution among male participants, the UK Biobank cohort, 2006-2014

Cancer site	Body fat mass and distribution	Number of events	Non-BMI adjusted *		BMI adjusted	
			HR (95% CI) **	p	HR (95% CI)	p
All cancers	BMI	7582	1.03 (1.00-1.06)	0.06		
	WHR	7620	1.05 (1.02-1.07)	< 0.001	1.04 (1.01-1.06)	0.002
	WBFM	7464	1.02 (1.00-1.05)	0.05	1.01 (0.98-1.03)	0.54
	BFP	7473	1.01 (0.98-1.03)	0.62	0.98 (0.96-1.00)	0.09
	TFP	7480	1.01 (0.98-1.03)	0.70	0.98 (0.96-1.00)	0.11
Obesity related cancers	BMI	1800	1.23 (1.17-1.29)	< 0.001		
	WHR	1806	1.21 (1.16-1.27)	< 0.001	1.12 (1.07-1.17)	< 0.001
	WBFM	1768	1.17 (1.12-1.22)	< 0.001	0.99 (0.95-1.04)	0.71
	BFP	1768	1.15 (1.09-1.21)	< 0.001	0.98 (0.93-1.03)	0.45
	TFP	1771	1.14 (1.08-1.20)	< 0.001	0.99 (0.94-1.04)	0.57
Esophageal adenocarcinoma	BMI	159	1.49 (1.29-1.71)	< 0.001		
	WHR	160	1.38 (1.24-1.53)	< 0.001	1.19 (1.02-1.40)	0.03
	WBFM	152	1.36 (1.21-1.52)	< 0.001	0.92 (0.81-1.05)	0.23
	BFP	152	1.43 (1.20-1.69)	< 0.001	1.02 (0.87-1.18)	0.84
	TFP	153	1.42 (1.17-1.72)	< 0.001	1.02 (0.86-1.21)	0.84
Cardia stomach	BMI	59	1.25 (0.95-1.64)	0.12		
	WHR	60	1.21 (0.94-1.56)	0.15	1.13 (0.91-1.42)	0.27
	WBFM	59	1.09 (0.85-1.40)	0.48	0.97 (0.77-1.23)	0.80
	BFP	59	1.02 (0.78-1.33)	0.89	0.88 (0.69-1.13)	0.31
	TFP	59	1.02 (0.78-1.32)	0.89	0.89 (0.72-1.12)	0.32
Colorectum	BMI	935	1.19 (1.11-1.28)	< 0.001		
	WHR	939	1.22 (1.15-1.29)	< 0.001	1.14 (1.07-1.22)	< 0.001
	WBFM	920	1.14 (1.07-1.21)	< 0.001	1.00 (0.94-1.07)	0.99
	BFP	920	1.14 (1.06-1.22)	< 0.001	1.01 (0.94-1.09)	0.71
	TFP	921	1.14 (1.06-1.22)	< 0.001	1.02 (0.95-1.09)	0.63
Liver	BMI	79	1.58 (1.29-1.94)	< 0.001		
	WHR	79	1.42 (1.27-1.59)	< 0.001	1.24 (1.07-1.44)	0.005
	WBFM	77	1.55 (1.35-1.77)	< 0.001	1.25 (1.00-1.57)	0.05
	BFP	77	1.71 (1.36-2.15)	< 0.001	1.27 (0.98-1.64)	0.08
	TFP	77	1.79 (1.39-2.32)	< 0.001	1.33 (1.01-1.77)	0.04
Kidney	BMI	244	1.28 (1.13-1.45)	< 0.001		
	WHR	244	1.19 (1.05-1.34)	0.01	1.06 (0.93-1.21)	0.37
	WBFM	240	1.17 (1.05-1.30)	0.004	0.93 (0.81-1.07)	0.28
	BFP	240	1.12 (0.98-1.27)	0.10	0.90 (0.78-1.03)	0.12
	TFP	241	1.11 (0.97-1.27)	0.14	0.91 (0.79-1.04)	0.15
Multiple myeloma	BMI	115	0.96 (0.78-1.19)	0.73		
	WHR	115	0.93 (0.79-1.09)	0.36	0.93 (0.79-1.09)	0.38
	WBFM	114	0.94 (0.79-1.13)	0.52	0.94 (0.77-1.14)	0.51

	BFP	114	0.91 (0.76-1.08)	0.28	0.89 (0.74-1.07)	0.20
	TFP	114	0.91 (0.76-1.09)	0.30	0.90 (0.75-1.07)	0.23
Pancreas	BMI	162	1.12 (0.92-1.36)	0.26		
	WHR	162	1.09 (0.92-1.30)	0.30	1.04 (0.89-1.22)	0.63
	WBFM	160	1.09 (0.93-1.29)	0.29	1.04 (0.91-1.19)	0.57
	BFP	160	1.02 (0.85-1.22)	0.81	0.92 (0.79-1.08)	0.32
	TFP	160	1.02 (0.85-1.22)	0.84	0.93 (0.80-1.08)	0.33
Lung	BMI	48	1.02 (0.73-1.42)	0.92		
	WHR	48	1.14 (0.89-1.46)	0.31	1.16 (0.90-1.48)	0.25
	WBFM	46	1.09 (0.85-1.40)	0.50	1.06 (0.79-1.42)	0.71
	BFP	46	1.07 (0.81-1.42)	0.62	1.02 (0.76-1.38)	0.88
	TFP	46	1.09 (0.82-1.46)	0.55	1.05 (0.78-1.41)	0.75
Prostate	BMI	3054	0.92 (0.88-0.96)	< 0.001		
	WHR	3055	0.96 (0.92-0.99)	0.02	1.00 (0.96-1.04)	0.88
	WBFM	3008	0.92 (0.89-0.96)	< 0.001	0.97 (0.93-1.00)	0.06
	BFP	3011	0.92 (0.89-0.96)	< 0.001	0.96 (0.93-1.00)	0.03
	TFP	3011	0.93 (0.90-0.96)	< 0.001	0.96 (0.93-1.00)	0.04

Note: BMI, body mass index; WHR, waist-to-hip ratio; WBFM, whole body fat mass

* For BMI, per 5 units (kg/m^2) increase estimates were presented; for body fat mass and distribution, per SD increase estimates were presented

** Adjusted for age, Townsend deprivation score, smoking status, pack-year, alcohol consumption, race, education, family history of cancer, intake of processed and red meat

Table 8. Hazard ratios (HR) and 95% confidence intervals (CI) of risk of cancer associated with body fat mass and distribution among female participants, UK Biobank cohort, 2006-2014

Cancer site	Body fat mass and distribution	Number of events	Non-BMI adjusted *		BMI adjusted	
			HR (95% CI) **	p	HR (95% CI)	p
All cancers	BMI	7353	1.09 (1.06-1.11)	< 0.001		
	WHR	7417	1.09 (1.06-1.11)	< 0.001	1.05 (1.03-1.08)	< 0.001
	WBFM	7304	1.10 (1.08-1.13)	< 0.001	1.05 (1.03-1.08)	< 0.001
	BFP	7306	1.08 (1.05-1.10)	< 0.001	1.00 (0.97-1.02)	0.86
	TFP	7298	1.07 (1.05-1.10)	< 0.001	1.01 (0.98-1.03)	0.54
Obesity related cancers	BMI	5132	1.13 (1.10-1.16)	< 0.001		
	WHR	5174	1.10 (1.07-1.13)	< 0.001	1.04 (1.01-1.07)	0.01
	WBFM	5100	1.15 (1.12-1.18)	< 0.001	1.06 (1.03-1.09)	< 0.001
	BFP	5101	1.13 (1.09-1.16)	< 0.001	1.01 (0.98-1.04)	0.64
	TFP	5095	1.12 (1.09-1.15)	< 0.001	1.02 (0.99-1.05)	0.26
Premenopausal breast ***	BMI	546	1.02 (0.94-1.10)	0.71		
	WHR	552	1.05 (0.96-1.14)	0.30	1.04 (0.95-1.14)	0.38
	WBFM	545	1.05 (0.97-1.14)	0.21	1.12 (1.03-1.21)	0.01
	BFP	545	1.05 (0.97-1.14)	0.21	1.08 (0.99-1.17)	0.09
	TFP	545	1.06 (0.98-1.15)	0.15	1.08 (0.99-1.17)	0.09
Postmenopausal breast ***	BMI	2145	1.08 (1.04-1.13)	< 0.001		
	WHR	2158	1.05 (1.01-1.10)	0.02	1.02 (0.98-1.06)	0.41
	WBFM	2128	1.11 (1.07-1.16)	< 0.001	1.08 (1.03-1.13)	< 0.001
	BFP	2128	1.11 (1.06-1.16)	< 0.001	1.05 (1.01-1.10)	0.02
	TFP	2126	1.11 (1.07-1.17)	< 0.001	1.07 (1.02-1.12)	0.01
Corpus uteri ****	BMI	459	1.62 (1.51-1.74)	< 0.001		
	WHR	465	1.28 (1.17-1.40)	< 0.001	1.03 (0.94-1.13)	0.50
	WBFM	457	1.59 (1.47-1.72)	< 0.001	1.01 (0.93-1.10)	0.87
	BFP	457	1.60 (1.43-1.79)	< 0.001	0.94 (0.86-1.03)	0.18
	TFP	456	1.46 (1.31-1.62)	< 0.001	0.95 (0.87-1.04)	0.24
Epithelial ovarian *****	BMI	272	0.98 (0.86-1.11)	0.70		
	WHR	275	1.01 (0.89-1.14)	0.90	1.02 (0.91-1.15)	0.68
	WBFM	270	1.05 (0.92-1.19)	0.49	1.20 (1.07-1.34)	0.003
	BFP	271	1.03 (0.90-1.18)	0.66	1.11 (0.97-1.27)	0.12
	TFP	271	1.05 (0.92-1.21)	0.47	1.11 (0.98-1.27)	0.10
Esophageal adenocarcinoma	BMI	35	1.24 (0.93-1.67)	0.15		
	WHR	36	1.28 (0.95-1.70)	0.17	1.09 (0.77-1.53)	0.63
	WBFM	36	1.51 (1.04-2.18)	0.03	1.22 (0.94-1.59)	0.14
	BFP	36	1.37 (0.91-2.05)	0.13	0.91 (0.66-1.27)	0.59
	TFP	36	1.27 (0.88-1.85)	0.20	0.92 (0.67-1.26)	0.60
Colorectum	BMI	762	1.03 (0.96-1.11)	0.41		
	WHR	767	1.14 (1.06-1.23)	< 0.001	1.14 (1.06-1.22)	< 0.001
	WBFM	761	1.04 (0.97-1.12)	0.31	1.02 (0.95-1.10)	0.56

	BFP	761	1.00 (0.93-1.08)	1.00	0.95 (0.88-1.03)	0.20
	TFP	760	0.99 (0.92-1.07)	0.86	0.96 (0.89-1.03)	0.26
Liver	BMI	57	1.02 (0.77-1.35)	0.89		
	WHR	58	1.15 (0.89-1.50)	0.29	1.08 (0.82-1.43)	0.58
	WBFM	56	1.06 (0.78-1.45)	0.70	1.04 (0.74-1.46)	0.82
	BFP	56	1.01 (0.74-1.39)	0.95	0.94 (0.69-1.29)	0.71
	TFP	56	1.00 (0.73-1.37)	1.00	0.95 (0.70-1.29)	0.73
Kidney	BMI	136	1.32 (1.16-1.52)	< 0.001		
	WHR	137	1.36 (1.14-1.62)	< 0.001	1.22 (1.03-1.46)	0.02
	WBFM	137	1.29 (1.13-1.48)	< 0.001	0.98 (0.85-1.12)	0.74
	BFP	137	1.30 (1.07-1.56)	0.01	0.98 (0.83-1.17)	0.83
	TFP	136	1.24 (1.03-1.49)	0.02	0.98 (0.83-1.17)	0.86
Multiple myeloma	BMI	104	1.12 (0.95-1.33)	0.17		
	WHR	104	1.14 (0.91-1.42)	0.25	1.08 (0.89-1.32)	0.45
	WBFM	102	1.11 (0.93-1.33)	0.24	0.96 (0.80-1.15)	0.66
	BFP	102	1.09 (0.89-1.34)	0.40	0.95 (0.80-1.13)	0.57
	TFP	102	1.09 (0.89-1.34)	0.40	0.98 (0.83-1.17)	0.85
Pancreas	BMI	153	1.27 (1.10-1.47)	0.002		
	WHR	155	1.19 (1.01-1.41)	0.04	1.09 (0.93-1.28)	0.28
	WBFM	151	1.28 (1.10-1.49)	0.001	1.03 (0.89-1.20)	0.67
	BFP	151	1.29 (1.07-1.55)	0.01	1.04 (0.88-1.23)	0.65
	TFP	151	1.23 (1.03-1.48)	0.02	1.02 (0.87-1.19)	0.83
Lung	BMI	93	0.79 (0.64-0.98)	0.04		
	WHR	93	1.01 (0.83-1.22)	0.96	1.11 (0.92-1.33)	0.29
	WBFM	92	0.80 (0.64-0.99)	0.04	0.97 (0.76-1.23)	0.80
	BFP	92	0.84 (0.70-1.01)	0.07	1.01 (0.82-1.24)	0.92
	TFP	92	0.86 (0.71-1.03)	0.09	1.00 (0.82-1.23)	0.99
Thyroid	BMI	86	1.19 (1.02-1.41)	0.03		
	WHR	86	1.09 (0.87-1.37)	0.43	1.01 (0.81-1.25)	0.95
	WBFM	85	1.21 (1.02-1.44)	0.03	1.05 (0.85-1.30)	0.67
	BFP	85	1.25 (1.03-1.53)	0.03	1.10 (0.90-1.33)	0.35
	TFP	85	1.21 (0.99-1.50)	0.07	1.06 (0.87-1.30)	0.57

Note: BMI, body mass index; WHR, waist-to-hip ratio; WBFM, whole body fat mass

* For BMI, per 5 units (kg/m^2) increase estimates were presented; for body fat mass and distribution, per SD increase estimates were presented

** Adjusted for age, Townsend deprivation score, smoking status, pack-year, alcohol consumption, race, education, family history of cancer, intake of processed and red meat

*** Additional adjustment for age at menarche, parity, and ever hormone therapy use

**** Excluding participants that had a hysterectomy, additional adjustment for menopausal status, age at menarche, parity, and ever hormone therapy use

***** Excluding participants that had an oophorectomy, additional adjustment for menopausal status, age at menarche, parity, and ever hormone therapy use

Table 9. Hazard ratios (HRs) and 95% confidence intervals (CIs) for total and cause-specific mortality and cancer risk associated with waist-to-hip ratio, among all participants and white never smokers with normal body mass index, the UK Biobank cohort, 2006-2016

	Waist-to-hip ratio categories at baseline *										Per SD increase		Per SD increase	
	Quintile 1		Quintile 2		Quintile 3		Quintile 4		Quintile 5					
	No. of cases	HR	No. of cases	HR (95% CI)	No. of cases	HR (95% CI)	No. of cases	HR (95% CI)	No. of cases	HR (95% CI)	HR (95% CI)	P value	HR (95% CI)	P value
	All participants **													
	N = 58,440		N = 39,849		N = 26,689		N = 16,106		N = 7,206		Non-BMI adjusted		BMI adjusted	
Mortality														
All causes	638	1.00	479	1.01 (0.89, 1.13)	447	1.25 (1.10, 1.41)	322	1.43 (1.24, 1.64)	166	1.55 (1.30, 1.85)	1.19 (1.13, 1.25)	< 0.001	1.21 (1.16, 1.26)	< 0.001
CVD	118	1.00	79	0.91 (0.69, 1.22)	97	1.48 (1.12, 1.95)	73	1.83 (1.34, 2.49)	23	1.24 (0.78, 1.97)	1.23 (1.10, 1.37)	< 0.001	1.21 (1.11, 1.32)	< 0.001
Cancer	322	1.00	283	1.14 (0.97, 1.33)	216	1.15 (0.96, 1.36)	148	1.22 (1.00, 1.49)	76	1.29 (1.00, 1.67)	1.11 (1.03, 1.20)	0.005	1.12 (1.05, 1.19)	< 0.001
Other causes ***	156	1.00	96	0.84 (0.65, 1.09)	116	1.36 (1.06, 1.73)	84	1.56 (1.19, 2.05)	59	2.32 (1.68, 3.20)	1.32 (1.20, 1.44)	< 0.001	1.34 (1.26, 1.43)	< 0.001
Cancer incidence														
All combined	1525	1.00	1204	1.08 (1.00, 1.16)	859	1.08 (1.00, 1.17)	528	1.08 (0.98, 1.20)	257	1.17 (1.03, 1.34)	1.05 (1.01, 1.09)	0.007	1.04 (1.01, 1.08)	0.02
Obesity related ****	688	1.00	583	1.10 (0.98, 1.23)	434	1.16 (1.02, 1.31)	267	1.10 (0.95, 1.27)	143	1.24 (1.03, 1.50)	1.08 (1.02, 1.14)	0.005	1.06 (1.01, 1.11)	0.02
	White never smokers *****													
	N = 35,772		N = 22,379		N = 13,929		N = 7,774		N = 3,188		Non-BMI adjusted		BMI adjusted	
Mortality														
All causes	298	1.00	190	0.96 (0.80, 1.15)	164	1.24 (1.03, 1.50)	94	1.24 (0.98, 1.58)	41	1.31 (0.94, 1.83)	1.15 (1.06, 1.25)	0.001	1.13 (1.05, 1.22)	0.002
CVD	55	1.00	30	0.87 (0.56, 1.37)	35	1.52 (0.99, 2.34)	17	1.37 (0.78, 2.39)	5	1.02 (0.41, 2.56)	1.19 (1.01, 1.39)	0.04	1.12 (0.96, 1.31)	0.14
Cancer	158	1.00	105	0.96 (0.75, 1.23)	78	1.06 (0.81, 1.39)	48	1.11 (0.80, 1.54)	19	1.03 (0.64, 1.67)	1.07 (0.95, 1.21)	0.29	1.04 (0.93, 1.17)	0.46
Other causes ***	71	1.00	46	0.98 (0.68, 1.43)	48	1.53 (1.06, 2.20)	23	1.28 (0.80, 2.07)	14	1.86 (1.02, 3.38)	1.23 (1.06, 1.44)	0.008	1.25 (1.13, 1.39)	< 0.001
Cancer incidence														
All combined	865	1.00	621	1.08 (0.98, 1.20)	419	1.13 (1.01, 1.27)	223	1.07 (0.92, 1.24)	95	1.12 (0.90, 1.39)	1.06 (1.01, 1.11)	0.03	1.03 (0.98, 1.08)	0.24
Obesity related ****	421	1.00	326	1.08 (0.93, 1.25)	231	1.17 (0.99, 1.37)	132	1.11 (0.91, 1.35)	64	1.22 (0.94, 1.60)	1.09 (1.02, 1.17)	0.01	1.06 (1.00, 1.13)	0.07

Note: BMI, body mass index.

* The quintiles of waist-to-hip ratio were used to categorize the whole study population into 5 groups, and the table presents only participants with normal BMI. Cut off points were as following: Q1: 0.20 – 0.88, Q2: 0.89 – 0.92, Q3: 0.93 – 0.95, Q4: 0.96 – 0.99, Q5: > 0.99 for males; Q1: 0.2 – 0.75, Q2: 0.76 – 0.79, Q3: 0.80 – 0.83, Q4: 0.84 – 0.87, Q5: > 0.88 for females. Waist-to-hip ratio < 0.20 or ≥ 2.00 were excluded as extremes.

** Adjusted for age, Townsend deprivation score, sex, smoking status, pack-year of smoking, alcohol consumption, race, education, family history of cancer, intake of processed and red meat

*** Excluding external causes

**** Including esophageal adenocarcinoma, cardia stomach cancer, colorectal cancer, liver cancer, gallbladder cancer, pancreatic cancer, kidney cancer, thyroid cancer, multiple myeloma, female breast cancer, cancer of corpus uteri, and epithelial ovarian cancer

***** Adjusted for age, Townsend deprivation score, sex, alcohol consumption, education, family history of cancer, intake of processed and red meat

Table 10. Hazard ratios (HRs) and 95% confidence intervals (CIs) for total and cause-specific mortality and cancer risk associated with whole body fat mass, among all participants and white never smokers with normal body mass index, the UK Biobank cohort, 2006-2016

	Whole body fat mass categories at baseline *										Per SD increase		Per SD increase	
	Quintile 1		Quintile 2		Quintile 3		Quintile 4		Quintile 5					
	No. of cases	HR	No. of cases	HR (95% CI)	No. of cases	HR (95% CI)	No. of cases	HR (95% CI)	No. of cases	HR (95% CI)	HR (95% CI)	P value	HR (95% CI)	P value
	All participants **													
	N = 78,320		N = 50,396		N = 15,703		N = 1,478		N = 11		Non-BMI adjusted		BMI adjusted	
Mortality														
All causes	1064	1.00	646	0.97 (0.87, 1.07)	232	1.13 (0.98, 1.31)	25	1.28 (0.86, 1.91)	1	9.60 (1.18, 78.14)	0.98 (0.87, 1.09)	0.66	1.08 (1.02, 1.14)	0.007
CVD	195	1.00	124	1.06 (0.84, 1.34)	44	1.26 (0.90, 1.77)	4	1.24 (0.46, 3.37)	0	–	1.09 (0.84, 1.42)	0.53	1.06 (0.93, 1.22)	0.37
Cancer	525	1.00	346	1.00 (0.87, 1.14)	125	1.15 (0.95, 1.41)	16	1.54 (0.94, 2.54)	0	–	1.13 (0.98, 1.31)	0.10	1.11 (1.03, 1.19)	0.007
Other causes ***	285	1.00	144	0.82 (0.67, 1.01)	53	1.00 (0.74, 1.35)	4	0.78 (0.29, 2.12)	1	41.70 (4.89, 355.90)	0.67 (0.53, 0.85)	0.001	1.02 (0.91, 1.15)	0.72
Cancer incidence														
All combined	2187	1.00	1525	1.03 (0.97, 1.10)	533	1.14 (1.04, 1.26)	44	0.99 (0.74, 1.34)	0	–	1.07 (1.00, 1.15)	0.06	1.03 (0.99, 1.06)	0.17
Obesity related ****	951	1.00	789	1.10 (1.00, 1.21)	313	1.30 (1.14, 1.48)	30	1.27 (0.89, 1.83)	0	–	1.16 (1.04, 1.29)	0.007	1.05 (1.00, 1.11)	0.05
	White never smokers *****													
	N = 44,044		N = 28,236		N = 8,693		N = 775		N = 6		Non-BMI adjusted		BMI adjusted	
Mortality														
All causes	384	1.00	269	1.06 (0.90, 1.24)	92	1.20 (0.95, 1.51)	10	1.45 (0.77, 2.73)	1	16.29 (1.79, 147.97)	1.10 (0.91, 1.32)	0.33	1.04 (0.95, 1.14)	0.36
CVD	68	1.00	48	1.14 (0.77, 1.69)	13	1.07 (0.59, 1.97)	2	1.90 (0.46, 7.91)	0	–	1.14 (0.73, 1.79)	0.56	0.96 (0.76, 1.21)	0.73
Cancer	194	1.00	148	1.09 (0.88, 1.36)	50	1.19 (0.86, 1.63)	4	1.05 (0.39, 2.81)	0	–	1.24 (0.98, 1.57)	0.07	1.09 (0.97, 1.21)	0.15
Other causes ***	105	1.00	60	0.87 (0.63, 1.21)	25	1.22 (0.77, 1.92)	3	1.62 (0.50, 5.19)	1	63.01 (6.24, 635.94)	0.78 (0.51, 1.18)	0.24	1.01 (0.83, 1.23)	0.92
Cancer incidence														
All combined	1087	1.00	802	1.11 (1.01, 1.21)	274	1.22 (1.07, 1.40)	24	1.20 (0.80, 1.79)	0	–	1.17 (1.06, 1.30)	0.002	1.03 (0.98, 1.08)	0.25

Obesity related ****	510	1.00	461	1.20 (1.06, 1.36)	167	1.30 (1.09, 1.56)	21	1.76 (1.14, 2.73)	0	−		1.25 (1.08, 1.44)	0.003	1.07 (0.99, 1.15)	0.08

Note: BMI, body mass index.

* The quintiles of whole body fat mass were used to categorize the whole study population into 5 groups, and the table presents only participants with normal BMI. Cut off points were as following: Q1: 5.0 – 15.6, Q2: 15.7 – 19.4, Q3: 19.5 – 23.1, Q4: 23.2 – 28.1, Q5: ≥ 28.2 for males; Q1: 5.0 – 18.6, Q2: 18.7 – 23.1, Q3: 23.2 – 27.6, Q4: 27.7 – 34.1, Q5: ≥ 34.2 for females. whole body fat mass < 0.20 or ≥ 2.00 were excluded as extremes.

** Adjusted for age, Townsend deprivation score, sex, smoking status, pack-year of smoking, alcohol consumption, race, education, family history of cancer, intake of processed and red meat

*** Excluding external causes

**** Including esophageal adenocarcinoma, cardia stomach cancer, colorectal cancer, liver cancer, gallbladder cancer, pancreatic cancer, kidney cancer, thyroid cancer, multiple myeloma, female breast cancer, cancer of corpus uteri, and epithelial ovarian cancer

***** Adjusted for age, Townsend deprivation score, sex, alcohol consumption, education, family history of cancer, intake of processed and red meat

Table 11. Hazard ratios (HRs) and 95% confidence intervals (CIs) for total and cause-specific mortality and cancer risk associated with body fat percentage, among all participants and white never smokers with normal body mass index, the UK Biobank cohort, 2006-2016

	Body fat percentage categories at baseline *										Per SD increase		Per SD increase	
	Quintile 1		Quintile 2		Quintile 3		Quintile 4		Quintile 5					
	No. of cases	HR	No. of cases	HR (95% CI)	No. of cases	HR (95% CI)	No. of cases	HR (95% CI)	No. of cases	HR (95% CI)	HR (95% CI)	P value	HR (95% CI)	P value
	All participants **													
	N = 74,701		N = 46,684		N = 20,118		N = 4,346		N = 344		Non-BMI adjusted		BMI adjusted	
Mortality														
All causes	935	1.00	580	0.92 (0.83, 1.03)	326	1.05 (0.92, 1.20)	112	1.32 (1.08, 1.61)	24	2.41 (1.58, 3.67)	1.02 (0.95, 1.09)	0.56	1.08 (1.03, 1.13)	0.003
CVD	169	1.00	101	0.92 (0.71, 1.18)	67	1.22 (0.91, 1.64)	29	1.82 (1.22, 2.71)	5	2.30 (0.91, 5.82)	1.13 (0.96, 1.33)	0.16	1.11 (0.98, 1.24)	0.10
Cancer	465	1.00	321	0.98 (0.85, 1.14)	169	1.05 (0.87, 1.26)	48	1.12 (0.83, 1.51)	10	2.20 (1.19, 4.10)	1.05 (0.96, 1.15)	0.27	1.06 (0.99, 1.12)	0.09
Other causes ***	243	1.00	132	0.82 (0.66, 1.01)	78	0.96 (0.74, 1.25)	30	1.31 (0.89, 1.95)	7	2.51 (1.15, 5.46)	0.91 (0.78, 1.05)	0.18	1.09 (0.99, 1.21)	0.08
Cancer incidence														
All combined	2043	1.00	1394	1.00 (0.93, 1.07)	691	1.05 (0.97, 1.15)	148	0.93 (0.78, 1.09)	19	1.24 (0.79, 1.96)	1.02 (0.97, 1.06)	0.46	1.00 (0.97, 1.03)	0.89
Obesity related ****	908	1.00	738	1.10 (0.99, 1.21)	347	1.11 (0.98, 1.26)	84	1.24 (0.99, 1.56)	7	1.64 (0.78, 3.48)	1.06 (0.99, 1.13)	0.09	1.02 (0.97, 1.06)	0.49
	White never smokers *****													
	N = 42,529		N = 26,088		N = 11,000		N = 2,162		N = 121		Non-BMI adjusted		BMI adjusted	
Mortality														
All causes	344	1.00	241	1.03 (0.87, 1.22)	129	1.17 (0.95, 1.44)	35	1.36 (0.95, 1.94)	8	4.14 (2.02, 8.51)	1.09 (0.97, 1.22)	0.17	1.05 (0.98, 1.14)	0.18
CVD	57	1.00	46	1.28 (0.86, 1.90)	23	1.36 (0.83, 2.24)	4	1.00 (0.36, 2.80)	2	5.75 (1.35, 24.47)	1.13 (0.84, 1.51)	0.42	1.02 (0.83, 1.25)	0.86
Cancer	173	1.00	133	1.08 (0.86, 1.36)	74	1.26 (0.95, 1.67)	15	1.11 (0.65, 1.90)	1	1.10 (0.15, 7.90)	1.12 (0.97, 1.30)	0.11	1.06 (0.96, 1.17)	0.27
Other causes ***	96	1.00	51	0.78 (0.55, 1.10)	28	0.88 (0.57, 1.37)	15	1.98 (1.12, 3.50)	4	6.42 (2.33, 17.65)	0.97 (0.75, 1.24)	0.79	1.07 (0.91, 1.27)	0.40
Cancer incidence														
All combined	1043	1.00	721	1.04 (0.95, 1.15)	355	1.15 (1.02, 1.30)	68	1.02 (0.80, 1.31)	3	0.70 (0.22, 2.17)	1.06 (0.99, 1.12)	0.08	1.00 (0.95, 1.04)	0.82

Obesity related ****	496	1.00	416	1.16 (1.01, 1.32)	202	1.24 (1.05, 1.46)	43	1.32 (0.96, 1.80)	3	2.16 (0.69, 6.79)	1.12 (1.02, 1.22)	0.02	1.03 (0.97, 1.10)	0.31

Note: BMI, body mass index.

* The quintiles of body fat percentage were used to categorize the whole study population into 5 groups, and the table presents only participants with normal BMI. Cut off points were as following: Q1: 6.0 – 20.7, Q2: 20.8 – 24.1, Q3: 24.2 – 26.9, Q4: 27.0 – 29.9, Q5: ≥ 30.0 for males; Q1: 6.0 – 30.7, Q2: 30.8 – 34.9, Q3: 35.0 – 38.4, Q4: 38.5 – 42.5, Q5: ≥ 42.6 for females. Body fat percentage < 6.0 or ≥ 60.0 were excluded as extremes.

** Adjusted for age, Townsend deprivation score, sex, smoking status, pack-year of smoking, alcohol consumption, race, education, family history of cancer, intake of processed and red meat

*** Excluding external causes

**** Including esophageal adenocarcinoma, cardia stomach cancer, colorectal cancer, liver cancer, gallbladder cancer, pancreatic cancer, kidney cancer, thyroid cancer, multiple myeloma, female breast cancer, cancer of corpus uteri, and epithelial ovarian cancer

***** Adjusted for age, Townsend deprivation score, sex, alcohol consumption, education, family history of cancer, intake of processed and red meat

Table 12. Hazard ratios (HRs) and 95% confidence intervals (CIs) for total and cause-specific mortality and cancer risk associated with trunk fat percentage, among all participants and white never smokers with normal body mass index, the UK Biobank cohort, 2006-2016

	Trunk fat percentage categories at baseline *										Per SD increase		Per SD increase	
	Quintile 1		Quintile 2		Quintile 3		Quintile 4		Quintile 5					
	No. of cases	HR	No. of cases	HR (95% CI)	No. of cases	HR (95% CI)	No. of cases	HR (95% CI)	No. of cases	HR (95% CI)	HR (95% CI)	P value	HR (95% CI)	P value
	All participants **													
	N = 70,717		N = 44,126		N = 22,989		N = 7,497		N = 1,041		Non-BMI adjusted		BMI adjusted	
Mortality														
All causes	873	1.00	574	1.02 (0.92, 1.14)	341	1.05 (0.93, 1.20)	158	1.32 (1.11, 1.56)	40	1.90 (1.38, 2.62)	1.03 (0.97, 1.10)	0.30	1.08 (1.03, 1.13)	0.001
CVD	156	1.00	99	1.01 (0.78, 1.30)	71	1.25 (0.94, 1.68)	35	1.59 (1.09, 2.31)	11	2.61 (1.40, 4.87)	1.12 (0.97, 1.30)	0.13	1.11 (1.00, 1.24)	0.06
Cancer	432	1.00	315	1.09 (0.95, 1.27)	189	1.13 (0.95, 1.35)	69	1.14 (0.88, 1.47)	13	1.29 (0.74, 2.23)	1.05 (0.97, 1.14)	0.24	1.05 (0.99, 1.12)	0.11
Other causes ***	230	1.00	130	0.89 (0.71, 1.10)	72	0.85 (0.65, 1.11)	48	1.50 (1.09, 2.06)	12	2.07 (1.14, 3.76)	0.95 (0.84, 1.08)	0.46	1.11 (1.01, 1.22)	0.03
Cancer incidence														
All combined	1916	1.00	1309	1.03 (0.96, 1.10)	778	1.10 (1.01, 1.20)	261	1.06 (0.93, 1.21)	37	0.98 (0.71, 1.36)	1.02 (0.98, 1.06)	0.33	1.00 (0.97, 1.03)	0.82
Obesity related ****	865	1.00	667	1.09 (0.98, 1.21)	391	1.15 (1.02, 1.30)	147	1.30 (1.09, 1.55)	18	1.18 (0.74, 1.88)	1.05 (0.99, 1.12)	0.11	1.02 (0.97, 1.06)	0.53
	White never smokers *****													
	N = 39,966		N = 24,904		N = 12,627		N = 3,985		N = 513		Non-BMI adjusted		BMI adjusted	
Mortality														
All causes	319	1.00	239	1.12 (0.95, 1.33)	127	1.10 (0.89, 1.35)	59	1.46 (1.09, 1.93)	14	2.35 (1.36, 4.04)	1.11 (1.00, 1.23)	0.05	1.08 (1.01, 1.17)	0.04
CVD	55	1.00	45	1.29 (0.87, 1.93)	21	1.12 (0.67, 1.87)	9	1.37 (0.66, 2.83)	3	3.15 (0.97, 10.20)	1.09 (0.85, 1.39)	0.52	1.02 (0.85, 1.22)	0.85
Cancer	157	1.00	132	1.22 (0.96, 1.54)	79	1.33 (1.01, 1.75)	26	1.25 (0.82, 1.91)	2	0.67 (0.17, 2.69)	1.15 (1.01, 1.31)	0.03	1.09 (0.99, 1.20)	0.07
Other causes ***	89	1.00	51	0.86 (0.61, 1.22)	24	0.74 (0.47, 1.16)	23	1.98 (1.23, 3.17)	7	3.88 (1.76, 8.56)	1.03 (0.83, 1.29)	0.78	1.12 (0.96, 1.30)	0.17
Cancer incidence														
All combined	977	1.00	681	1.06 (0.96, 1.17)	389	1.15 (1.02, 1.29)	133	1.18 (0.98, 1.42)	12	0.78 (0.44, 1.38)	1.06 (1.01, 1.12)	0.03	1.01 (0.97, 1.05)	0.64

Obesity related ****	475	1.00	376	1.12 (0.98, 1.28)	221	1.22 (1.04, 1.44)	79	1.33 (1.05, 1.69)	10	1.35 (0.72, 2.54)	1.11 (1.02, 1.20)	0.01	1.04 (0.98, 1.11)	0.18

Note: BMI, body mass index.

* The quintiles of trunk fat percentage were used to categorize the whole study population into 5 groups, and the table presents only participants with normal BMI. Cut off points were as following: Q1: 2.0 – 22.3, Q2: 22.4 – 26.3, Q3: 26.4 – 29.5, Q4: 29.6 – 33.0, Q5: ≥ 33.1 for males; Q1: 2.0 – 27.6, Q2: 27.7 – 32.4, Q3: 32.5 – 36.4, Q4: 36.5 – 40.7, Q5: ≥ 40.8 for females. Trunk fat percentage < 2.0 or ≥ 70.0 were excluded as extremes.

** Adjusted for age, Townsend deprivation score, sex, smoking status, pack-year of smoking, alcohol consumption, race, education, family history of cancer, intake of processed and red meat

*** Excluding external causes

**** Including esophageal adenocarcinoma, cardia stomach cancer, colorectal cancer, liver cancer, gallbladder cancer, pancreatic cancer, kidney cancer, thyroid cancer, multiple myeloma, female breast cancer, cancer of corpus uteri, and epithelial ovarian cancer

***** Adjusted for age, Townsend deprivation score, sex, alcohol consumption, education, family history of cancer, intake of processed and red meat

2. Discussion

Using data from the UK Biobank cohort, we investigated BMI, WHR, WBFM, BFP, and TFP in relation to total and cause-specific mortality and risk of cancer. Consistent with previous studies, we found that a higher BMI was associated with total and cause-specific mortality and risk of esophageal adenocarcinoma, colorectal and liver cancers among males, postmenopausal breast cancer, cancer of corpus uteri and pancreatic cancer among females and kidney cancer among both males and females. Of body fat mass and distribution, only WHR and WBFM were found to be associated with total mortality, independent of BMI. Additional associations, independent of BMI, were found for WHR with mortality due to CVD, cancer, and other causes and WBFM with cancer mortality.

Our findings for a positive association of WHR, an indicator for central obesity or abdominal adiposity, with increased all-cause mortality and cause-specific mortality are supported by multiple large cohort studies (de Koning et al. 2007; Zhang et al. 2008; Pischon et al. 2008; Song et al. 2013; Zhang et al. 2013). WHR reflects the relative amount of visceral fat over peripheral fat, which makes it another good anthropometric measurement of disease risk in addition to BMI. This finding emphasizes the need to quantify visceral adipose tissue in assessing disease risk in clinical and research settings. Previous studies showed age may modify the association of BMI with mortality outcomes. We extended this finding to WHR and WBFM, and showed that similar to BMI, both WHR and WBFM were more strongly associated with total mortality in younger than older populations.

Some previous studies reported that WHR is a risk factor for postmenopausal breast cancer, colon cancer and gastric cancer, but several of them were limited by their case-control design, or incomplete adjustment for BMI in the analyses (Thorpe and Ferraro 2004; Keimling et al. 2013;

Huang et al. 1999). In the present study, the associations between WHR and risk of most cancers diminished or disappeared after we adjusted for BMI, suggesting that some previously discovered WHR-incident cancer associations might be due to effects of BMI. Interestingly, we observed a positive association of WHR and colorectal cancer among both men and women, even after adjustment for BMI, despite the fact that no significant association was found for BMI and colorectal cancer among women. High WHR may be an indicator of chronically high levels of circulating insulin and insulin-like growth factors (Larsson and Wolk 2007c; Kaaks et al. 2000), and thus might be associated with increased colorectal cancer risk, regardless of the sex. WHR has been associated with kidney cancer, primarily renal cell cancer, in women, which is in concordance with our findings (Adams et al. 2008b), suggesting a combined effect of altered circulating concentrations of estrogen and other hormones and glucose metabolism on the carcinogenesis.

We found that WBFM confers additional risk to deaths and some cancers independent of BMI. The WBFM and cancer association was more evident in women than men, which could partly be explained by higher percentage of body fat, the major source of estrogen synthesis among postmenopausal women. We found increased epithelial ovarian cancer and breast cancer risk associated with WBFM but not with WHR, which suggests that these associations are mediated through endogenous estrogen hormones pathway rather insulin resistance pathway. Elevated estrogen levels caused by overall fatness may be associated with carcinogenesis through increased cell proliferation, stimulated angiogenesis, and decreased apoptosis. It is suggested that overall body fat is the underlying adiposity risk factor of hormone dependent breast and epithelial ovarian cancer.

Recent study reported higher body fat levels are associated with breast cancer among postmenopausal women with normal BMI (Iyengar et al. 2018). Similarly, DXA-derived whole body fat mass and trunk fat mass are positively associated with invasive breast cancer risk, with BMI and other conventional breast cancer risk factor adjustment (Arthur et al. 2020). We here demonstrate that higher WHR and other body fat mass and distribution are associated with increased risk of death and developing obesity-related cancer for population with normal BMI. This could be an important public health message that population with very high fat mass and abdominal adiposity need further attention to disease screening and preventions, even they fall into normal BMI range. Recent observation that enlarged adipocytes and inflammation are found in the breast cancer tissue of women with normal BMI (Iyengar et al. 2017) could partly explain the finding, which emphasize the normal BMI categorization is inadequate in the association of breast cancer risk with body fat.

This is, to our knowledge, the largest prospective cohort study to investigate the association of WHR, WBFM, BFP and TFP with disease mortality and cancer incidence. This large sample size and detailed information on baseline characteristics allow us to carefully adjust for potential influences of confounding factors and evaluate potential effect modification. To eliminate possible confounding effects due to cigarette smoking, we conducted analyses among never smokers for mortality analyses. To minimize potential influence of reverse causation on our study results, we excluded first two years' follow-up after study enrollment and excluded participants with prior diagnoses of fatal diseases.

One limitation of the present study is that the fat measures were ascertained using the BIA method, which is not as accurate as direct measures like the DXA or CT scan. However, BIA has proven to be reliable when used in Western populations who are without significant fluid and electrolyte abnormalities (Dehghan and Merchant 2008). BIA technique is virtually the only existing method applicable to large study populations to address the potential etiology of percentage of body fat or absolute fat mass on adverse health outcomes (Franssen et al. 2014). Further, in some site-specific analyses, we could not draw reliable results given small sample size for certain cancer types, especially for our attempts to study the associations with cancer among never smokers.

In conclusion, WHR and excessive body fat and trunk fat confer additional risks of deaths and multiple cancers beyond the level contributed by BMI. Different associations of WHR and WBFM with several cancers provide additional insights into the possible mechanisms for the obesity-cancer association. Our study provides strong evidence that disease prevention programs should be designed not only to reduce body weight but also to control visceral fat and total fat mass.

CHAPTER VI

FINDINGS FOR SPECIFIC AIM 2: TO DETERMINE THE ASSOCIATIONS OF BMI, WHRadjBMI, BODY FAT MASS AND DISTRIBUTION WITH BREAST CANCER RISK AMONG EUROPEAN POPULATION USING MENDELIAN RANDOMIZATION.

1. Results

For phenotype BMI and WHRadjBMI, 164 and 72 SNPs identified from previous GWAS were included in the MR analysis. For body fat mass and distribution (body fat percentage, BMI adjusted body fat percentage, whole body fat mass, BMI adjusted whole body fat mass, trunk fat percentage, BMI adjusted trunk fat percentage, trunk fat mass, and BMI adjusted trunk fat mass), GWAS on UK Biobank data (Manhattan plots for the GWAS see Appendix B) were conducted and the number of identified SNPs at GWAS significance ($p<5\times10^{-8}$) for each trait ranged from 98 to 354 (Table 13, Appendix C). The variance of each trait explained by its associated variants ranged from 2.03% for WHRadjBMI to 3.80% for whole body fat mass (Table 13).

Table 13. Summary of instrument variables for body fat measure traits used in the study

Body fat measure traits	Number of variants	Variance explained (%)	F statistics
BMI	164	2.67	30.3
WHR adjusted for BMI (WHRadjBMI)	72	2.03	52.1
Body fat percentage	98	2.11	39.8
Whole body fat mass	111	2.80	47.0
Trunk fat percentage	100	2.77	51.5
Trunk fat mass	117	2.91	46.3
Body fat percentage adjusted for BMI	168	3.06	34.0
Whole body fat mass adjusted for BMI	354	3.80	20.2
Trunk fat percentage adjusted for BMI	151	2.44	30.0
Trunk fat mass adjusted for BMI	290	3.57	23.1

Note: BMI, Body mass index; WHRadjBMI, Waist-to-hip ratio adjusted for body mass index.

In Mendelian randomization using BCAC summary statistics, since SNPs were identified from published or self-performed GWAS, all genetic instruments were associated with corresponding body fat mass and distribution. An inverse association was observed for genetically predicted BMI and WHRadjBMI (marginally significant) with breast cancer, and a positive association was observed for whole body fat mass adjusted for BMI and trunk fat mass adjusted for BMI (Table 14). One unit increase in wPRS-BMI and wPRS-WHRadjBMI were associated with a 28% and 13% decreased risk of breast cancer, respectively (BMI: OR=0.72, 95% CI=0.65-0.80, $p = 1.11\times10^{-10}$; WHRadjBMI: OR=0.87, 95% CI=0.78-0.98, p=0.03). One unit increase in wPRS-WBFMadjBMI and wPRS-TFMadjBMI were associated with a 11% and 12% increased risk of breast cancer, respectively (WBFMadjBMI: OR=1.11, 95% CI=1.05-1.16, $p = 1.42\times10^{-4}$; TFMadjBMI: OR=1.12, 95% CI=1.05-1.18, $p = 1.59\times10^{-4}$). Using Egger's regression, the significance of the Egger's intercept indicated a strong horizontal pleiotropic effect for wPRS-BMI instruments (p=0.003). The estimates from MR-Egger regression, weighted median, and maximum likelihood method remain significant in association of BMI on breast cancer risk. No association was observed for other body fat mass and distribution weighted polygenic scores. Stratified analyses showed consistent associations regardless of estrogen receptor status (Figure 5).

Using individual level data from UK Biobank cohort, I found subjects developed breast cancer were older, more likely to have family history of breast cancer, and have higher amount of body fatness than controls (Table 15). Genetically predicted BMI, BFP, WBFM, TFP and TFM were moderately or strongly correlated with each other, but not correlated with genetically predicted body fat mass and distribution with BMI adjustment (Table 16). In addition, genetically

Table 14. Associations of genetically predicted body fat measure traits with breast cancer risk: results from summary Mendelian randomization analysis

Exposure	Model *	OR (95%)	*P* value	$P_{heterogeneity}$ **
BMI	IVW	0.72 (0.65, 0.80)	1.11×10^{-10}	5.68×10^{-45}
	Egger's	0.55 (0.45, 0.67)	8.00×10^{-9}	
	Egger's intercept	1.01 (1.00, 1.01)	0.003	
	Weighted median	0.69 (0.62, 0.77)	3.39×10^{-11}	
	Maximum likelihood	0.72 (0.65, 0.79)	1.57×10^{-10}	
WHRadjBMI	IVW	0.87 (0.78, 0.98)	0.03	1.81×10^{-20}
	Egger's	0.60 (0.40, 0.92)	0.02	
	Egger's intercept	1.01 (1.00, 1.02)	0.07	
	Weighted median	0.78 (0.69, 0.88)	5.72×10^{-5}	
	Maximum likelihood	0.87 (0.77, 0.98)	0.03	
Body fat percentage	IVW	0.90 (0.79, 1.03)	0.14	7.80×10^{-54}
	Egger's	0.36 (0.22, 0.58)	2.54×10^{-5}	
	Egger's intercept	1.02 (1.01, 1.04)	8.46×10^{-5}	
	Weighted median	0.97 (0.87, 1.08)	0.58	
	Maximum likelihood	0.90 (0.79, 1.04)	0.15	
Whole body fat mass	IVW	0.89 (0.79, 1.02)	0.09	2.82×10^{-69}
	Egger's	0.44 (0.29, 0.67)	1.11×10^{-4}	
	Egger's intercept	1.02 (1.01, 1.03)	4.72×10^{-4}	
	Weighted median	0.93 (0.84, 1.03)	0.16	
	Maximum likelihood	0.89 (0.78, 1.02)	0.09	
Trunk fat percentage	IVW	0.92 (0.81, 1.06)	0.26	3.40×10^{-58}
	Egger's	0.35 (0.21, 0.59)	6.91×10^{-5}	
	Egger's intercept	1.02 (1.01, 1.04)	1.44×10^{-4}	
	Weighted median	0.97 (0.87, 1.08)	0.52	
	Maximum likelihood	0.92 (0.80, 1.06)	0.27	
Trunk fat mass	IVW	0.94 (0.83, 1.06)	0.29	3.15×10^{-60}
	Egger's	0.44 (0.29, 0.67)	1.02×10^{-4}	
	Egger's intercept	1.02 (1.01, 1.03)	2.00×10^{-4}	
	Weighted median	0.95 (0.86, 1.05)	0.32	
	Maximum likelihood	0.93 (0.82, 1.06)	0.28	
Body fat percentage adjusted for BMI	IVW	1.05 (0.95, 1.16)	0.32	1.29×10^{-76}
	Egger's	0.76 (0.55, 1.06)	0.10	

	Egger's intercept	1.01 (1.00, 1.02)	0.04	
	Weighted median	0.98 (0.91, 1.07)	0.66	
	Maximum likelihood	1.05 (0.95, 1.16)	0.33	
Whole body fat mass adjusted for BMI	IVW	1.11 (1.05, 1.16)	1.42×10^{-4}	2.65×10^{-82}
	Egger's	1.00 (0.86, 1.16)	0.98	
	Egger's intercept	1.00 (1.00, 1.01)	0.17	
	Weighted median	1.03 (0.98, 1.08)	0.28	
	Maximum likelihood	1.11 (1.05, 1.17)	1.49×10^{-4}	
Trunk fat percentage adjusted for BMI	IVW	1.10 (1.00, 1.21)	0.05	1.06×10^{-48}
	Egger's	0.72 (0.52, 1.00)	0.05	
	Egger's intercept	1.01 (1.00, 1.02)	0.01	
	Weighted median	1.01 (0.93, 1.10)	0.74	
	Maximum likelihood	1.10 (1.00, 1.21)	0.05	
Trunk fat mass adjusted for BMI	IVW	1.12 (1.05, 1.18)	1.59×10^{-4}	5.47×10^{-60}
	Egger's	0.92 (0.78, 1.09)	0.32	
	Egger's intercept	1.01 (1.00, 1.01)	0.02	
	Weighted median	1.01 (0.95, 1.07)	0.85	
	Maximum likelihood	1.12 (1.06, 1.19)	1.53×10^{-4}	

Note: BMI, Body mass index; WHRadjBMI, Waist-to-hip ratio adjusted for body mass index; IVW, inverse variance weighted method.

* Associations of body fat measure traits with breast cancer on IVW, MR-Egger, weighted median, and maximum likelihood methods. For MR-Egger, the intercept is the average pleiotropic effect; an intercept significantly different from zero implies directional pleiotropy.

** Heterogeneity test for causal ratio estimates of all genetic variants used as the instrumental variable.

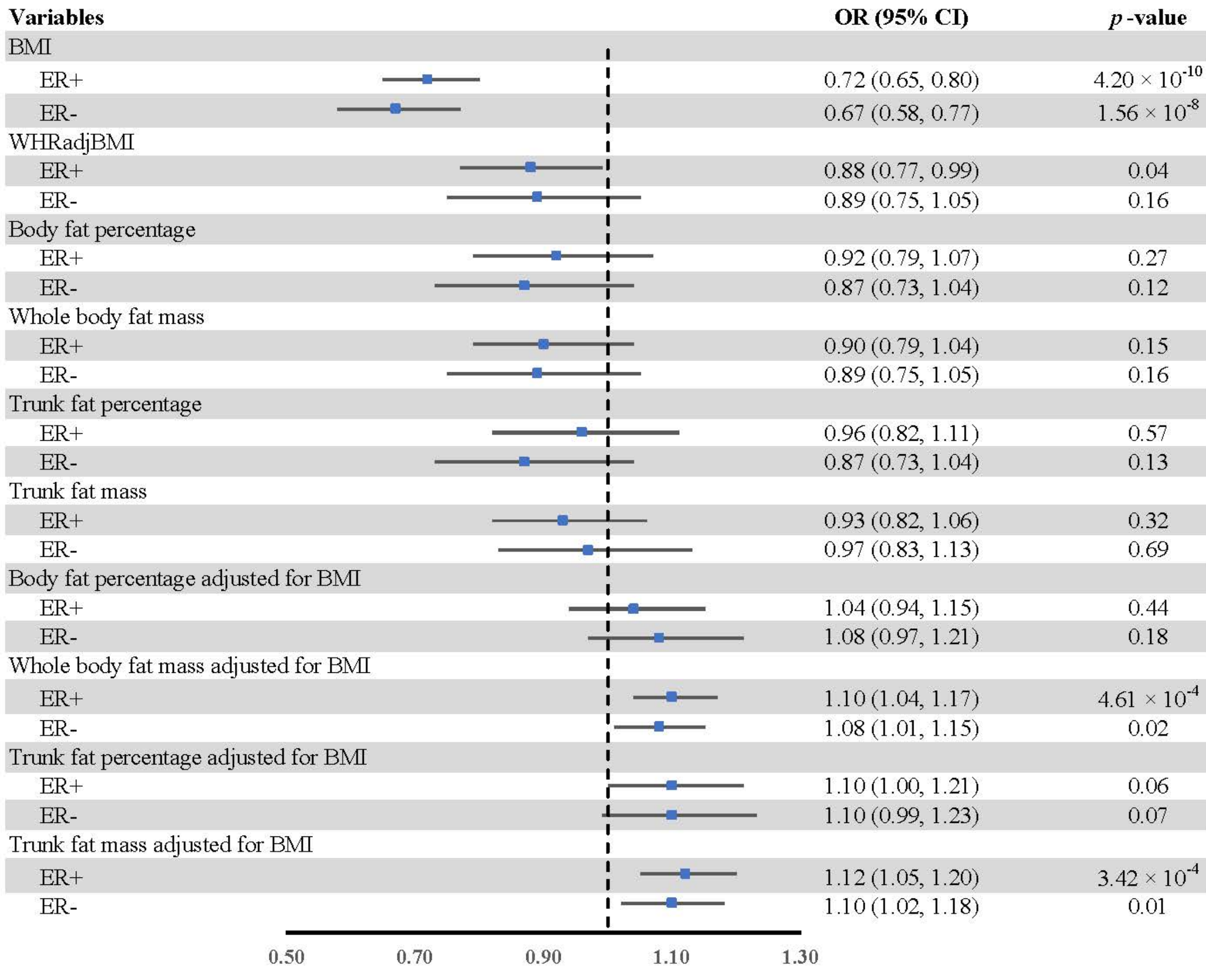


Figure 5. Stratified analysis for associations of body fat measure traits with breast cancer risk by estrogen receptor status: results from summary Mendelian randomization

Note: BMI, Body mass index; WHRadjBMI, Waist-to-hip ratio adjusted for body mass index; ER+, estrogen receptor positive; ER-, estrogen receptor negative.

Table 15. Selected characteristics of participants in the UK Biobank cohort in Mendelian randomization

Variables	Number of participants	Case	Control
Age at baseline (years), mean ± SD	181034	59.3 ± 7.0	56.5 ± 7.9
Family history of breast cancer (yes), N (%)	181034	1684 (17.9)	18406 (10.7)
Ever smoke (yes), N (%)	181034	4060 (43.2)	69066 (40.2)
Reproductive factors			
Age at menarche (years), mean ± SD	175980	12.9 ± 1.6	13.0 ± 1.6
Age at first live birth (years), mean ± SD	123827	25.4 ± 4.4	25.4 ± 4.6
Age at menopause (years), mean ± SD	104311	49.4 ± 5.0	49.8 ± 5.1
Parity (numbers), mean ± SD	180930	1.8 ± 1.1	1.8 ± 1.2
Postmenopausal status, N (%)	180896	7007 (74.7)	104579 (60.9)
Ever use of HRT, N (%)	180601	3850 (41.0)	67510 (39.3)
Ever use of contraceptive, N (%)	180719	7425 (79.1)	141916 (82.7)
Parous (yes), N (%)	180930	7601 (81.0)	140158 (81.7)
Anthropometrics			
Height (cm), mean ± SD	180677	163.0 ± 6.2	163.0 ± 6.2
Weight (kg), mean ± SD	180539	72.0 ± 13.2	71.5 ± 14.0
BMI (kg/m^2), mean ± SD	180486	27.2 ± 4.9	27.0 ± 5.2
Waist-to-hip ratio, mean ± SD	180694	0.82 ± 0.07	0.82 ± 0.07
Body fat percentage, mean ± SD	178074	37.1 ± 6.5	36.5 ± 6.9
Whole body fat mass (kg), mean ± SD	178028	27.4 ± 9.4	26.9 ± 10.0
Trunk fat percentage, mean ± SD	177971	34.7 ± 7.4	34.1 ± 7.8
Trunk fat mass (kg), mean ± SD	177961	13.9 ± 5.0	13.6 ± 5.3

Note: BMI, body mass index; HRT, hormone replacement therapy.

Table 16. Pearson's correlations between instrumental variables for body fat measure traits in controls

	BMI	WHRadjBMI	BFP	WBFM	TFP	TFM	BFPadjBMI	WBFMadjBMI	TFPadjBMI	TFMadjBMI
BMI	1.00									
WHRadjBMI	-0.01	1.00								
BFP	0.44	-0.05	1.00							
WBFM	0.47	-0.03	0.78	1.00						
TFP	0.40	-0.05	0.83	0.72	1.00					
TFM	0.43	-0.04	0.76	0.90	0.76	1.00				
BFPadjBMI	-0.01	0.03	0.17	0.09	0.28	0.16	1.00			
WBFMadjBMI	0.02	0.01	0.13	0.14	0.21	0.22	0.52	1.00		
TFPadjBMI	0.01	0.02	0.20	0.12	0.32	0.20	0.85	0.57	1.00	
TFMadjBMI	0.02	0	0.14	0.15	0.22	0.24	0.50	0.90	0.57	1.00

Note: BMI, body mass index; WHRadjBMI, waist-to-hip ratio adjusted for BMI; BFP, body fat percentage; WBFM, whole body fat mass; TFP, trunk fat percentage; TFM, trunk fat mass; BFPadjBMI, body fat percentage adjusted for BMI; WBFMadjBMI, whole body fat mass adjusted for BMI; TFPadjBMI, trunk fat percentage adjusted for BMI; TFMadjBMI, trunk fat mass adjusted for BMI.

predicted WBFMadjBMI, TFPadjBMI, and TFMadjBMI were strongly correlated with each other.

I evaluated the associations of genetically predicted body fatness with each measured body fat measure among controls and their associations with traditional breast cancer risk factors among all subjects (Table 17-26). Genetically predicted BMI, BFP, WBFM, TFP, and TFM were strongly and positively associated with measured BMI, WHR, BFP, WBFM, TFP and TFM, while the associations of genetically predicted WHRadjBMI with BMI, BFP, WBFM, TFP and TFM were negative (p<0.001). Genetically predicted BFPadjBMI, WBFMadjBMI, TFPadjBMI, and TFMadjBMI were negatively associated with BMI measured at baseline, but positively associated with BFP, WBFM, TFP and TFM (p<0.001). Among traditional breast cancer risk factors, age at menarche was negatively associated with genetically predicted BMI, BFP, WBFM, TFP, and TFM, and positively associated with BFPadjBMI, WBFMadjBMI, TFPadjBMI, and TFMadjBMI (p<0.001). Younger age at menopause and age at first live birth were found in increased genetically predicted BFP, WBFM, TFP and TFM (p<0.001). Higher odds of smoking and lower odds of ever use contraceptive were associated with increased genetically predicted BMI, BFP, WBFM, TFP and TFM (p<0.001).

I found per 5kg/m^2 increase in genetically predicted BMI was inversely associated with 30% decreased breast cancer risk (OR=0.70, 95% CI=0.61-0.81, p<0.001) (Table 27 and Figure 6) and with 30% decreased breast cancer among postmenopausal women (OR=0.70, 95% CI=0.60-0.83, p<0.001)(Figure 6). No associations with breast cancer were found in other genetically predicted body fatness. Adjusting for traditional breast cancer risk factors described above and/or other body fat mass and distribution did not notably change the observed association with breast cancer risk. Stratified analysis was further performed by hormone therapy use (HRT), smoking status (ever/never), and family history of breast cancer among postmenopausal women. The associations were consistent except for subjects with family history of breast cancer. No interaction was found for hormone therapy use (HRT), smoking status (ever/never), and family history of breast cancer in associations of genetically predicted BMI with breast cancer risk.

Table 17. Associations of genetically predicted BMI with measured body fat measure traits and traditional breast cancer risk factors

Variables	Summary Effect *	Standard Error	*P*-value
Measured body fat traits at baseline among controls			
BMI (kg/m^2)	1.00	0.017	< 0.001
Height (cm)	3.54×10^{-3}	0.020	0.862
Weight (kg)	2.65	0.046	< 0.001
Waist-to-hip ratio	5.59×10^{-3}	2.29×10^{-4}	< 0.001
Body fat percentage (%)	1.10	0.023	< 0.001
Whole body fat mass (kg)	1.84	0.033	< 0.001
Trunk fat percentage (%)	1.13	0.026	< 0.001
Trunk fat mass (kg)	0.898	0.017	< 0.001
Traditional risk factors at baseline **			
Age (years)	0.025	0.025	0.321
Family history of breast cancer (yes versus no)	4.07×10^{-3}	0.010	0.690
Smoking (ever versus never)	0.053	6.53×10^{-3}	< 0.001
Age at menarche (years)	-0.147	5.19×10^{-3}	< 0.001
Age at first live birth (years)	-0.153	0.018	< 0.001
Age at menopause (years)	7.77×10^{-3}	0.022	0.719
Parity (numbers)	4.27×10^{-3}	3.71×10^{-3}	0.249
Postmenopausal status (yes versus no)	2.03×10^{-3}	7.92×10^{-3}	0.798
Use of HRT (ever versus never)	-2.23×10^{-3}	6.56×10^{-3}	0.733
Use of contraceptive (ever versus never)	-0.032	8.46×10^{-3}	< 0.001
Parous (yes versus no)	0.010	8.28×10^{-3}	0.221

Note: BMI, body mass index; HRT, hormone replacement therapy.
* The linear regression coefficient is presented for continuous variables and natural log-scale odd ratio for dichotomous variables, per unit (kg/m^2) increase of genetically predicted BMI.
** The linear regression models fitting body fat measure traits at baseline included only controls; models of all other traditional risk factors included all subjects with the measurement.

Table 18. Associations of genetically predicted WHRadjBMI with measured body fat measure traits and traditional breast cancer risk factors

Variables	Summary Effect *	Standard Error	*P*-value
Measured body fat traits at baseline among controls			
BMI (kg/m^2)	-0.740	0.078	< 0.001
Height (cm)	0.191	0.094	0.042
Weight (kg)	-1.76	0.211	< 0.001
Waist-to-hip ratio	0.056	1.05×10^{-3}	< 0.001
Body fat percentage (%)	-0.510	0.105	< 0.001
Whole body fat mass (kg)	-1.17	0.153	< 0.001
Trunk fat percentage (%)	-0.648	0.119	< 0.001
Trunk fat mass (kg)	-0.571	0.080	< 0.001
Traditional risk factors at baseline **			
Age (years)	-0.205	0.116	0.08
Family history of breast cancer (yes versus no)	-0.015	0.047	0.755
Smoking (ever versus never)	0.024	0.030	0.432
Age at menarche (years)	-8.51×10^{-3}	0.024	0.722
Age at first live birth (years)	-0.081	0.081	0.318
Age at menopause (years)	0.056	0.099	0.569
Parity (numbers)	0.045	0.017	0.008
Postmenopausal status (yes versus no)	-0.077	0.036	0.035
Use of HRT (ever versus never)	0.037	0.030	0.215
Use of contraceptive (ever versus never)	6.52×10^{-3}	0.039	0.867
Parous (yes versus no)	0.106	0.038	0.006

Note: BMI, body mass index; HRT, hormone replacement therapy.

* The linear regression coefficient is presented for continuous variables and natural log-scale odd ratio for dichotomous variables, per unit (standard deviation) increase of inverse normal transformed genetically predicted WHRadjBMI.

** The linear regression models fitting body fat measure traits at baseline included only controls; models of all other traditional risk factors included all subjects with the measurement.

Table 19. Associations of genetically predicted body fat percentage with measured body fat measure traits and traditional breast cancer risk factors

Variables	Summary Effect *	Standard Error	*P*-value
Measured body fat traits at baseline among controls			
BMI (kg/m^2)	0.695	0.012	< 0.001
Height (cm)	0.061	0.015	< 0.001
Weight (kg)	1.89	0.033	< 0.001
Waist-to-hip ratio	3.17×10^{-3}	1.68×10^{-4}	< 0.001
Body fat percentage (%)	1.00	0.017	< 0.001
Whole body fat mass (kg)	1.47	0.024	< 0.001
Trunk fat percentage (%)	1.10	0.019	< 0.001
Trunk fat mass (kg)	0.772	0.013	< 0.001
Traditional risk factors at baseline **			
Age (years)	0.013	0.019	0.496
Family history of breast cancer (yes versus no)	3.71×10^{-3}	7.48×10^{-3}	0.620
Smoking (ever versus never)	0.031	4.79×10^{-3}	< 0.001
Age at menarche (years)	-0.075	0.004	< 0.001
Age at first live birth (years)	-0.148	0.013	< 0.001
Age at menopause (years)	-0.060	0.016	< 0.001
Parity (numbers)	2.06×10^{-3}	2.72×10^{-3}	0.448
Postmenopausal status (yes versus no)	0.011	5.80×10^{-3}	0.055
Use of HRT (ever versus never)	0.011	4.81×10^{-3}	0.028
Use of contraceptive (ever versus never)	-0.026	6.21×10^{-3}	< 0.001
Parous (yes versus no)	9.13×10^{-3}	6.07×10^{-3}	0.132

Note: BMI, body mass index; HRT, hormone replacement therapy.

* The linear regression coefficient is presented for continuous variables and natural log-scale odd ratio for dichotomous variables, per unit (%) increase of genetically predicted body fat percentage.

** The linear regression models fitting body fat measure traits at baseline included only controls; models of all other traditional risk factors included all subjects with the measurement.

Table 20. Associations of genetically predicted whole body fat mass with measured body fat measure traits and traditional breast cancer risk factors

Variables	Summary Effect *	Standard Error	*P*-value
Measured body fat traits at baseline among controls			
BMI (kg/m^2)	0.464	0.008	< 0.001
Height (cm)	0.203	9.23×10^{-3}	< 0.001
Weight (kg)	1.41	0.021	< 0.001
Waist-to-hip ratio	2.47×10^{-3}	1.04×10^{-4}	< 0.001
Body fat percentage (%)	0.623	0.010	< 0.001
Whole body fat mass (kg)	1.00	0.015	< 0.001
Trunk fat percentage (%)	0.693	0.012	< 0.001
Trunk fat mass (kg)	0.524	7.79×10^{-3}	< 0.001
Traditional risk factors at baseline **			
Age (years)	0.022	0.011	0.060
Family history of breast cancer (yes versus no)	7.38×10^{-3}	4.62×10^{-3}	0.110
Smoking (ever versus never)	0.025	2.96×10^{-3}	< 0.001
Age at menarche (years)	-0.046	0.002	< 0.001
Age at first live birth (years)	-0.086	7.97×10^{-3}	< 0.001
Age at menopause (years)	-0.029	0.010	0.003
Parity (numbers)	2.32×10^{-3}	1.68×10^{-3}	0.166
Postmenopausal status (yes versus no)	0.011	3.58×10^{-3}	0.003
Use of HRT (ever versus never)	5.25×10^{-3}	2.97×10^{-3}	0.077
Use of contraceptive (ever versus never)	-0.019	3.83×10^{-3}	< 0.001
Parous (yes versus no)	5.37×10^{-3}	3.75×10^{-3}	0.152

Note: BMI, body mass index; HRT, hormone replacement therapy.

* The linear regression coefficient is presented for continuous variables and natural log-scale odd ratio for dichotomous variables, per unit (kg) increase of genetically predicted body fat percentage.

** The linear regression models fitting body fat measure traits at baseline included only controls; models of all other traditional risk factors included all subjects with the measurement.

Table 21. Associations of genetically predicted trunk fat percentage with measured body fat measure traits and traditional breast cancer risk factors

Variables	Summary Effect *	Standard Error	*P*-value
Measured body fat traits at baseline among controls			
BMI (kg/m^2)	0.535	0.011	< 0.001
Height (cm)	0.195	0.013	< 0.001
Weight (kg)	1.59	0.029	< 0.001
Waist-to-hip ratio	2.36×10^{-3}	1.46×10^{-4}	< 0.001
Body fat percentage (%)	0.867	0.014	< 0.001
Whole body fat mass (kg)	1.25	0.021	< 0.001
Trunk fat percentage (%)	1.00	0.016	< 0.001
Trunk fat mass (kg)	0.69	0.011	< 0.001
Traditional risk factors at baseline **			
Age (years)	7.25×10^{-3}	0.016	0.653
Family history of breast cancer (yes versus no)	8.75×10^{-3}	6.50×10^{-3}	0.179
Smoking (ever versus never)	0.028	4.17×10^{-3}	< 0.001
Age at menarche (years)	-0.054	0.003	< 0.001
Age at first live birth (years)	-0.105	0.011	< 0.001
Age at menopause (years)	-0.046	0.014	< 0.001
Parity (numbers)	1.77×10^{-3}	2.37×10^{-3}	0.455
Postmenopausal status (yes versus no)	7.83×10^{-3}	5.04×10^{-3}	0.120
Use of HRT (ever versus never)	5.47×10^{-3}	4.18×10^{-3}	0.191
Use of contraceptive (ever versus never)	-0.018	5.40×10^{-3}	< 0.001
Parous (yes versus no)	3.93×10^{-3}	5.28×10^{-3}	0.456

Note: BMI, body mass index; HRT, hormone replacement therapy.
* The linear regression coefficient is presented for continuous variables and natural log-scale odd ratio for dichotomous variables, per unit (%) increase of genetically predicted body fat percentage.
** The linear regression models fitting body fat measure traits at baseline included only controls; models of all other traditional risk factors included all subjects with the measurement.

Table 22. Associations of genetically predicted trunk fat mass with measured body fat measure traits and traditional breast cancer risk factors

Variables	Summary Effect *	Standard Error	*P*-value
Measured body fat traits at baseline among controls			
BMI (kg/m^2)	0.793	0.014	< 0.001
Height (cm)	0.559	0.017	< 0.001
Weight (kg)	2.59	0.038	< 0.001
Waist-to-hip ratio	4.21×10^{-3}	1.93×10^{-4}	< 0.001
Body fat percentage (%)	1.16	0.019	< 0.001
Whole body fat mass (kg)	1.89	0.028	< 0.001
Trunk fat percentage (%)	1.34	0.022	< 0.001
Trunk fat mass (kg)	1.00	0.015	< 0.001
Traditional risk factors at baseline **			
Age (years)	0.023	0.021	0.280
Family history of breast cancer (yes versus no)	0.014	8.60×10^{-3}	0.108
Smoking (ever versus never)	0.043	5.51×10^{-3}	< 0.001
Age at menarche (years)	-0.078	0.004	< 0.001
Age at first live birth (years)	-0.133	0.015	< 0.001
Age at menopause (years)	-0.060	0.018	< 0.001
Parity (numbers)	1.74×10^{-4}	3.13×10^{-3}	0.956
Postmenopausal status (yes versus no)	0.014	6.66×10^{-3}	0.032
Use of HRT (ever versus never)	7.18×10^{-3}	5.53×10^{-3}	0.194
Use of contraceptive (ever versus never)	-0.036	7.14×10^{-3}	< 0.001
Parous (yes versus no)	6.83×10^{-4}	6.98×10^{-3}	0.922

Note: BMI, body mass index; HRT, hormone replacement therapy.

* The linear regression coefficient is presented for continuous variables and natural log-scale odd ratio for dichotomous variables, per unit (kg) increase of genetically predicted body fat percentage.

** The linear regression models fitting body fat measure traits at baseline included only controls; models of all other traditional risk factors included all subjects with the measurement.

Table 23. Associations of genetically predicted BFPadjBMI with measured body fat measure traits and traditional breast cancer risk factors

Variables	Summary Effect *	Standard Error	*P*-value
Measured body fat traits at baseline among controls			
BMI (kg/m^2)	-0.278	0.063	< 0.001
Height (cm)	2.93	0.075	< 0.001
Weight (kg)	1.84	0.170	< 0.001
Waist-to-hip ratio	2.33×10^{-3}	8.49×10^{-4}	0.006
Body fat percentage (%)	3.12	0.084	< 0.001
Whole body fat mass (kg)	2.83	0.123	< 0.001
Trunk fat percentage (%)	4.49	0.095	< 0.001
Trunk fat mass (kg)	2.30	0.064	< 0.001
Traditional risk factors at baseline **			
Age (years)	-0.042	0.093	0.650
Family history of breast cancer (yes versus no)	-0.010	0.038	0.783
Smoking (ever versus never)	-9.19×10^{-3}	0.024	0.703
Age at menarche (years)	0.088	0.019	< 0.001
Age at first live birth (years)	-7.92×10^{-3}	0.065	0.903
Age at menopause (years)	-0.153	0.080	0.05
Parity (numbers)	-0.023	0.014	0.099
Postmenopausal status (yes versus no)	0.031	0.029	0.292
Use of HRT (ever versus never)	8.30×10^{-3}	0.024	0.732
Use of contraceptive (ever versus never)	-0.032	0.031	0.313
Parous (yes versus no)	-0.013	0.031	0.671

Note: BFPadjBMI, body fat percentage adjusted for body mass index; BMI, body mass index; HRT, hormone replacement therapy.
* The linear regression coefficient is presented for continuous variables and natural log-scale odd ratio for dichotomous variables, per unit (standard deviation) increase of inverse normal transformed genetically predicted BFPadjBMI.
** The linear regression models fitting body fat measure traits at baseline included only controls; models of all other traditional risk factors included all subjects with the measurement.

Table 24. Associations of genetically predicted WBFMadjBMI with measured body fat measure traits and traditional breast cancer risk factors

Variables	Summary Effect *	Standard Error	*P*-value
Measured body fat traits at baseline among controls			
BMI (kg/m^2)	-0.346	0.037	< 0.001
Height (cm)	5.75	0.043	< 0.001
Weight (kg)	4.15	0.101	< 0.001
Waist-to-hip ratio	7.71×10^{-5}	5.07×10^{-4}	0.879
Body fat percentage (%)	1.73	0.050	< 0.001
Whole body fat mass (kg)	2.76	0.073	< 0.001
Trunk fat percentage (%)	3.00	0.056	< 0.001
Trunk fat mass (kg)	2.14	0.038	< 0.001
Traditional risk factors at baseline **			
Age (years)	0.011	0.056	0.844
Family history of breast cancer (yes versus no)	0.048	0.022	0.032
Smoking (ever versus never)	-3.13×10^{-3}	0.014	0.828
Age at menarche (years)	0.123	0.011	< 0.001
Age at first live birth (years)	0.240	0.039	< 0.001
Age at menopause (years)	-0.014	0.048	0.767
Parity (numbers)	-0.035	8.18×10^{-3}	< 0.001
Postmenopausal status (yes versus no)	6.89×10^{-3}	0.017	0.693
Use of HRT (ever versus never)	-0.023	0.014	0.112
Use of contraceptive (ever versus never)	-0.050	0.019	0.008
Parous (yes versus no)	-0.084	0.018	< 0.001

Note: WBFMadjBMI, whole body fat mass adjusted for body mass index; BMI, body mass index; HRT, hormone replacement therapy.

* The linear regression coefficient is presented for continuous variables and natural log-scale odd ratio for dichotomous variables, per unit (standard deviation) increase of inverse normal transformed genetically predicted WBFMadjBMI.

** The linear regression models fitting body fat measure traits at baseline included only controls; models of all other traditional risk factors included all subjects with the measurement.

Table 25. Associations of genetically predicted TFPadjBMI with measured body fat measure traits and traditional breast cancer risk factors

Variables	Summary Effect *	Standard Error	*P*-value
Measured body fat traits at baseline among controls			
BMI (kg/m^2)	-0.237	0.062	< 0.001
Height (cm)	3.84	0.075	< 0.001
Weight (kg)	2.74	0.169	< 0.001
Waist-to-hip ratio	6.37×10^{-4}	8.44×10^{-4}	0.45
Body fat percentage (%)	3.07	0.084	< 0.001
Whole body fat mass (kg)	3.16	0.122	< 0.001
Trunk fat percentage (%)	4.59	0.094	< 0.001
Trunk fat mass (kg)	2.52	0.064	< 0.001
Traditional risk factors at baseline **			
Age (years)	-0.064	0.093	0.490
Family history of breast cancer (yes versus no)	0.016	0.037	0.670
Smoking (ever versus never)	-0.025	0.024	0.301
Age at menarche (years)	0.069	0.019	< 0.001
Age at first live birth (years)	0.118	0.064	0.07
Age at menopause (years)	-0.111	0.079	0.159
Parity (numbers)	-0.038	0.014	0.005
Postmenopausal status (yes versus no)	4.23×10^{-4}	0.029	0.988
Use of HRT (ever versus never)	-0.019	0.024	0.437
Use of contraceptive (ever versus never)	-0.038	0.031	0.221
Parous (yes versus no)	-0.054	0.030	0.078

Note: TFPadjBMI, trunk fat percentage adjusted for body mass index; BMI, body mass index; HRT, hormone replacement therapy.

* The linear regression coefficient is presented for continuous variables and natural log-scale odd ratio for dichotomous variables, per unit (standard deviation) increase of inverse normal transformed genetically predicted TFPadjBMI.

** The linear regression models fitting body fat measure traits at baseline included only controls; models of all other traditional risk factors included all subjects with the measurement.

Table 26. Associations of genetically predicted TFMadjBMI with measured body fat measure traits and traditional breast cancer risk factors

Variables	Summary Effect *	Standard Error	*P*-value
Measured body fat traits at baseline among controls			
BMI (kg/m^2)	-0.343	0.042	< 0.001
Height (cm)	6.11	0.048	< 0.001
Weight (kg)	4.48	0.112	< 0.001
Waist-to-hip ratio	5.56×10^{-4}	5.64×10^{-4}	0.324
Body fat percentage (%)	1.87	0.056	< 0.001
Whole body fat mass (kg)	2.97	0.081	< 0.001
Trunk fat percentage (%)	3.25	0.063	< 0.001
Trunk fat mass (kg)	2.30	0.042	< 0.001
Traditional risk factors at baseline **			
Age (years)	0.021	0.062	0.736
Family history of breast cancer (yes versus no)	0.034	0.025	0.170
Smoking (ever versus never)	1.07×10^{-3}	0.016	0.947
Age at menarche (years)	0.119	0.013	< 0.001
Age at first live birth (years)	0.248	0.043	< 0.001
Age at menopause (years)	-2.29×10^{-3}	0.053	0.965
Parity (numbers)	-0.036	9.10×10^{-3}	< 0.001
Postmenopausal status (yes versus no)	0.014	0.019	0.479
Use of HRT (ever versus never)	-0.023	0.016	0.150
Use of contraceptive (ever versus never)	-0.050	0.021	0.016
Parous (yes versus no)	-0.095	0.020	< 0.001

Note: TFMadjBMI, trunk fat mass adjusted for body mass index; BMI, body mass index; HRT, hormone replacement therapy.

* The linear regression coefficient is presented for continuous variables and natural log-scale odd ratio for dichotomous variables, per unit (standard deviation) increase of inverse normal transformed genetically predicted TFMadjBMI.

** The linear regression models fitting body fat measure traits at baseline included only controls; models of all other traditional risk factors included all subjects with the measurement.

Table 27. Associations of genetically predicted body fat measure traits with breast cancer risk, individual level Mendelian randomization in UK Biobank data

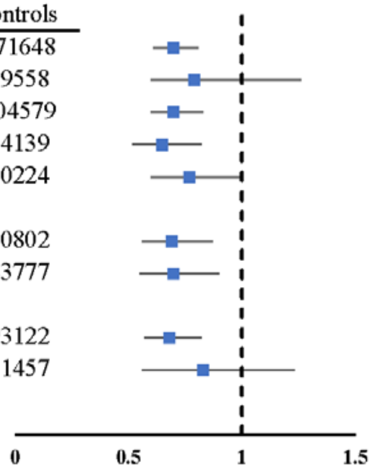
	OR (95% CI) *	*P* value	OR (95% CI) **	*P* value	OR (95% CI) ***	*P* value
BMI (per 5kg/m^2 increase)	0.70 (0.61, 0.81)	< 0.001	0.69 (0.58, 0.82)	< 0.001	0.66 (0.55, 0.79)	< 0.001
WHRadjBMI (per SD increase)	0.97 (0.85, 1.11)	0.648	0.95 (0.80, 1.11)	0.497	0.94 (0.80, 1.11)	0.482
BFP (per 5% increase)	0.93 (0.84, 1.03)	0.181	0.95 (0.81, 1.10)	0.488	0.91 (0.78, 1.06)	0.239
WBFM (per 5kg increase)	0.95 (0.90, 1.02)	0.16	0.94 (0.86, 1.03)	0.197	0.90 (0.82, 0.99)	0.029
TFP (per 5% increase)	0.98 (0.89, 1.07)	0.656	0.98 (0.86, 1.12)	0.742	0.94 (0.82, 1.07)	0.358
TFM (per 5kg increase)	0.93 (0.83, 1.05)	0.258	0.97 (0.81, 1.16)	0.733	0.89 (0.74, 1.07)	0.202
BFPadjBMI (per SD increase)	1.04 (0.94, 1.16)	0.442	1.03 (0.91, 1.17)	0.648	1.02 (0.89, 1.16)	0.793
WBFMadjBMI (per SD increase)	1.06 (0.99, 1.12)	0.093	1.05 (0.97, 1.13)	0.239	0.97 (0.89, 1.05)	0.47
TFPadjBMI (per SD increase)	1.04 (0.94, 1.16)	0.442	1.06 (0.93, 1.21)	0.35	1.03 (0.90, 1.17)	0.677
TFMadjBMI (per SD increase)	1.05 (0.98, 1.13)	0.14	1.05 (0.97, 1.15)	0.236	0.98 (0.89, 1.07)	0.649

Note: BMI, body mass index; WHRadjBMI, waist-to-hip ratio adjusted for BMI; BFP, body fat percentage; WBFM, whole body fat mass; TFP, trunk fat percentage; TFM, trunk fat mass; BFPadjBMI, body fat percentage adjusted for BMI; WBFMadjBMI, whole body fat mass adjusted for BMI; TFPadjBMI, trunk fat percentage adjusted for BMI; TFMadjBMI, trunk fat mass adjusted for BMI; SD, standard deviation.

* Adjusted for age at baseline, age squared, first eight principal components, and array.

** Additionally adjusted for breast cancer risk factors (age at menarche, age at first live birth, use of contraceptive, parity, smoking, and family history of breast cancer) shown in Table 17 to 26.

*** Further mutual adjustments of other body fat mass and distribution.



	Number of cases	Number of controls	OR (95% CI) *	*P* -value	OR (95% CI) **	*P* -value	OR (95% CI) ***	*P* -value
All subjects	9386	171648	0.70 (0.61, 0.81)	< 0.001	0.69 (0.58, 0.82)	< 0.001	0.66 (0.55, 0.79)	< 0.001
Premenopausal	867	39558	0.79 (0.50, 1.26)	0.325	0.76 (0.41, 1.40)	0.377	0.81 (0.44, 1.51)	0.513
Postmenopausal	7007	104579	0.70 (0.60, 0.83)	< 0.001	0.71 (0.58, 0.87)	0.001	0.66 (0.54, 0.82)	< 0.001
HRT use (Never)	3899	54139	0.65 (0.52, 0.82)	< 0.001	0.66 (0.51, 0.87)	0.003	0.63 (0.48, 0.83)	0.001
HRT use (Ever)	3091	50224	0.77 (0.60, 0.99)	0.04	0.78 (0.58, 1.05)	0.11	0.71 (0.52, 0.97)	0.03
					P for interaction = 0.31			
Smoking status (Never)	3876	60802	0.69 (0.56, 0.87)	0.001	0.69 (0.52, 0.90)	0.006	0.64 (0.49, 0.85)	0.002
Smoking status (Ever)	3131	43777	0.70 (0.55, 0.90)	0.006	0.75 (0.55, 1.02)	0.067	0.70 (0.51, 0.95)	0.023
					P for interaction = 0.89			
Family history (No)	5750	93122	0.68 (0.57, 0.82)	< 0.001	0.70 (0.56, 0.88)	0.002	0.64 (0.51, 0.81)	< 0.001
Family history (Yes)	1257	11457	0.83 (0.56, 1.23)	0.349	0.75 (0.46, 1.23)	0.256	0.77 (0.47, 1.28)	0.32
					P for interaction = 0.37			

Figure 6. Stratified analysis for associations of genetically predicted body mass index with breast cancer risk: results from summary Mendelian randomization

* Adjusted for age at baseline, age squared, first eight principal components, and array.

** Additionally adjusted for breast cancer risk factors, age at menarche, age at first live birth, use of contraceptive, parity, smoking, and family history of breast cancer when applicable.

*** Further mutual adjustments of other body fat mass and distribution.

2. Discussion

Utilizing data from UK Biobank and BCAC consortia, I found an inverse association between genetically predicted BMI and breast cancer risk, whereas measured BMI has been established to be positively associated with postmenopausal breast cancer. Among premenopausal females, inverse associations of BMI and breast cancer have been reported. Several mechanisms have been proposed to explain the association that higher BMI is linked with decreased breast cancer risk among premenopausal women (Schoemaker et al. 2018). Before menopause, the amount of estrogen produced are mainly from ovaries and only a little is produced by adipose tissue in lean women, whereas most estrogens derived from the conversion of androgens in the adipose tissue in obese women. High levels of estrogens released into the circulation from the adipose tissue is highly associated with breast cancer risk. Therefore, for the younger women, fat tissue produced estrogens might signal ovaries to produce less estrogen, which might link to lower breast cancer risk (Laudisio et al. 2018).

The contradictory findings in observed BMI and genetically predicted BMI with breast cancer among postmenopausal women have been reported in two previous studies (Guo et al. 2016; Shu et al. 2019), suggesting a complex relationship of breast cancer risk with genetic variants of BMI, adult weight gain due to genetic determinants, dietary factors and other environmental factors. Many evidences have shown a consistent inverse association of early life BMI and breast cancer risk among both pre- and post-menopausal women (Baer et al. 2010; Willett et al. 1985). Genetically predicted BMI has been shown to be positively associated with weight change from age 20 to middle-aged, and negatively associated with weight change after reading middle age (Rukh et al. 2016). A more recent paper illustrates that genetic risk alleles of BMI are associated with increased early adulthood weight gain in women, but not in later life or in men (Song et al.

2018). Moreover, the magnitude of association between measured BMI and genetic risk score for BMI is larger among more recent birth cohort, suggesting obesogenic environment might modify the associations of identified genetic variants of BMI and attained BMI in adulthood (Walter et al. 2016). From our and other findings, I speculate that late life BMI is a composite results of early life BMI, which might correlate with genetic variants of BMI, and a weight change during later adulthood, which might correlate more with obesogenic environments, including dietary and environmental factors. Thus, increased postmenopausal breast cancer risk among overweight and obese women with measured BMI might largely due to dietary and environmental factors associated adult weight gain. The BMI associated SNPs may have little influence on weight gain in later adulthood.

Results on associations of WHR with breast cancer risk are not consistent. I found an inverse association in summary statistics MR in BCAC but no significant finding in individual level MR conducted among UK Biobank. In previous observational studies, although many reported a positive association on WHR and breast cancer risk (Kyrgiou et al. 2017; Huang et al. 1999; Organization 2011), not all were properly adjusted for BMI, indicating a possibility that the observed associations were due to overall obesity and breast cancer risk. I reported an observed WHR and breast cancer association substantially attenuated after adjusting for BMI in a large Chinese cohort (Liu et al. 2016). In Aim 1 of this dissertation, I also found a null association on breast cancer risk and WHR with BMI adjustment, while there is a positive association among postmenopausal women before BMI adjustment. Previous MR on BMI adjusted WHR breast cancer association, our group found inverse association using individual level BCAC data and summary statistics from DIAbetes Genetics Replication And Meta-analysis (DIAGRAM) Consortium (Shu et al. 2019), while no association was found in UK Biobank data when use 48

SNPs identified from GWAS on WHRadjBMI (Emdin et al. 2017). It is likely that genetically predicted WHRadjBMI may indicate abdominal adiposity in early life, which could not be a precise measure for WHR in late life, or an accumulation of visceral fat after reaching middle age. Furthermore, WHR obesity association might be more likely to through insulin resistance pathway rather endogenous estrogen hormones. With BMI adjustment, WHR might be less associated with breast cancer risk compared to other body fat related measure.

In Aim 1, I found the increased risk of WHR and body fat mass and distribution with mortality and cancer incidence among participants with normal BMI. Abundant evidence shows that body fat distribution is influenced by genetic loci distinct from those regulating BMI (Heid, Jackson, Randall, Winkler, Qi, Steinthorsdottir, Thorleifsson, Zillikens, Speliotes, Mägi, et al. 2010). Many attempts were put to identify individual variation in WHR accounting for BMI to address the heritability independent of overall body weight (Heid, Jackson, Randall, Winkler, Qi, Steinthorsdottir, Thorleifsson, Zillikens, Speliotes, Mägi, et al. 2010; Shungin et al. 2015; Randall et al. 2013; Heid, Jackson, Randall, Winkler, Qi, Steinthorsdottir, Thorleifsson, Zillikens, Speliotes, Magi, et al. 2010). In this study, I performed GWAS on measures of body fat composition and distribution and identified independent body fat phenotype related genetic variants to generate more powerful instruments for MR analysis. Since the purpose of this GWAS is to identify SNPs to act as instrumental variables for MR study, I did not conduct independent replication study and claim novel variants. Further studies could be implemented to replicate the findings, compare with existing GWAS studies, and functional assessment to identify potential actionable target to control excess body fat.

Null associations were found in MR analyses on breast cancer risk with body fat percentage, whole body fat mass, trunk fat percentage, and trunk fat mass, with or without BMI adjustment, in

UK Biobank individual level data. Higher body fat has been associated with increased breast cancer risk among postmenopausal women with normal BMI (Iyengar et al. 2018). However, the genetically predicted body fat mass and distribution instruments are possible measures of early life body fat, are not associated with breast cancer risk. It is likely that not the early life body fat nor body weight, but the gain in the overall and abdominal fat associated with increased breast cancer risk in late life. Summary MR analysis suggested an increased risk of breast cancer with whole body fat mass and trunk fat mass with BMI adjustment and MR-Egger's regression and weighted median methods both show no association, which is consistent with findings in individual level data. The results suggest that confounding bias might be introduced from these instruments and violated the independence and exclusion restriction assumption for MR analysis. More studies on these body fat associated SNPs are warranted to explore their associations with other potential breast cancer risk factors.

Mendelian randomization analyses minimize the biases of selection bias and reverse causality, which are commonly encountered in traditional epidemiological studies. The pleiotropic effects of IVs could not be fully tested using statistical methods and SNPs explain small variance of the body fat trait, which are major limitations of MR. Sensitivity analyses using MR-Egger and weighted median method rectified the results for BMI and breast cancer association and yielded similar results. Our findings of BMI and breast cancer association echo with previous studies and the finding of no associations for WHRadjBMI agrees with our observational study using the same population in Aim 1. Although no association from MR analysis was found, identified body fat measure genetic instruments could be utilized in further studies. In addition, our results might be undermined due to multiple comparison because I study the association of breast cancer with 10 body fat related measures. However, the only found significant association of BMI on breast cancer reaches the stringent Bonferroni corrected significance level ($P < 0.05/10 = 0.005$). Moreover, this study and most GWAS in body fat focused only on European-ancestral sample, and body fat distributions differ across ancestral groups, suggesting studies in other populations are needed.

In summary, this study provided additional evidence on genetically predicted body fat mass and distribution are likely to associated more with early life characteristics on body weight and body fat mass, which might not or inversely associate with female breast cancer risk. Further research to identify novel loci for body fat independent of BMI are needed to improve the understanding of underlying biological mechanisms for body fat composition and distribution, and to explain the paradoxical inverse association with breast cancer observed in observational studies and Mendelian randomization studies.

CHAPTER VII

FINDINGS FOR SPECIFIC AIM 3: TO INVESTIGATE THE ASSOCIATIONS OF GENETIC PREDICTED BMI, WHR, AND BODY FAT MASS AND DISTRIBUTION WITH MEASURED BODY WEIGHT AND FAT CHANGES AMONG AGE GROUPS IN EUROPEAN POPULATION.

1. Results

Basic characteristics of study participants were presented in Table 28. 181034 unrelated white British ancestry females with baseline body fat measurements were included for Aim 3 analysis. A subset of subjects (N=7463) had a repeat assessment, which were included to study body weight and body fatness changes in middle and late adulthood. Subjects had repeated measures tend to be slightly thinner compared to the whole cohort. After 4.3 ± 1.0 years of follow-up, body fat mass and distribution did not change substantially among subjects. Notably, body weight decreased, while WHR and body fat percentage increased slightly on average.

Not surprisingly, genetically predicted body fat mass and distribution of interest showed positive associations with body weight measured at baseline, except for genetically predicted WHRadjBMI and BFPadjBMI, which showed no association (Table 29). However, although the associations were not significant ($p>0.05$), increased genetically predicted body fat mass and distribution without BMI adjustment were linked with decreased body weight changes from baseline to repeated assessment.

Table 28. Anthropometric characteristics of female participants at baseline and follow-up

	All subjects at baseline		Subjects with repeated measures		
				Baseline	Follow-up
	N	Mean ± SD	N	Mean ± SD	Mean ± SD
Age (years)	181034	56.7 ± 7.9	7463	56.6 ± 7.1	60.9 ± 7.1
Height (cm)	180677	162.7 ± 6.2	7456	163.1 ± 6.1	163.1 ± 6.1
Weight (kg)	180539	71.5 ± 13.9	7454	70.4 ± 13.5	69.9 ± 13.4
BMI (kg/m^2)	180486	27.0 ± 5.1	7453	26.5 ± 4.9	26.5 ± 5.0
Hip circumference (cm)	180707	103.4 ± 10.3	7457	102.3 ± 10.0	102.8 ± 10.4
Waist circumference (cm)	180723	84.6 ± 12.5	7457	82.6 ± 11.9	84.6 ± 12.3
Waist-to-hip ratio	180694	0.816 ± 0.070	7457	0.806 ± 0.068	0.821 ± 0.065
Body fat percentage (%)	178074	36.6 ± 6.9	7331	36.0 ± 6.7	36.5 ± 6.7
Whole body fat mass (kg)	178028	26.9 ± 10.0	7330	26.1 ± 9.6	26.3 ± 9.6
Trunk fat percentage (%)	177971	34.1 ± 7.8	7329	33.8 ± 7.6	34.1 ± 7.6
Trunk fat mass (kg)	177961	13.7 ± 5.2	7328	13.3 ± 5.1	13.4 ± 5.0

Note: BMI, body mass index; SD, standard deviation.

Table 29. Associations between genetically predicted body fat measure traits with adult body weight and changes in body weight

	Per unit effect size in body weight at baseline, kg (95% CI) *	*P*	Per unit effect size in body weight change, kg (95% CI) **	*P*
wPRS-BMI (per 5kg/m^2)	13.49 (11.39, 15.60)	< 0.001	-0.65 (-1.45, 0.15)	0.11
wPRS-WHRadjBMI (per SD)	-1.44 (-3.34, 0.46)	0.14	-0.31 (-1.02, 0.39)	0.39
wPRS-BFP (per 5%)	8.56 (7.05, 10.07)	< 0.001	-0.02 (-0.59, 0.55)	0.95
wPRS-BFPadjBMI (per SD)	1.09 (-0.47, 2.65)	0.17	0.55 (-0.03, 1.13)	0.06
wPRS-WBFM (per 5kg)	6.57 (5.63, 7.51)	< 0.001	-0.08 (-0.44, 0.28)	0.67
wPRS-WBFMadjBMI (per SD)	3.95 (3.03, 4.88)	< 0.001	0.49 (0.14, 0.84)	0.006
wPRS-TFP (per 5%)	7.54 (6.23, 8.84)	< 0.001	-0.01 (-0.50, 0.48)	0.97
wPRS-TFPadjBMI (per SD)	2.00 (0.46, 3.54)	0.01	0.52 (-0.05, 1.10)	0.08
wPRS-TFM (per 5kg)	12.26 (10.51, 14.01)	< 0.001	-0.15 (-0.82, 0.52)	0.66
wPRS-TFMadjBMI (per SD)	3.85 (2.82, 4.88)	< 0.001	0.51 (0.12, 0.89)	0.01

Note: wPRS, weighted polygenic risk score; BMI, body mass index; WHRadjBMI, waist-to-hip ratio adjusted for BMI; BFP, body fat percentage; WBFM, whole body fat mass; TFP, trunk fat percentage; TFM, trunk fat mass; BFPadjBMI, body fat percentage adjusted for BMI; WBFMadjBMI, whole body fat mass adjusted for BMI; TFPadjBMI, trunk fat percentage adjusted for BMI; TFMadjBMI, trunk fat mass adjusted for BMI; SD, standard deviation.

* Adjusted for age at baseline, age squared, first eight principal components, and array.

** Adjusted for age at baseline, age squared, first eight principal components, array, baseline body weight, and years of follow-up.

In UK Biobank cohort, genetically predicted body fat mass and distribution were linear correlated with baseline body fat mass and distribution in the same direction (p<0.001) (Table 30). For example, for every 5kg/m^2 increase in genetically predicted BMI, BMI at baseline would increase 4.73 kg/m^2 (95%CI=3.96-5.50 kg/m^2, p-value<0.001). Per 1-SD increase in genetically predicted inverse normal transformed WHRadjBMI, WHR at baseline increases by 0.06 (95%CI=0.05-0.07, p-value<0.001). No association was found for genetically predicted BMI on BMI changes. Genetically predicted body fat mass and distribution with BMI adjustment (WHRadjBMI, BFPadjBMI, WBFMadjBMI, TFPadjBMI, and TFMadjBMI) were positively associated with their corresponding body fat measure changes. For instance, 0.54kg increase (95%CI=0.25kg-0.83kg, p-value<0.001) would be expected for whole body fat mass if genetically predicted WBFMadjBMI increase by one standard deviation. Relationship of genetically predicted body fat mass and distribution with changes of measured values varied by age (Table 31). For genetically predicted WHRadjBMI, BFPadjBMI, and TFP, oldest age group (60-70) observed largest increases in changes of body fat mass and distribution compared to other age groups, whereas the association of wPRS-WBFMadjBMI on whole body fat mass change was the opposite. For instance, for each SD increase in transformed WHRadjBMI, measured WHR change in 60-70 years old group was 0.02 (95%CI=0.01-0.03, p-value<0.001) versus 0.005 (95%CI=-0.01-0.02, p-value=0.56) and 0.01 (95%CI=0.001-0.02, p-value=0.03) among 40-49 and 50-59 years group, respectively. For each SD increase in transformed WBFMadjBMI, measured whole body fat mass change in 60-70 years old group was 0.38kg (95%CI=-0.03-0.79kg, p-value=0.07) versus 1.15kg increase among 40-49 years (95%CI=0.34-1.96kg, p-value=0.005) and 0.44kg (95%CI=-0.01-0.89, p-value=0.05) increase among 50-59 years females. At significance level of 0.005 when taking multiple comparison into consideration, I did not find interaction of age group with genetic scores of body fatness on their association with measured body fatness change.

Genetically predicted body fat mass and distribution were associated with higher measured body fatness across all ages when examining these associations in all included female subjects in UK Biobank cohort (p<0.001) (Table 32). The effect size of the associations varied by age group (p for interaction < 0.001), except for genetically predicted WHRadjBMI on WHR at baseline. Though the effect differs by body fat traits, the associations were generally weaker in women in relatively older age groups (≥60 years). For example, the mean BMI difference per 5kg/m^2 increment in genetically predicted BMI decreased from 5.61kg/m^2 (95%CI=5.07-6.16 kg/m^2, p-value<0.001) at 40-44 years to 3.99kg/m^2 (95%CI=3.65-4.34 kg/m^2, p-value<0.001) at ages of 65-70 years old.

The associations of genetically predicted body fat mass and distribution with fatness change patterns from age 10 to middle or late adulthood were explored. Compared with the odds of being in the thinner at age 10 to normal weight at baseline group, higher genetically predicted body fat mass and distribution were associated with increased odds of being in the other groups (Table 33). One kg/m^2 increase in genetically predicted BMI was associated with around 60% increased odds of being in plumper at age 10 to normal weight at baseline (OR=1.61, 95%CI=1.60-1.62) and around average body size at age 10 to overweight at baseline (OR=1.55, 95%CI=1.54-1.57), whereas 1kg/m^2 increase was associated with 2-fold odds of being plumper at age and overweight at baseline (OR=1.99, 95%CI=1.97-2.02). Genetically predicted BFP, WBFM, TFP and TFM were associated with 30% to 54% increased odds of being plumper at age 10 and baseline compared to being thinner at both time points.

Table 30. Associations between genetically predicted body fat measure traits with body fat mass and distribution at baseline and changes in body fat mass and distribution

	Per unit effect size in body fat mass and distribution at baseline, (95% CI) *	*P*	Per unit effect size in body fat measure change, (95% CI) **	*P*	Per unit effect size in body fat measure percent change, (95% CI) **	*P*
	BMI at baseline (kg/m^2)		BMI change (kg/m^2)		BMI percent change	
wPRS-BMI (per 5kg/m^2)	4.73 (3.96, 5.50)	< 0.001	-0.22 (-0.53, 0.08)	0.15	-0.01 (-0.02, 0.003)	0.17
	WHR at baseline		WHR change		WHR percent change	
wPRS-WHRadjBMI (per SD)	0.06 (0.05, 0.07)	< 0.001	0.01 (0.008, 0.02)	< 0.001	0.02 (0.009, 0.03)	< 0.001
	BFP at baseline (%)		BFP change (%)		BFP percent change	
wPRS-BFP (per 5%)	4.38 (3.63, 5.13)	< 0.001	0.18 (-0.20, 0.56)	0.36	0.009 (-0.003, 0.02)	0.13
wPRS-BFPadjBMI (per SD)	3.01 (2.24, 3.78)	< 0.001	0.76 (0.37, 1.15)	< 0.001	0.02 (0.008, 0.03)	0.001
	WBFM at baseline (kg)		WBFM change (kg)		WBFM percent change	
wPRS-WBFM (per 5kg)	4.51 (3.83, 5.18)	< 0.001	-0.02 (-0.32, 0.28)	0.90	0.003 (-0.008, 0.01)	0.58
wPRS-WBFMadjBMI (per SD)	2.65 (1.98, 3.32)	< 0.001	0.54 (0.25, 0.83)	< 0.001	0.01 (0.004, 0.03)	0.007
	TFP at baseline (%)		TFP change (%)		TFP percent change	
wPRS-TFP (per 5%)	4.63 (3.89, 5.36)	< 0.001	0.37 (-0.04, 0.78)	0.08	0.02 (0.002, 0.03)	0.03
wPRS-TFPadjBMI (per SD)	4.26 (3.39, 5.13)	< 0.001	1.07 (0.59, 1.56)	< 0.001	0.03 (0.01, 0.05)	0.01
	TFM at baseline (kg)		TFM change (kg)		TFM percent change	
wPRS-TFM (per 5kg)	4.57 (3.91, 5.24)	< 0.001	0.13 (-0.19, 0.45)	0.42	0.02 (-0.01, 0.04)	0.24
wPRS-TFMadjBMI (per SD)	2.08 (1.69, 2.47)	< 0.001	0.40 (0.22, 0.59)	< 0.001	0.02 (0.006, 0.04)	0.007

Note: wPRS, weighted polygenic risk score; BMI, body mass index; WHRadjBMI, waist-to-hip ratio adjusted for BMI; BFP, body fat percentage; WBFM, whole body fat mass; TFP, trunk fat percentage; TFM, trunk fat mass; BFPadjBMI, body fat percentage adjusted for BMI; WBFMadjBMI, whole body fat mass adjusted for BMI; TFPadjBMI, trunk fat percentage adjusted for BMI; TFMadjBMI, trunk fat mass adjusted for BMI; SD, standard deviation.

* Adjusted for age at baseline, age squared, first eight principal components, and array.

** Adjusted for age at baseline, age squared, first eight principal components, array, baseline body fat mass and distribution, and years of follow-up.

Table 31. Relationship of genetically predicted body fat measure traits with body fat measure change at different age at baseline

Age at baseline (years)	N	Per unit effect size in body fat measure change, (95% CI) *	*P*	*P* for interaction **
		wPRS-BMI (per 5kg/m^2) with measured BMI change		
40-49	1392	-0.16 (-0.97, 0.65)	0.70	0.24
50-59	2983	-0.43 (-0.91, 0.06)	0.08	
60-70	3067	-0.08 (-0.52, 0.36)	0.73	
		wPRS-WHRadjBMI (per SD) with measured WHR change		
40-49	1394	0.005 (-0.01, 0.02)	0.56	0.41
50-59	2986	0.01 (0.001, 0.02)	0.03	
60-70	3065	0.02 (0.01, 0.03)	< 0.001	
		wPRS-BFP (per 5%) with measured BFP change		
40-49	1359	0.09 (-0.87, 1.05)	0.86	0.42
50-59	2921	0.06 (-0.56, 0.67)	0.85	
60-70	2974	0.29 (-0.27, 0.85)	0.31	
		wPRS-BFPadjBMI (per SD) with measured BFP change		
40-49	1359	0.73 (-0.28, 1.75)	0.16	0.62
50-59	2921	0.62 (0.005, 1.24)	0.05	
60-70	2974	0.91 (0.34, 1.48)	0.002	
		wPRS-WBFM (per 5kg) with measured WBFM change		
40-49	1358	-0.09 (-0.89, 0.72)	0.83	0.40
50-59	2919	-0.09 (-0.57, 0.38)	0.70	
60-70	2974	0.07 (-0.35, 0.49)	0.75	
		wPRS-WBFMadjBMI (per SD) with measured WBFM change		
40-49	1358	1.15 (0.34, 1.96)	0.005	0.02
50-59	2919	0.44 (-0.01, 0.89)	0.05	
60-70	2974	0.38 (-0.03, 0.79)	0.07	
		wPRS-TFP (per 5%) with measured TFP change		
40-49	1359	-0.30 (-1.31, 0.70)	0.55	0.22
50-59	2919	0.31 (-0.34, 0.97)	0.35	
60-70	2974	0.69 (0.08, 1.31)	0.03	
		wPRS-TFPadjBMI (per SD) with measured TFP change		
40-49	1359	1.10 (-0.09, 2.29)	0.07	0.52
50-59	2919	1.03 (0.26, 1.79)	0.009	
60-70	2974	1.09 (0.37, 1.81)	0.003	
		wPRS-TFM (per 5kg) with measured TFM change		
40-49	1359	-0.05 (-0.85, 0.75)	0.90	0.35
50-59	2919	-0.03 (-0.54, 0.48)	0.91	
60-70	2973	0.36 (-0.10, 0.82)	0.12	
		wPRS-TFMadjBMI (per SD) with measured TFM change		
40-49	1359	0.62 (0.14, 1.10)	0.01	0.12
50-59	2919	0.33 (0.04, 0.62)	0.02	
60-70	2973	0.38 (0.11, 0.64)	0.006	

Note: wPRS, weighted polygenic risk score; BMI, body mass index; WHRadjBMI, waist-to-hip ratio adjusted for BMI; BFP, body fat percentage; WBFM, whole body fat mass; TFP, trunk fat percentage; TFM, trunk fat mass; BFPadjBMI, body fat percentage adjusted for BMI; WBFMadjBMI, whole body fat mass adjusted for BMI; TFPadjBMI, trunk fat percentage adjusted for BMI; TFMadjBMI, trunk fat mass adjusted for BMI; SD, standard deviation.

* Adjusted for age at baseline, age squared, first eight principal components, array, baseline body fat mass and distribution, and years of follow-up.

** *P* for interaction were computed using likelihood ratio test comparing models with and without product terms between age groups and PRS of body fat measure traits.

Table 32. Relationship of genetically predicted body fat measure traits with body fat mass and distribution at different age at baseline in females in UK Biobank data

Age at baseline (years)	N	Per unit effect size in body fat mass and distribution, (95% CI)	*P*	*P* for interaction **
		wPRS-BMI (per 5kg/m^2) with BMI *		
40-44	16806	5.61 (5.07, 6.16)	< 0.001	< 0.001
45-49	23190	5.74 (5.28, 6.20)	< 0.001	
50-54	28156	5.36 (4.94, 5.78)	< 0.001	
55-59	33668	5.08 (4.70, 5.46)	< 0.001	
60-64	45649	4.56 (4.25, 4.87)	< 0.001	
65-70	33017	3.99 (3.65, 4.34)	< 0.001	
		wPRS-WHRadjBMI (per SD) with WHR ***		
40-44	16813	0.060 (0.055, 0.066)	< 0.001	0.36
45-49	23204	0.058 (0.053, 0.063)	< 0.001	
50-54	28182	0.059 (0.054, 0.063)	< 0.001	
55-59	33711	0.064 (0.060, 0.068)	< 0.001	
60-64	45710	0.059 (0.056, 0.063)	< 0.001	
65-70	33074	0.061 (0.056, 0.065)	< 0.001	
		wPRS-BFP (per 5%) with BFP *		
40-44	16525	5.45 (4.90, 5.99)	< 0.001	< 0.001
45-49	22947	5.65 (5.19, 6.11)	< 0.001	
50-54	27873	5.20 (4.79, 5.61)	< 0.001	
55-59	33267	5.17 (4.81, 5.53)	< 0.001	
60-64	45005	4.48 (4.19, 4.78)	< 0.001	
65-70	32457	4.21 (3.87, 4.55)	< 0.001	
		wPRS-BFPadjBMI (per SD) with BFP ***		
40-44	16525	3.24 (2.97, 3.51)	< 0.001	< 0.001
45-49	22947	3.63 (3.40, 3.86)	< 0.001	
50-54	27873	3.50 (3.29, 3.71)	< 0.001	
55-59	33267	3.50 (3.31, 3.69)	< 0.001	
60-64	45005	3.33 (3.17, 3.49)	< 0.001	
65-70	32457	3.35 (3.17, 3.54)	< 0.001	
		wPRS-WBFM (per 5kg) with WBFM *		
40-44	16524	5.40 (4.91, 5.89)	< 0.001	< 0.001
45-49	22938	5.59 (5.18, 6.01)	< 0.001	
50-54	27867	5.36 (4.99, 5.73)	< 0.001	
55-59	33257	5.33 (5.00, 5.66)	< 0.001	
60-64	44995	4.40 (4.13, 4.67)	< 0.001	
65-70	32447	4.12 (3.82, 4.42)	< 0.001	
		wPRS-WBFMadjBMI (per SD) with WBFM ***		
40-44	16524	3.34 (3.19, 3.49)	< 0.001	< 0.001
45-49	22938	3.58 (3.45, 3.70)	< 0.001	
50-54	27867	3.55 (3.43, 3.66)	< 0.001	
55-59	33257	3.39 (3.28, 3.49)	< 0.001	
60-64	44995	3.41 (3.32, 3.50)	< 0.001	

65-70	32447	3.29 (3.18, 3.39)	< 0.001	
		wPRS-TFP (per 5%) with TFP *		
40-44	16512	5.22 (4.68, 5.76)	< 0.001	< 0.001
45-49	22933	5.53 (5.08, 5.98)	< 0.001	
50-54	27851	5.35 (4.95, 5.75)	< 0.001	
55-59	33248	5.08 (4.73, 5.43)	< 0.001	
60-64	44979	4.48 (4.18, 4.78)	< 0.001	
65-70	32448	4.42 (4.08, 4.75)	< 0.001	
		wPRS-TFPadjBMI (per SD) with TFP ***		
40-44	16512	4.81 (4.43, 5.19)	< 0.001	< 0.001
45-49	22933	5.02 (4.70, 5.34)	< 0.001	
50-54	27851	4.91 (4.62, 5.20)	< 0.001	
55-59	33248	4.85 (4.59, 5.12)	< 0.001	
60-64	44979	4.79 (4.56, 5.02)	< 0.001	
65-70	32448	4.86 (4.59, 5.13)	< 0.001	
		wPRS-TFM (per 5kg) with TFM *		
40-44	16509	5.53 (5.04, 6.01)	< 0.001	< 0.001
45-49	22932	5.53 (5.12, 5.93)	< 0.001	
50-54	27851	5.29 (4.92, 5.65)	< 0.001	
55-59	33246	5.19 (4.87, 5.51)	< 0.001	
60-64	44976	4.50 (4.23, 4.76)	< 0.001	
65-70	32447	4.21 (3.92, 4.51)	< 0.001	
		wPRS-TFMadjBMI (per SD) with TFM ***		
40-44	16509	2.60 (2.47, 2.73)	< 0.001	< 0.001
45-49	22932	2.71 (2.60, 2.82)	< 0.001	
50-54	27851	2.67 (2.57, 2.77)	< 0.001	
55-59	33246	2.61 (2.52, 2.70)	< 0.001	
60-64	44976	2.61 (2.54, 2.69)	< 0.001	
65-70	32447	2.50 (2.40, 2.59)	< 0.001	

Note: wPRS, weighted polygenic risk score; BMI, body mass index; WHRadjBMI, waist-to-hip ratio adjusted for BMI; BFP, body fat percentage; WBFM, whole body fat mass; TFP, trunk fat percentage; TFM, trunk fat mass; BFPadjBMI, body fat percentage adjusted for BMI; WBFMadjBMI, whole body fat mass adjusted for BMI; TFPadjBMI, trunk fat percentage adjusted for BMI; TFMadjBMI, trunk fat mass adjusted for BMI; SD, standard deviation.

* Adjusted for age at baseline, age squared, first eight principal components, array.

** *P* for interaction were computed using likelihood ratio test comparing models with and without product terms between age groups and PRS of body fat measure traits.

*** Adjusted for age at baseline, age squared, first eight principal components, array, and BMI at baseline.

Table 33. Associations of change patterns of body fatness from self-reported age 10 comparative body size to baseline measurement (overweight or non-overweight) with genetically predicted body fat measure traits in females in UK Biobank data

	Thinner to normal weight	Average to normal weight	Plumper to normal weight	Thinner to overweight	Average to overweight	Plumper to overweight
			Body mass index			
Number of subjects	26037	37611	7713	28957	53448	24216
Mean BMI at baseline (kg/m^2) (SD)	22.4 (1.8)	22.7 (1.7)	22.9 (1.6)	29.4 (4.1)	29.6 (4.1)	31.5 (5.4)
Mean predicted BMI (kg/m^2) (SD)	26.8 (0.7)	26.9 (0.7)	27.1 (0.7)	27.0 (0.7)	27.1 (0.7)	27.2 (0.7)
OR (95% CI) per 1kg/m^2 increment in predicted BMI *	1.00 (reference)	1.21 (1.20, 1.22)	1.61 (1.60, 1.62)	1.36 (1.35, 1.38)	1.55 (1.54, 1.57)	1.99 (1.97, 2.02)
			Body fat percentage			
Number of subjects	25686	37135	7612	28563	52737	23859
Mean BFP at baseline (%) (SD)	31.1 (4.9)	30.4 (4.8)	30.8 (4.8)	40.6 (4.6)	40.0 (4.8)	41.6 (5.3)
Mean predicted BFP (%) (SD)	36.4 (1.0)	36.4 (1.0)	36.6 (1.0)	36.6 (1.0)	36.6 (1.0)	36.7 (1.0)
OR (95% CI) per 1% increment in predicted BFP *	1.00 (reference)	1.06 (1.05, 1.07)	1.23 (1.23, 1.24)	1.23 (1.22, 1.25)	1.28 (1.27, 1.29)	1.45 (1.43, 1.46)
			Whole body fat mass			
Number of subjects	25670	37112	7609	28563	52737	23858
Mean WBFM at baseline (kg) (SD)	19.0 (4.4)	18.6 (4.2)	19.0 (4.2)	31.8 (8.1)	31.5 (8.3)	35.1 (10.5)
Mean predicted WBFM (kg) (SD)	26.6 (1.6)	26.7 (1.6)	27.0 (1.6)	27.0 (1.6)	27.0 (1.6)	27.3 (1.6)
OR (95% CI) per 1kg increment in predicted WBFM *	1.00 (reference)	1.05 (1.04, 1.06)	1.16 (1.15, 1.18)	1.15 (1.15, 1.16)	1.19 (1.18, 1.20)	1.30 (1.29, 1.31)
			Trunk fat percentage			
Number of subjects	25668	37115	7611	28552	52692	23851
Mean TFP at baseline (%) (SD)	28.5 (6.1)	27.6 (6.0)	28.1 (6.1)	38.5 (5.5)	37.7 (5.7)	39.2 (6.1)
Mean predicted TFP (%) (SD)	33.9 (1.1)	34.0 (1.1)	34.2 (1.2)	34.2 (1.1)	34.2 (1.1)	34.2 (1.2)
OR (95% CI) per 1% increment in predicted TFP *	1.00 (reference)	1.04 (1.03, 1.05)	1.18 (1.18, 1.19)	1.18 (1.17, 1.19)	1.20 (1.19, 1.21)	1.33 (1.32, 1.34)
			Trunk fat mass			
Number of subjects	25666	37114	7610	28549	52690	23850
Mean TFM at baseline (kg) (SD)	9.7 (2.8)	9.3 (2.7)	9.6 (2.8)	16.4 (4.3)	16.0 (4.4)	17.6 (5.2)
Mean predicted TFM (kg) (SD)	13.5 (0.9)	13.5 (0.9)	13.7 (0.9)	13.7 (0.9)	13.7 (0.9)	13.8 (0.9)
OR (95% CI) per 1% increment in predicted TFM *	1.00 (reference)	1.07 (1.06, 1.08)	1.28 (1.28, 1.28)	1.27 (1.25, 1.28)	1.32 (1.31, 1.34)	1.54 (1.53, 1.56)

Note: wPRS, weighted polygenic risk score; BMI, body mass index; WHRadjBMI, waist-to-hip ratio adjusted for BMI; BFP, body fat percentage; WBFM, whole body fat mass; TFP, trunk fat percentage; TFM, trunk fat mass; BFPadjBMI, body fat percentage adjusted for BMI; WBFMadjBMI, whole body fat mass adjusted for BMI; TFPadjBMI, trunk fat percentage adjusted for BMI; TFMadjBMI, trunk fat mass adjusted for BMI; SD, standard deviation.

* Multinomial logistic regression was used to derive ORs and 95% CIs. Adjusted for age at baseline, age squared, first eight principal components, and array.

** Multinomial logistic regression was used to derive ORs and 95% CIs. Adjusted for age at baseline, age squared, first eight principal components, array, and BMI at baseline.

Table 34. Associations of change patterns of body fatness from self-reported age 10 comparative body size to baseline measurement (obese or non-obese) with genetically predicted body fat measure traits in females in UK Biobank data

	Thinner to non-obese	Average to non-obese	Plumper to non-obese	Thinner to obese	Average to obese	Plumper to obese
Body mass index						
Number of subjects	45336	72136	19471	9658	18923	12458
Mean BMI at baseline (kg/m^2) (SD)	24.4 (2.9)	24.8 (2.7)	25.6 (2.7)	34.0 (3.8)	34.0 (3.8)	35.4 (4.8)
Mean predicted BMI (kg/m^2) (SD)	26.9 (0.7)	27.0 (0.7)	27.1 (0.7)	27.1 (0.7)	27.1 (0.7)	27.3 (0.7)
OR (95% CI) per 1kg/m^2 increment in predicted BMI *	1.00 (reference)	1.19 (1.18, 1.20)	1.55 (1.55, 1.56)	1.45 (1.44, 1.45)	1.63 (1.63, 1.64)	2.01 (2.01, 2.02)
Body fat percentage						
Number of subjects	44761	71234	19218	9488	18638	12253
Mean BFP at baseline (%) (SD)	34.2 (5.7)	33.9 (5.6)	35.1 (5.4)	44.8 (3.7)	44.2 (3.8)	45.1 (4.1)
Mean predicted BFP (%) (SD)	36.4 (1.0)	36.5 (1.0)	36.6 (1.0)	36.7 (1.0)	36.7 (1.0)	36.8 (1.0)
OR (95% CI) per 1% increment in predicted BFP *	1.00 (reference)	1.05 (1.05, 1.06)	1.21 (1.20, 1.22)	1.29 (1.29, 1.30)	1.34 (1.32, 1.35)	1.47 (1.46, 1.47)
Whole body fat mass						
Number of subjects	44745	71211	19214	9488	18638	12253
Mean WBFM at baseline (kg) (SD)	22.8 (6.1)	22.7 (6.0)	24.2 (6.0)	39.9 (8.0)	39.5 (8.0)	42.2 (9.7)
Mean predicted WBFM (kg) (SD)	26.7 (1.6)	26.8 (1.6)	27.1 (1.6)	27.2 (1.6)	27.2 (1.6)	27.4 (1.6)
OR (95% CI) per 1kg increment in predicted WBFM *	1.00 (reference)	1.05 (1.04, 1.05)	1.15 (1.14, 1.16)	1.19 (1.18, 1.20)	1.22 (1.21, 1.23)	1.32 (1.30, 1.33)
Trunk fat percentage						
Number of subjects	44737	71183	19213	9483	18624	12249
Mean TFP at baseline (%) (SD)	31.9 (6.8)	31.4 (6.7)	32.8 (6.6)	42.5 (4.9)	41.8 (4.9)	42.5 (5.2)
Mean predicted TFP (%) (SD)	34.0 (1.1)	34.0 (1.2)	34.2 (1.2)	34.3 (1.2)	34.3 (1.1)	34.4 (1.1)
OR (95% CI) per 1% increment in predicted TFP *	1.00 (reference)	1.03 (1.02, 1.04)	1.16 (1.15, 1.17)	1.22 (1.21, 1.22)	1.23 (1.22, 1.25)	1.34 (1.33, 1.35)
Trunk fat mass						
Number of subjects	45336	72136	19471	9658	18923	12458
Mean TFM at baseline (kg) (SD)	11.7 (3.7)	11.5 (3.6)	12.4 (3.6)	20.2 (4.3)	19.8 (4.2)	20.8 (4.8)
Mean predicted TFM (kg) (SD)	13.5 (0.9)	13.6 (0.9)	13.7 (0.9)	13.8 (0.9)	13.8 (0.9)	13.9 (0.9)
OR (95% CI) per 1% increment in predicted TFM *	1.00 (reference)	1.06 (1.05, 1.08)	1.25 (1.24, 1.27)	1.33 (1.33, 1.34)	1.38 (1.36, 1.40)	1.58 (1.56, 1.60)

Note: wPRS, weighted polygenic risk score; BMI, body mass index; WHRadjBMI, waist-to-hip ratio adjusted for BMI; BFP, body fat percentage; WBFM, whole body fat mass; TFP, trunk fat percentage; TFM, trunk fat mass; BFPadjBMI, body fat percentage adjusted for BMI; WBFMadjBMI, whole body fat mass adjusted for BMI; TFPadjBMI, trunk fat percentage adjusted for BMI; TFMadjBMI, trunk fat mass adjusted for BMI; SD, standard deviation.

* Multinomial logistic regression was used to derive ORs and 95% CIs. Adjusted for age at baseline, age squared, first eight principal components, and array.

** Multinomial logistic regression was used to derive ORs and 95% CIs. Adjusted for age at baseline, age squared, first eight principal components, array, and BMI at baseline.

2. Discussion

Using UK Biobank data, including genetic data and cohort data with repeated measures, this study examines the effect of genetic obesity related variants on adulthood measures and changes of body weight and composition, and change patterns. Genetically predicted body fat traits (BMI, WHR, BFP, WBFM, TFP, and TFM) are all strongly and positively associated with higher body weight and higher body fatness measures at all adult ages. The relationship of body fat associated genetic variants with body weight and fat composition change could not be fully established in the short follow-up period at late adulthood among subjects. However, I observe a similar trend for all the genetically predicted fatness associated with decreased body weight change. Moreover, the association of PRS with measured body fatness differs by age group where the association declines at around 50 years old and for female after 60 years old, the association is much lower than younger group. Our findings also indicate that individuals with more body fatness associated alleles are more likely to have larger body size in early life and gain weight as they aged.

For body fatness measures without BMI adjustment, it is intuitive that genetically predicted body fat mass and distribution are associated with higher body weight and body fat measure at adulthood. For those adjusted for BMI, the same direction but less strong associations are observed, suggests that BMI could not explain all of body fatness measured in WHR, BFP, WBFM, TFP or TFM. In Aim 1, I found these body fat mass and distribution might have additional risk on chronic diseases and death for individuals with normal BMI. Here I show that these genetic variants are predictor for body weight in all ages, independent of BMI. Moreover, BMI measurement might be a different measure of obesity for older population comparing to the youth due to muscle loss. For an equivalent BMI, older adults tend to have more body fat than their younger counterpart. To our knowledge, no GWAS has been conducted on BMI adjusted BFP, WBFM, TFP, or TFM. In addition to BMI and BMI adjusted WHR, GWAS have been conducted on BMI adjusted waist circumference (Shungin et al. 2015) and recently on body fat ratios (Rask-Andersen et al. 2019; Randall et al. 2013), which is useful to differentiate adipose tissue distribution. Although it is not easy to interpret the BMI adjusted body fat mass and distribution and the adjustment methodology is not impeccable, more in-depth studies on body fat and BMI adjusted body fat are warranted to identify novel targets for obesity-related disease prevention and treatment.

As an important component of obesity, weight gain and disease risk association need further elucidation, while most epidemiologic studies have focused solely on attained body weight or BMI during midlife. In order to better understand mechanisms in obesity and chronic diseases, genetic determinants of obesity are studied on their association with weight change in addition to attained body weight. I find no associations in genetically predicted body fat mass and distribution with changes of body weight and other measured body fatness. This is the first attempt to study body fat genetic factors with change of body size and composition in addition to BMI. In line with our study, earlier studies have reported inversed relationship between higher number of BMI increasing alleles and weight gain during and after middle-age adulthood, while is associated with increased weight gain in younger age (Rukh et al. 2016). Only 31 BMI-associated variants were studied in Rukh's study. In a more recent study using a genetic risk score comprising 97 adult BMI-associated variants, no association with BMI change was found in middle or late adulthood but increases early adulthood weight gain in women (Song et al. 2018). Similar to our study population and length of follow-up duration, a Danish study reported similar findings to ours that no association of weight change of around 5 years after middle adulthood with a genetic score comprising 30 BMI SNPs (Sandholt et al. 2014).

The magnitude of association of body weight and size with genetically predicted fatness varies significantly by age and weaker association was found in older age group roughly after age 50. Recent study agrees with our findings in BMI with BMI genetic variants and reports the associations decline in late adulthood after peak at 60 years of age in women (Song et al. 2018). The explanation of the different effect size is still unclear. The association of rs9939609, single SNP in FTO gene, and obesity was observed to decline with older age (Rukh et al. 2016). A study with over 65 years follow-up indicates that the causes and consequences of BMI changes differ across the lifespan (Dahl et al. 2014). Genetic factors might exert stronger effect in early ages, while environmental factors play major roles in the elders. Adult BMI associated variants are primarily identified from GWAS conducted among middle-aged population, which might have different effects on younger or older group.

Earlier study on weight change patterns found a 10-allele increment in the BMI polygenic risk score is associated with 40% to 115% increased odds of being in the medium-medium, lean-heavy and medium-heavy groups, compared to the odds of being in the lean-medium group (Song et al. 2017). Our results illustrate the same trend and we further show people with higher body fat mass and distribution related polygenic scores have higher odds of being in the group of higher body fat mass and distribution both at age 10 and at baseline. Moreover, the same associations are observed for genetically predicted body fatness measures. The findings suggest additional body fat genetic factors are associated with further body fat gain in addition to younger age obesity. The association of body fatness change trajectories with body fat genetic variants also helps to explain that body fatness trajectories predict different subsequent risk for chronic diseases and mortality (Song, Hu, et al. 2016; Song, Willett, et al. 2016; Zheng et al. 2017).

To our knowledge, this is the first and largest study to comprehensively examine the effects of genetic risk scores of body fat mass and distribution in addition to BMI on changes in adiposity and weight change patterns in adulthood. The strengths of our study comprise the large sample size in studying age effect on body fat genetic variants on measured body fatness, inclusion of body fat mass and distribution in addition to BMI, use of all previously identified or self-identified SNPs associated with BMI to comprehensively study the associations. We acknowledge that our study has several limitations. For example, length of follow-up is relatively short for body weight change in middle and late adulthood. Reanalyzing the UK Biobank cohort could be considered when longer follow-up data on body weight and fatness is collected. Further, self-reported comparative body size might lead to misclassification bias. However, with the purpose of studying weight change patterns, such error is unlikely to cause substantial influence. The generalization of the findings might be undermined because we only focused on associations in middle and late adulthood among European females. Studies have demonstrated that genetic associations from different ancestry and sex are heterogeneous.

In conclusion, our study suggests that genetically predicted body fat mass and distribution are associated with body weight and body fatness at all adult ages, with the effect size of the association being weaker among older group. Individuals with more body fatness increasing alleles are likely to be plumper and higher in weight throughout life. Future studies are warranted to further investigate the association of body weight and composition change with body fat related genetic variants and biologic mechanisms in age-related effect on the associations.

APPENDIX

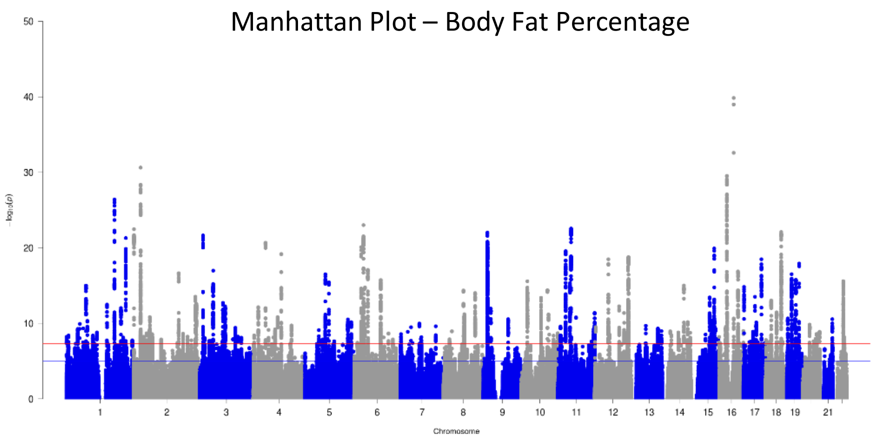
Appendix A. Acknowledgements for using summary statistics from BCAC data

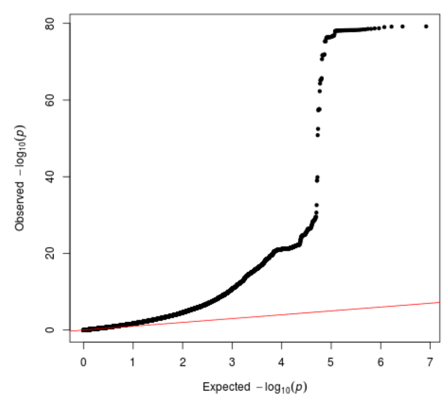
The breast cancer genome-wide association analyses were supported by the Government of Canada through Genome Canada and the Canadian Institutes of Health Research, the 'Ministère de l'Économie, de la Science et de l'Innovation du Québec' through Genome Québec and grant PSR-SIIRI-701, The National Institutes of Health (U19 CA148065, X01HG007492), Cancer Research UK (C1287/A10118, C1287/A16563, C1287/A10710) and The European Union (HEALTH-F2-2009-223175 and H2020 633784 and 634935). All studies and funders are listed in Michailidou et al (2017).

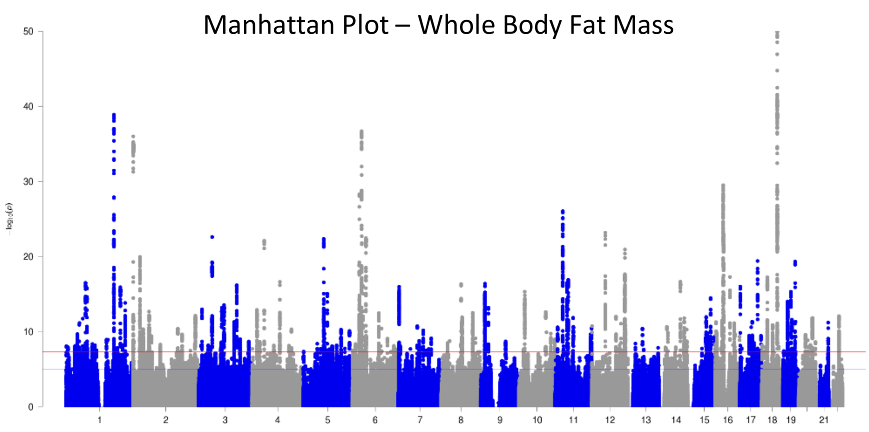
Funding for BCAC and iCOGS came from: Cancer Research UK [grant numbers C1287/A16563, C1287/A10118, C1287/A10710, C12292/A11174, C1281/A12014, C5047/A8384, C5047/A15007, C5047/A10692, C8197/A16565], the European Union's Horizon 2020 Research and Innovation Programme (grant numbers 634935 and 633784 for BRIDGES and B-CAST respectively), the European Community's Seventh Framework Programme under grant agreement n° 223175 [HEALTHF2-2009-223175] (COGS), the National Institutes of Health [CA128978] and Post-Cancer GWAS initiative [1U19 CA148537, 1U19 CA148065-01 (DRIVE) and 1U19 CA148112 - the GAME-ON initiative], the Department of Defence [W81XWH-10-1-0341], and the Canadian Institutes of Health Research CIHR) for the CIHR Team in Familial Risks of Breast Cancer [grant PSR-SIIRI-701]. All studies and funders as listed in Michailidou K et al (2013 and 2015) and in Guo Q et al (2015) are acknowledged for their contributions.

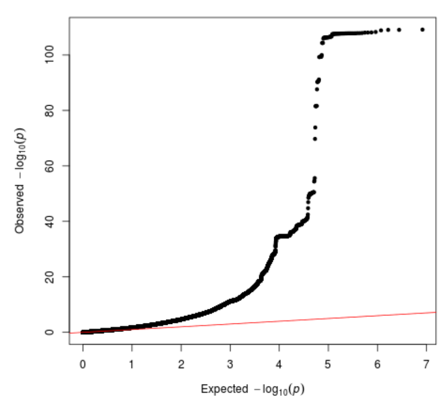
Appendix B. Manhattan and QQ plots for body fat measure traits.

I performed GWAS using our UK Biobank genetic data. Manhattan and QQ plots for body fat percentage, whole body fat mass, trunk fat percentage, trunk fat mass, body fat percentage adjusted for BMI, whole body fat mass adjusted for BMI, trunk fat percentage adjusted for BMI, and trunk fat mass adjusted for BMI are shown here. Traditional genome-wide significance ($p < 5 \times 10^{-8}$) and suggestive significance ($p < 10^{-5}$) are indicated by the red and blue horizontal lines, respectively.

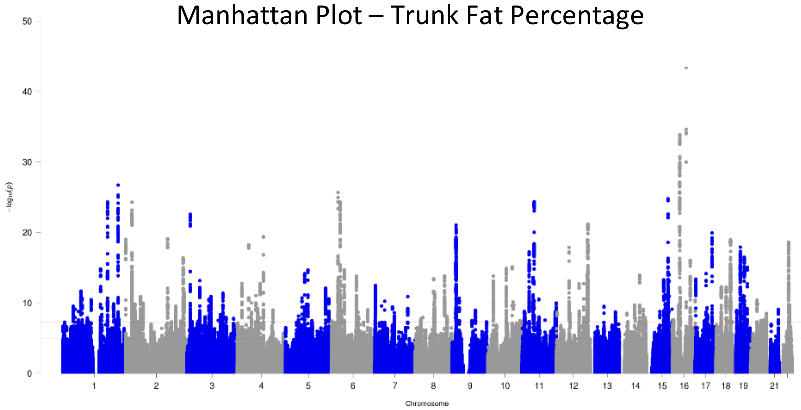


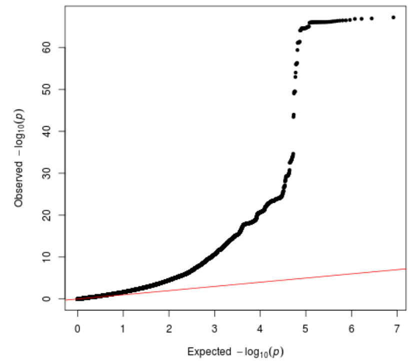




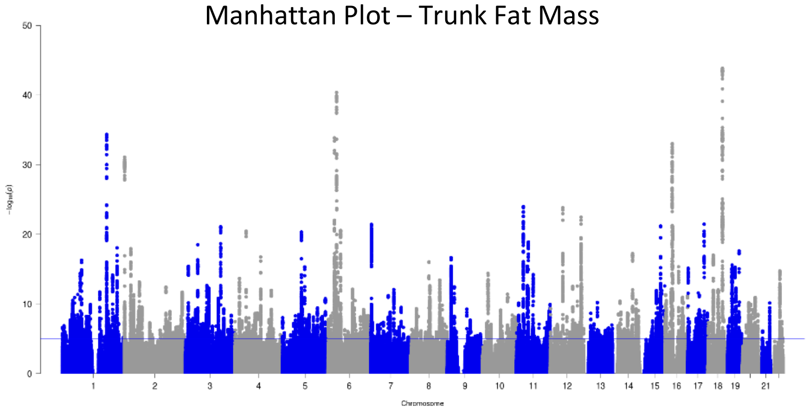


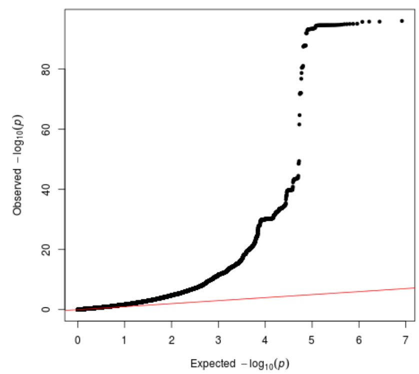
Manhattan Plot – Trunk Fat Percentage



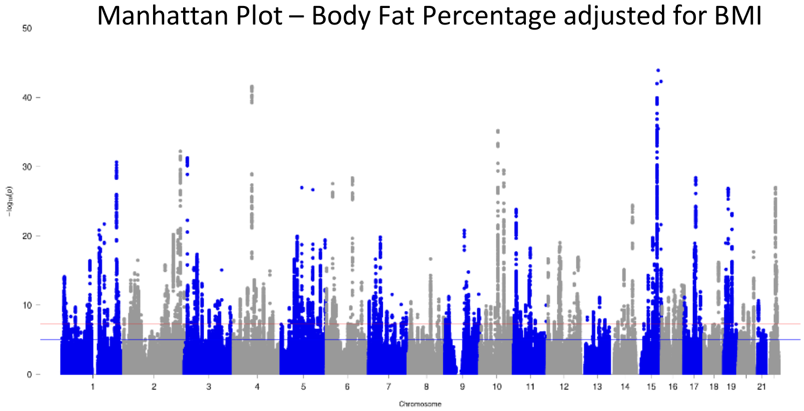


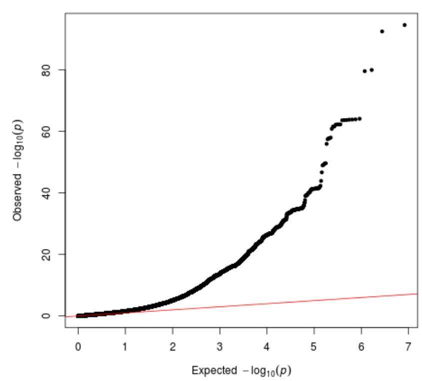
Manhattan Plot – Trunk Fat Mass



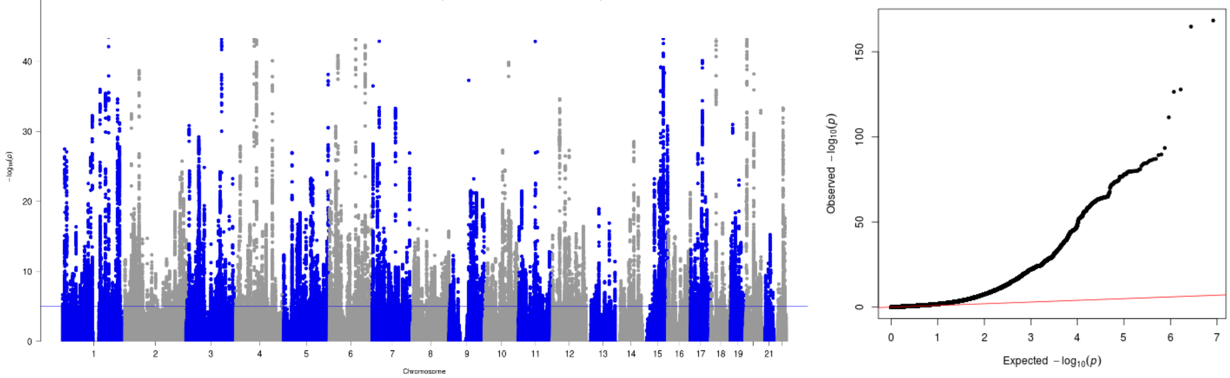


Manhattan Plot – Body Fat Percentage adjusted for BMI

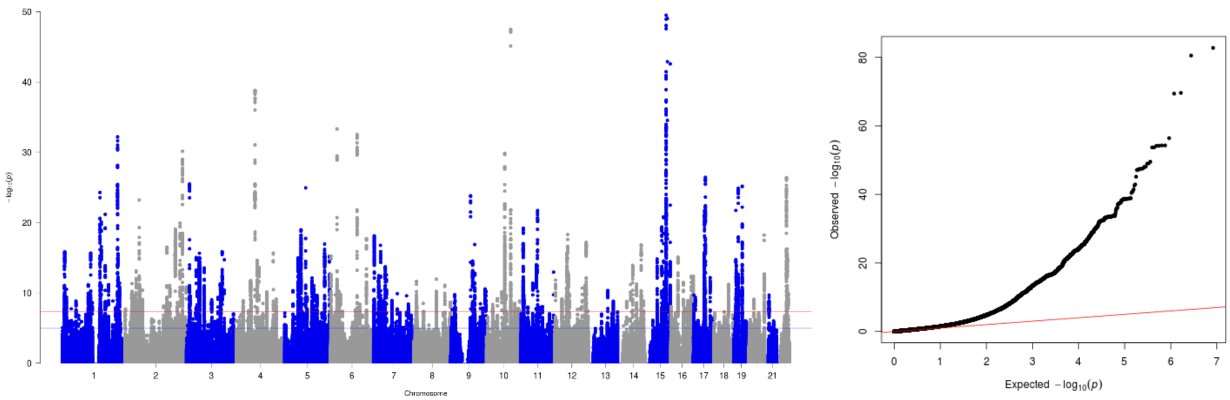




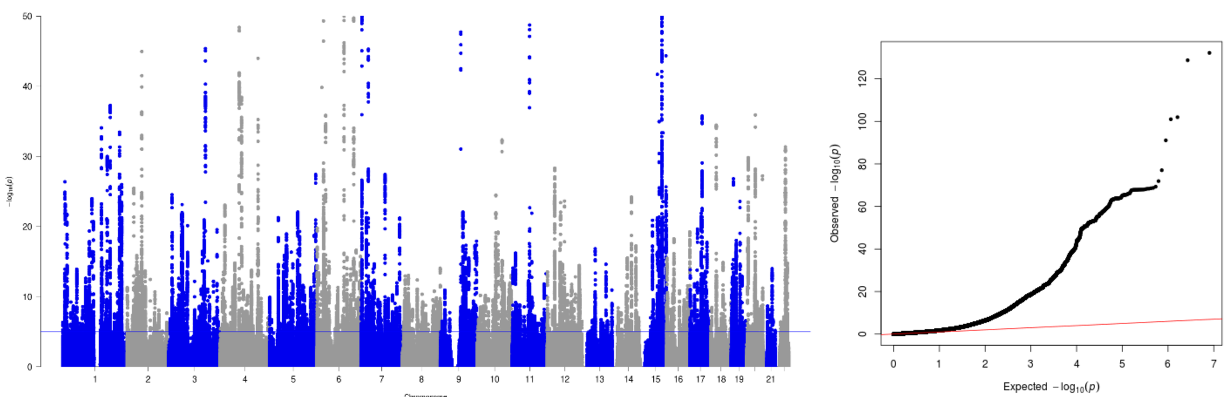
Manhattan Plot – Whole Body Fat Mass adjusted for BMI



Manhattan Plot – Trunk Fat Percentage adjusted for BMI



Manhattan Plot – Trunk Fat Mass adjusted for BMI



Appendix C. Association of the selected SNPs with body fat mass and distribution and breast cancer risk in BCAC

SNP	Chr	Position (hg19)	Effect alleles *	Other alleles	Estimates from GWAS **			Estimates from BCAC ***	
					EAF ****	beta	se	beta	se
				Body fat measure trait – BMI					
rs12711521	1	11090916	C	A	0.210	0.013	0.0028	-0.007	0.0079
rs3766160	1	15808872	G	A	0.740	0.012	0.0025	-0.010	0.0071
rs3765407	1	23419374	G	T	0.180	0.015	0.0030	-0.011	0.0087
rs2296172	1	39835817	G	A	0.200	0.015	0.0027	0.015	0.0077
rs12140153	1	62579891	G	T	0.910	0.030	0.0050	-0.012	0.0116
rs540742	1	78585086	T	C	0.780	0.012	0.0026	0.006	0.0075
rs1801265	1	98348885	G	A	0.230	0.013	0.0026	0.004	0.0074
rs197412	1	112308953	C	T	0.410	0.013	0.0022	0.000	0.0065
rs2297792	1	156011444	C	T	0.610	0.013	0.0023	-0.026	0.0065
rs16849342	1	201754444	C	G	0.050	0.020	0.0046	-0.009	0.0134
rs11583200	1	50559820	C	T	0.400	0.018	0.0031	-0.005	0.0064
rs1555543	1	96944797	C	A	0.590	0.022	0.0038	-0.005	0.0065
rs2815752	1	72812440	A	G	0.610	0.033	0.0031	-0.019	0.0064
rs2820292	1	201784287	C	A	0.560	0.020	0.0031	-0.001	0.0063
rs543874	1	177889480	G	A	0.190	0.048	0.0039	-0.030	0.0079
rs657452	1	49589847	A	G	0.390	0.023	0.0031	-0.006	0.0064
rs977747	1	47684677	T	G	0.390	0.017	0.0031	-0.003	0.0064
rs1550116	2	25022598	G	A	0.140	0.016	0.0032	-0.018	0.0095
rs11676272	2	25141538	G	A	0.490	0.029	0.0023	-0.040	0.0066
rs4851287	2	100915772	A	G	0.350	0.013	0.0023	-0.007	0.007
rs7601000	2	242610773	T	A	0.210	0.012	0.0028	0.012	0.0093
rs11688816	2	63053048	G	A	0.530	0.017	0.0031	0.002	0.0062
rs1528435	2	181550962	T	C	0.630	0.018	0.0031	-0.013	0.0065
rs17203016	2	208255518	G	A	0.200	0.021	0.0039	-0.001	0.008
rs2176040	2	227092802	A	G	0.370	0.014	0.0031	-0.002	0.0064
rs2867125	2	622827	C	T	0.830	0.060	0.0040	-0.039	0.0081
rs2890652	2	142959931	C	T	0.180	0.025	0.0051	0.008	0.0084
rs492400	2	219349752	C	T	0.420	0.016	0.0031	0.003	0.0064
rs7599312	2	213413231	G	A	0.720	0.022	0.0034	-0.023	0.0071
rs887912	2	59302877	T	C	0.290	0.023	0.0034	0.000	0.007
rs1801282	3	12393125	G	C	0.120	0.024	0.0035	-0.017	0.0094
rs56084453	3	44762830	A	G	0.790	0.012	0.0027	-0.021	0.0082
rs3732530	3	47618953	C	A	0.350	0.015	0.0025	0.005	0.0067
rs1062633	3	49924940	C	T	0.490	0.019	0.0023	0.017	0.0062
rs13303	3	52558008	C	T	0.560	0.011	0.0023	-0.016	0.0063

rs56384862	3	58395863	G	A	0.340	0.013	0.0023	-0.009	0.0068
rs7653652	3	88189341	C	T	0.840	0.015	0.0030	-0.028	0.0087
rs1052618	3	136574501	G	A	0.690	0.011	0.0024	-0.013	0.0068
rs9438	3	154018887	C	G	0.400	0.013	0.0022	-0.002	0.0065
rs11546878	3	183976103	C	T	0.840	0.017	0.0029	0.010	0.0085
rs2178403	3	184039666	A	G	0.250	0.014	0.0025	0.007	0.0072
rs13078807	3	85884150	G	A	0.200	0.030	0.0039	-0.012	0.0078
rs16851483	3	141275436	T	G	0.070	0.048	0.0077	0.014	0.0129
rs3849570	3	81792112	A	C	0.360	0.019	0.0034	0.007	0.0066
rs34811474	4	25408838	G	A	0.790	0.024	0.0026	0.005	0.0089
rs3749591	4	120214030	G	T	0.310	0.012	0.0023	-0.008	0.0068
rs10938397	4	45182527	G	A	0.430	0.040	0.0031	-0.014	0.0062
rs13107325	4	103188709	T	C	0.070	0.048	0.0068	0.017	0.0125
rs17001654	4	77129568	G	C	0.150	0.031	0.0053	-0.034	0.009
rs6893216	5	74442964	T	C	0.880	0.018	0.0034	-0.013	0.0096
rs2307111	5	75003678	T	C	0.590	0.023	0.0025	-0.016	0.0063
rs6234	5	95728974	C	G	0.270	0.017	0.0025	0.003	0.0074
rs30187	5	96124330	C	T	0.650	0.010	0.0024	-0.002	0.0066
rs1045706	5	108714298	C	T	0.570	0.011	0.0022	0.007	0.0065
rs459552	5	112176756	T	A	0.220	0.012	0.0026	-0.006	0.0073
rs7715256	5	153537893	G	T	0.420	0.016	0.0031	-0.010	0.0063
rs2228210	6	12122174	A	G	0.670	0.014	0.0023	0.003	0.0064
rs41312309	6	34498328	T	C	0.080	0.021	0.0038	-0.025	0.0112
rs11755393	6	34824636	G	A	0.360	0.020	0.0024	-0.001	0.0065
rs78648104	6	50683009	T	C	0.910	0.020	0.0037	-0.020	0.0111
rs12199003	6	55196587	T	C	0.370	0.011	0.0023	-0.007	0.0067
rs13191362	6	163033350	A	G	0.880	0.028	0.0048	0.013	0.0098
rs9374842	6	120185665	T	C	0.740	0.023	0.0035	-0.005	0.0073
rs9400239	6	108977663	C	T	0.690	0.019	0.0033	0.004	0.0068
rs987237	6	50803050	G	A	0.180	0.045	0.0040	0.008	0.0081
rs215607	7	32338337	G	A	0.220	0.013	0.0027	-0.009	0.0078
rs2301680	7	93116299	G	A	0.500	0.014	0.0024	-0.004	0.0062
rs1805123	7	150645534	T	G	0.780	0.017	0.0026	-0.016	0.0073
rs1167827	7	75163169	G	A	0.550	0.020	0.0033	0.011	0.0063
rs16907751	8	81375457	C	T	0.910	0.047	0.0066	-0.011	0.0104
rs17405819	8	76806584	T	C	0.700	0.022	0.0033	-0.014	0.0067
rs4741510	9	15591372	T	A	0.590	0.012	0.0023	0.014	0.0063
rs1105223	9	126128211	T	C	0.600	0.011	0.0022	-0.008	0.0068
rs2280843	9	131585069	G	A	0.730	0.015	0.0026	-0.005	0.0072
rs10733682	9	129460914	A	G	0.480	0.017	0.0031	-0.023	0.0063
rs10968576	9	28414339	G	A	0.310	0.025	0.0033	-0.003	0.0067
rs1928295	9	120378483	T	C	0.550	0.019	0.0031	0.002	0.0063
rs6477694	9	111932342	C	T	0.370	0.017	0.0031	-0.013	0.0065
rs2274741	10	27303605	T	A	0.160	0.016	0.0033	0.024	0.009

rs3088142	10	76854564	T	C	0.430	0.017	0.0023	0.001	0.0064
rs11189513	10	99969568	A	G	0.680	0.014	0.0024	-0.005	0.0066
rs284860	10	104572963	T	C	0.410	0.010	0.0023	0.009	0.0063
rs3781409	10	126715629	T	C	0.250	0.011	0.0025	-0.003	0.007
rs17094222	10	102395440	C	T	0.210	0.025	0.0038	-0.002	0.0079
rs7899106	10	87410904	G	A	0.050	0.040	0.0071	-0.016	0.0148
rs7903146	10	114758349	C	T	0.710	0.023	0.0034	-0.036	0.0069
rs7126805	11	828916	A	G	0.710	0.011	0.0027	0.019	0.0072
rs5219	11	17409572	C	T	0.640	0.012	0.0023	0.012	0.0064
rs80317617	11	27362257	C	T	0.070	0.019	0.0043	0.010	0.0127
rs6265	11	27679916	C	T	0.820	0.041	0.0028	0.009	0.0078
rs11555762	11	43876698	T	C	0.310	0.014	0.0023	0.004	0.0068
rs12273892	11	64480930	A	T	0.840	0.015	0.0032	-0.007	0.0087
rs15818	11	118952173	G	A	0.400	0.013	0.0023	-0.009	0.0064
rs3817334	11	47650993	T	C	0.410	0.026	0.0031	-0.004	0.0063
rs12828016	12	998365	G	T	0.610	0.014	0.0022	0.007	0.0064
rs3184504	12	111884608	C	T	0.550	0.013	0.0023	0.031	0.0062
rs1169081	12	122405912	G	T	0.700	0.012	0.0024	0.002	0.0068
rs7978353	12	122617989	A	G	0.590	0.010	0.0022	-0.002	0.0068
rs11057405	12	122781897	G	A	0.900	0.031	0.0055	0.025	0.0109
rs7138803	12	50247468	A	G	0.380	0.032	0.0031	-0.005	0.0064
rs1933437	13	28624294	G	A	0.390	0.016	0.0023	0.005	0.0063
rs1441264	13	79580919	A	G	0.610	0.018	0.0032	-0.008	0.0069
rs4771122	13	28020180	G	A	0.240	0.030	0.0046	-0.026	0.0072
rs1051695	14	33293122	A	G	0.450	0.016	0.0022	-0.007	0.0066
rs1131877	14	103342049	C	T	0.250	0.017	0.0026	-0.020	0.0074
rs861539	14	104165753	G	A	0.640	0.013	0.0023	-0.021	0.0063
rs10132280	14	25928179	C	A	0.680	0.023	0.0034	-0.004	0.0069
rs11847697	14	30515112	T	C	0.040	0.049	0.0084	-0.013	0.0161
rs12885454	14	29736838	C	A	0.640	0.021	0.0033	-0.004	0.0065
rs11071896	15	66821250	A	G	0.750	0.013	0.0025	-0.028	0.007
rs2277598	15	73027478	C	T	0.630	0.015	0.0024	-0.008	0.0065
rs2241423	15	68086838	G	A	0.780	0.031	0.0037	-0.009	0.0074
rs3736485	15	51748610	A	G	0.450	0.018	0.0031	-0.012	0.0063
rs1053874	16	3707747	A	G	0.320	0.012	0.0025	-0.001	0.0071
rs1049205	16	4942099	C	T	0.460	0.012	0.0022	-0.015	0.0069
rs1136001	16	15131974	G	T	0.700	0.011	0.0024	-0.014	0.0075
rs7191155	16	19800213	T	C	0.830	0.017	0.0029	-0.003	0.0084
rs9652588	16	20370810	C	T	0.500	0.013	0.0022	-0.008	0.0062
rs4077410	16	29998200	G	A	0.510	0.017	0.0022	0.002	0.0063
rs2111119	16	53671754	C	T	0.910	0.020	0.0042	-0.008	0.0113
rs61747555	16	71885423	A	G	0.790	0.015	0.0029	0.002	0.0077
rs455527	16	89644001	T	C	0.940	0.020	0.0045	0.021	0.0136
rs1558902	16	53803574	A	T	0.420	0.082	0.0031	-0.062	0.0063

rs2080454	16	49062590	C	A	0.410	0.017	0.0031	-0.003	0.0067
rs7359397	16	28885659	T	C	0.400	0.031	0.0031	0.004	0.0064
rs9925964	16	31129895	A	G	0.620	0.019	0.0031	-0.017	0.0065
rs1885987	17	2203025	T	G	0.650	0.010	0.0023	0.018	0.0069
rs6065	17	4836381	T	C	0.080	0.024	0.0042	0.030	0.0117
rs203462	17	19812541	T	C	0.610	0.010	0.0023	-0.009	0.0064
rs2306590	17	34854280	G	A	0.610	0.016	0.0024	0.011	0.0071
rs7406910	17	46688256	C	T	0.900	0.018	0.0038	-0.008	0.0109
rs9891146	17	65988049	T	C	0.290	0.015	0.0028	0.000	0.0073
rs3760128	17	73886888	G	A	0.350	0.013	0.0027	0.012	0.0071
rs4889891	17	77768654	C	A	0.520	0.012	0.0030	0.038	0.0063
rs1000940	17	5283252	G	A	0.320	0.019	0.0034	0.006	0.0067
rs1808579	18	21104888	C	T	0.530	0.017	0.0031	0.010	0.0063
rs571312	18	57839769	A	C	0.240	0.056	0.0036	-0.023	0.0073
rs7239883	18	40147671	G	A	0.390	0.023	0.0031	-0.004	0.0064
rs7243357	18	56883319	T	G	0.810	0.022	0.0040	-0.008	0.0082
rs2396359	19	1819125	T	C	0.760	0.015	0.0026	0.001	0.0076
rs11554159	19	18285944	A	G	0.260	0.015	0.0025	0.006	0.007
rs17751061	19	19413092	C	T	0.860	0.021	0.0046	-0.036	0.0086
rs1800437	19	46181392	G	C	0.800	0.031	0.0027	-0.047	0.008
rs2075803	19	51628529	G	A	0.560	0.010	0.0022	0.004	0.0063
rs17724992	19	18454825	A	G	0.750	0.019	0.0035	0.004	0.0071
rs2075650	19	45395619	A	G	0.850	0.026	0.0045	0.020	0.0092
rs29941	19	34309532	G	A	0.670	0.018	0.0033	-0.013	0.0066
rs3810291	19	47569003	A	G	0.670	0.028	0.0036	-0.024	0.0067
rs2228273	20	18296076	A	G	0.080	0.024	0.0041	-0.009	0.0119
rs2076559	20	25187213	A	G	0.330	0.016	0.0023	-0.018	0.0067
rs2836754	21	40291740	C	T	0.610	0.016	0.0032	-0.005	0.0064
rs5758651	22	42609148	T	C	0.800	0.012	0.0027	-0.006	0.0077
Body fat measure trait – WHRadjBMI									
rs10494217	1	119469188	T	G	0.170	0.018	0.0035	-0.017	0.0082
rs3851294	1	205130413	G	A	0.910	0.034	0.0046	0.008	0.0109
rs2645294	1	119574587	T	C	0.580	0.031	0.0035	0.005	0.0064
rs10919388	1	170372503	C	A	0.720	0.024	0.0040	0.010	0.0072
rs714515	1	172352990	G	A	0.430	0.027	0.0034	-0.020	0.0062
rs2820443	1	219753509	T	C	0.720	0.035	0.0037	0.018	0.0069
rs905938	1	154991389	T	C	0.740	0.025	0.0040	0.021	0.0071
rs7586970	2	188343497	T	C	0.700	0.016	0.0031	-0.013	0.0067
rs1385167	2	66200648	G	A	0.150	0.029	0.0049	-0.014	0.0091
rs12692737	2	165554309	A	C	0.300	0.032	0.0038	-0.009	0.0064
rs1034405	3	50597092	G	A	0.130	0.016	0.0040	0.029	0.0093
rs13303	3	52558008	T	C	0.450	0.019	0.0028	0.016	0.0063
rs17451107	3	156797609	T	C	0.610	0.026	0.0036	0.006	0.0064
rs2371767	3	64718258	G	C	0.720	0.036	0.0039	-0.010	0.0069

rs17819328	3	12489342	G	T	0.430	0.021	0.0035	0.014	0.0064
rs10804591	3	129334233	A	C	0.800	0.025	0.0042	-0.022	0.0078
rs6784615	3	52506426	T	C	0.940	0.040	0.0077	0.013	0.0138
rs7657817	4	89668859	C	T	0.820	0.016	0.0036	-0.026	0.0086
rs3733526	4	120528327	G	A	0.190	0.015	0.0035	0.003	0.0083
rs3805389	4	56482750	A	G	0.280	0.027	0.0038	-0.012	0.0071
rs303084	4	124066948	A	G	0.800	0.023	0.0042	-0.008	0.0076
rs459193	5	55806751	A	G	0.260	0.026	0.0038	-0.004	0.0075
rs6556301	5	176527577	T	G	0.360	0.022	0.0040	-0.010	0.0065
rs1045241	5	118729286	C	T	0.710	0.035	0.0037	-0.012	0.007
rs7705502	5	173320815	A	G	0.330	0.027	0.0036	-0.032	0.0067
rs3936510	5	55860866	T	G	0.180	0.026	0.0046	-0.022	0.0082
rs1334576	6	7211818	G	A	0.560	0.017	0.0028	0.020	0.0063
rs9469913	6	34827085	A	T	0.850	0.021	0.0053	0.004	0.0082
rs1776897	6	34195011	G	T	0.080	0.052	0.0069	-0.017	0.0111
rs1294410	6	6738752	C	T	0.630	0.031	0.0035	0.007	0.0064
rs1358980	6	43764551	T	C	0.470	0.039	0.0036	-0.024	0.0062
rs1936805	6	127452116	T	C	0.510	0.043	0.0034	-0.022	0.0063
rs7759742	6	32381736	A	T	0.510	0.023	0.0034	0.001	0.0062
rs2303361	7	6449496	C	T	0.220	0.014	0.0032	0.007	0.0077
rs3812316	7	73020337	C	G	0.880	0.021	0.0044	-0.034	0.0107
rs1534696	7	26397239	C	A	0.440	0.027	0.0037	-0.007	0.0064
rs7801581	7	27223771	T	C	0.240	0.027	0.0042	0.000	0.0074
rs10245353	7	25858614	A	C	0.200	0.035	0.0043	-0.021	0.0081
rs12679556	8	72514228	G	T	0.250	0.027	0.0040	-0.014	0.0072
rs7830933	8	23603324	A	G	0.770	0.037	0.0040	-0.010	0.0072
rs10991437	9	107735920	A	C	0.110	0.031	0.0054	0.008	0.0098
rs17417407	10	95931087	T	G	0.170	0.018	0.0036	-0.004	0.0083
rs7917772	10	104487443	A	G	0.620	0.027	0.0035	0.009	0.0064
rs7114037	11	65403651	C	A	0.950	0.029	0.0065	-0.006	0.0147
rs11231693	11	63862612	A	G	0.060	0.041	0.0075	-0.026	0.014
rs3764002	12	108618630	C	T	0.740	0.014	0.0030	0.003	0.0083
rs11057353	12	124265687	T	C	0.370	0.018	0.0028	-0.014	0.0067
rs4765219	12	124440110	C	A	0.670	0.028	0.0036	-0.001	0.0069
rs10783615	12	54349773	G	A	0.140	0.036	0.0049	-0.026	0.0101
rs2071449	12	54428011	A	C	0.370	0.028	0.0036	-0.019	0.0067
rs10842707	12	26471364	T	C	0.230	0.032	0.0040	0.010	0.0074
rs863750	12	124505444	T	C	0.590	0.026	0.0035	-0.018	0.0064
rs1042704	14	23312594	A	G	0.200	0.021	0.0033	0.025	0.008
rs1051860	14	58838668	A	G	0.410	0.013	0.0030	0.004	0.0063
rs3959569	15	42115747	C	G	0.350	0.017	0.0047	0.009	0.0066
rs1440372	15	67033151	C	T	0.710	0.024	0.0038	-0.001	0.0076
rs8030605	15	56504598	A	G	0.140	0.030	0.0053	0.001	0.0099
rs3747579	16	4445327	C	T	0.300	0.018	0.0030	-0.019	0.0079

rs9922085	16	67397580	G	C	0.940	0.034	0.0067	-0.021	0.0153
rs2925979	16	81534790	T	C	0.310	0.032	0.0037	-0.008	0.0068
rs8066985	17	68453345	A	G	0.500	0.026	0.0034	-0.002	0.0062
rs4646404	17	17420199	G	A	0.670	0.027	0.0039	0.008	0.0068
rs12454712	18	60845884	T	C	0.610	0.035	0.0042	0.008	0.0064
rs11554159	19	18285944	A	G	0.260	0.015	0.0031	0.006	0.007
rs2287922	19	49232226	A	G	0.490	0.014	0.0029	0.008	0.0063
rs4081724	19	33824946	G	A	0.850	0.035	0.0051	0.009	0.009
rs224331	20	34022387	A	C	0.640	0.017	0.0036	-0.006	0.0065
rs979012	20	6623374	T	C	0.340	0.027	0.0036	0.013	0.0066
rs6090583	20	45558831	A	G	0.480	0.022	0.0034	-0.002	0.0066
rs2294239	22	29449477	A	G	0.590	0.025	0.0035	0.009	0.0062
Body fat measure trait – Body fat percentage									
rs6686901	1	42436054	C	T	0.460	0.017	0.0025	0.001	0.0063
rs7536940	1	50251567	T	A	0.385	0.018	0.0025	-0.008	0.0066
rs12140153	1	62579891	G	T	0.903	0.029	0.0043	-0.012	0.0116
rs61765651	1	72754314	C	T	0.807	0.027	0.0031	-0.009	0.0082
rs3104464	1	77966230	A	G	0.225	0.021	0.0029	0.008	0.0075
rs115584674	1	150346106	A	G	0.941	0.042	0.0052	0.027	0.014
rs543874	1	177889480	G	A	0.208	0.036	0.0030	-0.030	0.0079
rs2678204	1	201800511	G	T	0.342	0.020	0.0026	-0.007	0.0066
rs2494196	1	219762581	A	C	0.288	0.029	0.0027	-0.019	0.007
rs6751993	2	635864	G	A	0.828	0.036	0.0033	-0.038	0.0082
rs10203386	2	25136866	A	T	0.452	0.032	0.0025	-0.043	0.0067
rs4671328	2	58935282	T	G	0.450	0.018	0.0025	0.001	0.0063
rs78343493	2	165502911	A	G	0.119	0.035	0.0038	0.009	0.0093
rs1913657	2	227107501	C	T	0.354	0.021	0.0026	-0.003	0.0065
rs10209821	2	228980358	T	C	0.341	0.018	0.0026	0.000	0.007
rs62190394	2	230624929	T	C	0.314	0.021	0.0027	-0.012	0.0066
rs7649970	3	12392272	T	C	0.121	0.040	0.0038	-0.018	0.0093
3:49959570	3	49959570	C	CA	0.525	0.023	0.0025	0.017	0.0063
rs3911063	3	85906928	T	C	0.677	0.021	0.0026	0.004	0.0066
rs4857330	3	94037499	T	C	0.448	0.020	0.0025	-0.001	0.0062
rs10662785	3	131620696	GTTT	G	0.273	0.019	0.0028	-0.003	0.0073
rs2192527	4	18329824	G	A	0.465	0.019	0.0025	0.003	0.0062
rs10938397	4	45182527	G	A	0.434	0.026	0.0025	-0.014	0.0062
rs58383713	4	80796055	A	C	0.196	0.021	0.0031	0.004	0.0078
rs987469	4	89706643	C	G	0.539	0.018	0.0025	-0.004	0.0062
rs13107325	4	103188709	T	C	0.075	0.047	0.0047	0.017	0.0125
rs57800857	4	140863365	A	C	0.635	0.018	0.0026	0.014	0.0067
rs6861649	5	50864788	C	T	0.607	0.017	0.0025	0.010	0.0064
rs2112347	5	75015242	T	G	0.641	0.024	0.0026	-0.018	0.0064
rs34483452	5	87986314	A	C	0.135	0.033	0.0036	-0.003	0.009
rs2963468	5	158003020	A	G	0.767	0.021	0.0029	0.011	0.0075

rs245775	5	170532105	G	A	0.729	0.020	0.0028	0.000	0.0069
rs2183947	6	26159356	G	A	0.776	0.030	0.0029	-0.004	0.0075
rs35778344	6	28599105	A	G	0.199	0.021	0.0031	-0.029	0.0088
rs2178899	6	31606756	A	T	0.870	0.028	0.0037	-0.005	0.0096
rs3736896	6	34735883	C	T	0.204	0.034	0.0030	-0.008	0.0075
rs9471333	6	40362023	C	T	0.450	0.022	0.0025	0.001	0.0068
rs1928185	6	50935513	C	T	0.168	0.031	0.0033	0.012	0.0082
rs9320823	6	98429337	C	T	0.602	0.023	0.0025	0.011	0.0063
rs4549685	7	39326478	C	T	0.670	0.018	0.0026	0.012	0.0066
rs4718964	7	70038969	T	G	0.412	0.018	0.0025	0.002	0.0063
7:130438531	7	130438531	C	CTTTTTT	0.517	0.017	0.0025	0.023	0.0067
rs7845090	8	73449940	G	A	0.289	0.024	0.0027	0.012	0.0072
rs12678759	8	76786941	C	T	0.705	0.020	0.0027	-0.015	0.0068
rs4876611	8	116671848	G	A	0.716	0.023	0.0027	0.011	0.0069
rs9776097	9	15647348	G	T	0.559	0.027	0.0025	0.007	0.0063
rs1319424	9	16726000	G	A	0.254	0.020	0.0028	0.018	0.0075
rs377741138	9	28412183	G	GAAAA	0.342	0.020	0.0026	-0.002	0.0067
rs12339822	9	92187178	G	A	0.543	0.018	0.0025	-0.004	0.0063
rs11012732	10	21830104	G	A	0.331	0.024	0.0026	0.042	0.0066
rs10999460	10	72428283	T	C	0.266	0.023	0.0028	0.000	0.0071
rs11187838	10	96038686	G	A	0.568	0.021	0.0025	0.006	0.0063
rs12357890	10	99762693	G	A	0.560	0.019	0.0025	0.002	0.0067
rs11042030	11	8690718	T	C	0.726	0.019	0.0028	-0.001	0.0069
rs61888762	11	27709630	G	C	0.322	0.027	0.0026	-0.005	0.0067
rs60572790	11	43692383	C	T	0.317	0.024	0.0027	0.010	0.0067
11:47720518	11	47720518	C	CAA	0.553	0.027	0.0025	0.002	0.0064
rs801732	11	65935502	T	A	0.642	0.019	0.0026	0.024	0.0066
11:130719075	11	130719075	A	ACTCC	0.526	0.017	0.0025	-0.003	0.0066
rs73041988	11	134517234	T	G	0.834	0.025	0.0033	0.002	0.0093
12:3346767	12	3346767	CTCT	C	0.903	0.029	0.0042	0.036	0.0121
rs12367809	12	50256063	T	C	0.368	0.025	0.0026	-0.004	0.0065
rs704061	12	89771903	C	T	0.453	0.020	0.0025	0.000	0.007
rs7980305	12	108098039	C	T	0.395	0.019	0.0025	0.016	0.0066
rs80272996	12	121994892	G	A	0.944	0.038	0.0056	0.037	0.0159
rs147730268	12	123024476	G	T	0.912	0.042	0.0044	0.029	0.0118
rs12311848	12	124486851	G	A	0.334	0.026	0.0026	0.002	0.0069
rs7982447	13	54453811	C	T	0.206	0.021	0.0030	-0.004	0.0077
13:99119385	13	99119385	TAA	T	0.710	0.019	0.0027	-0.024	0.0069
rs2370982	14	79890677	T	C	0.215	0.027	0.0030	0.011	0.0076
rs6575340	14	94023972	A	G	0.637	0.018	0.0026	-0.002	0.0065
rs28399271	15	67710011	G	A	0.737	0.023	0.0028	0.001	0.0071
rs7171864	15	73227249	A	G	0.661	0.019	0.0026	0.001	0.0068
rs4572348	15	84540163	A	G	0.718	0.028	0.0027	-0.009	0.0068
rs1879529	15	89414295	G	T	0.735	0.019	0.0028	-0.012	0.0082

rs12923476	16	24798079	G	A	0.745	0.020	0.0028	0.008	0.0071
rs8049439	16	28837515	C	T	0.406	0.031	0.0025	0.006	0.0064
rs4402589	16	29954654	G	T	0.553	0.020	0.0025	-0.003	0.0063
rs7193144	16	53810686	C	T	0.394	0.052	0.0025	-0.060	0.0063
rs11866219	16	69549749	A	C	0.417	0.024	0.0025	0.016	0.0066
rs546133832	17	1837168	T	TA	0.845	0.030	0.0034	-0.013	0.009
rs67856160	17	42286541	TA	T	0.227	0.025	0.0030	-0.001	0.0076
rs11079849	17	47090785	C	T	0.673	0.019	0.0026	0.002	0.007
rs55931203	17	65854602	T	C	0.188	0.031	0.0032	0.001	0.0082
rs1788808	18	21090023	A	G	0.503	0.020	0.0025	0.007	0.0063
rs2052607	18	40788387	G	A	0.655	0.020	0.0026	0.009	0.0066
rs538656	18	57850422	T	G	0.235	0.031	0.0029	-0.023	0.0073
rs188955288	19	4067314	C	T	0.810	0.023	0.0032	0.017	0.0086
rs55714539	19	18207397	C	A	0.343	0.024	0.0026	0.011	0.0067
rs113230003	19	18460956	G	A	0.740	0.020	0.0028	0.000	0.0073
rs113696534	19	30286037	GCCTGT AATC	G	0.330	0.019	0.0026	0.024	0.0066
rs7250833	19	33937277	T	C	0.289	0.025	0.0027	-0.010	0.007
rs10423928	19	46182304	T	A	0.806	0.030	0.0031	-0.047	0.008
rs76040172	21	46488959	G	A	0.945	0.040	0.0054	0.007	0.0144
rs13056506	22	38580917	G	T	0.401	0.023	0.0025	-0.040	0.0063
Body fat measure trait – Whole body fat mass									
rs6686901	1	42436054	C	T	0.460	0.017	0.0025	0.001	0.0063
rs7536940	1	50251567	T	A	0.385	0.019	0.0025	-0.008	0.0066
rs12140153	1	62579891	G	T	0.903	0.033	0.0043	-0.012	0.0116
rs61765651	1	72754314	C	T	0.807	0.029	0.0031	-0.009	0.0082
rs3104464	1	77966230	A	G	0.225	0.027	0.0029	0.008	0.0075
rs543874	1	177889480	G	A	0.208	0.044	0.0030	-0.030	0.0079
rs2678204	1	201800511	G	T	0.342	0.024	0.0026	-0.007	0.0066
rs2494196	1	219762581	A	C	0.288	0.023	0.0027	-0.019	0.007
rs6751993	2	635864	G	A	0.828	0.046	0.0033	-0.038	0.0082
rs10203386	2	25136866	A	T	0.452	0.025	0.0025	-0.043	0.0067
rs10084382	2	36768447	T	C	0.312	0.019	0.0027	-0.001	0.0068
rs4671328	2	58935282	T	G	0.450	0.020	0.0025	0.001	0.0063
rs12477088	2	67841326	T	C	0.590	0.017	0.0025	0.019	0.0063
rs78343493	2	165502911	A	G	0.119	0.028	0.0038	0.009	0.0093
rs62178054	2	181574287	T	C	0.628	0.018	0.0026	-0.012	0.0065
rs35882248	2	230627955	T	C	0.315	0.021	0.0027	-0.012	0.0066
rs7649970	3	12392272	T	C	0.121	0.031	0.0038	-0.018	0.0093
3:49959570	3	49959570	C	CA	0.525	0.027	0.0025	0.017	0.0063
rs62261725	3	85898626	A	G	0.673	0.022	0.0026	0.005	0.0066
rs4857330	3	94037499	T	C	0.448	0.021	0.0025	-0.001	0.0062
rs10662785	3	131620696	GTTT	G	0.273	0.021	0.0028	-0.003	0.0073
rs9858603	3	141095949	G	A	0.346	0.024	0.0026	0.042	0.0065
rs2192527	4	18329824	G	A	0.465	0.020	0.0025	0.003	0.0062

rs10938397	4	45182527	G	A	0.434	0.027	0.0025	-0.014	0.0062
rs13135092	4	103198082	G	A	0.083	0.042	0.0045	0.018	0.0121
rs11100870	4	145822014	T	G	0.450	0.018	0.0025	0.006	0.0063
rs2112347	5	75015242	T	G	0.641	0.028	0.0026	-0.018	0.0064
rs2636986	5	77385681	C	T	0.757	0.020	0.0029	0.008	0.0082
rs1477290	5	87988934	C	T	0.136	0.032	0.0036	-0.002	0.009
rs13174863	5	139080745	G	A	0.148	0.025	0.0035	0.019	0.0098
rs245775	5	170532105	G	A	0.729	0.020	0.0028	0.000	0.0069
rs2183947	6	26159356	G	A	0.776	0.036	0.0029	-0.004	0.0075
rs72843644	6	27211601	A	C	0.907	0.032	0.0042	-0.012	0.0109
rs35778344	6	28599105	A	G	0.199	0.022	0.0031	-0.029	0.0088
rs3130048	6	31613739	C	T	0.281	0.022	0.0027	-0.006	0.0072
rs9277988	6	33306235	C	T	0.196	0.022	0.0031	0.004	0.0079
rs9471333	6	40362023	C	T	0.450	0.023	0.0025	0.001	0.0068
rs16895130	6	41924931	G	A	0.269	0.019	0.0028	0.005	0.0071
rs72892910	6	50816887	T	G	0.170	0.036	0.0033	0.009	0.0081
rs9320823	6	98429337	C	T	0.602	0.020	0.0025	0.011	0.0063
rs6927268	6	108865663	T	G	0.795	0.022	0.0030	0.007	0.0078
rs6926186	6	130350294	G	A	0.305	0.018	0.0027	-0.044	0.0068
rs1182199	7	2862542	C	A	0.695	0.024	0.0027	-0.017	0.0067
rs4718964	7	70038969	T	G	0.412	0.018	0.0025	0.002	0.0063
rs10269774	7	92253972	A	G	0.324	0.019	0.0026	0.019	0.0065
rs10237306	7	121955981	T	G	0.380	0.017	0.0025	0.014	0.0068
rs7845090	8	73449940	G	A	0.289	0.025	0.0027	0.012	0.0072
rs200119412	8	77224420	C	T	0.559	0.019	0.0025	-0.014	0.0062
rs4876611	8	116671848	G	A	0.716	0.022	0.0027	0.011	0.0069
rs2954021	8	126482077	G	A	0.506	0.017	0.0025	0.013	0.0063
rs9776097	9	15647348	G	T	0.559	0.023	0.0025	0.007	0.0063
rs2383766	9	28412500	T	G	0.326	0.022	0.0026	-0.003	0.0067
rs11012732	10	21830104	G	A	0.331	0.023	0.0026	0.042	0.0066
rs12357890	10	99762693	G	A	0.560	0.020	0.0025	0.002	0.0067
rs41310284	10	102447647	C	A	0.898	0.029	0.0041	0.004	0.0112
rs10510025	10	118650996	T	C	0.246	0.020	0.0029	0.001	0.0074
rs11042030	11	8690718	T	C	0.726	0.020	0.0028	-0.001	0.0069
rs11030119	11	27728102	A	G	0.309	0.031	0.0027	-0.004	0.0069
rs60572790	11	43692383	C	T	0.317	0.025	0.0027	0.010	0.0067
rs11270408	11	47818703	ATTCACT	A	0.545	0.023	0.0025	-0.002	0.0064
rs801732	11	65935502	T	A	0.642	0.020	0.0026	0.024	0.0066
rs12785906	11	66951966	G	C	0.939	0.039	0.0053	0.013	0.0162
11:130719075	11	130719075	A	ACTCC	0.526	0.017	0.0025	-0.003	0.0066
rs73041988	11	134517234	T	G	0.834	0.024	0.0033	0.002	0.0093
rs57307148	12	1033183	A	C	0.214	0.022	0.0030	0.012	0.0076
rs12367809	12	50256063	T	C	0.368	0.028	0.0026	-0.004	0.0065
rs704061	12	89771903	C	T	0.453	0.019	0.0025	0.000	0.007

rs7980305	12	108098039	C	T	0.395	0.019	0.0025	0.016	0.0066
rs147730268	12	123024476	G	T	0.912	0.047	0.0044	0.029	0.0118
rs825453	12	124508758	A	T	0.393	0.019	0.0025	0.019	0.0064
rs4477562	13	54104968	T	C	0.129	0.027	0.0037	0.010	0.0099
rs4981693	14	29680331	A	G	0.773	0.022	0.0029	-0.001	0.0075
rs12883788	14	33303540	T	C	0.459	0.017	0.0025	-0.008	0.0064
rs2370982	14	79890677	T	C	0.215	0.028	0.0030	0.011	0.0076
rs6575340	14	94023972	A	G	0.637	0.020	0.0026	-0.002	0.0065
rs4906263	14	103249127	G	C	0.346	0.019	0.0026	-0.021	0.0065
rs28399271	15	67710011	G	A	0.737	0.022	0.0028	0.001	0.0071
rs7171864	15	73227249	A	G	0.661	0.018	0.0026	0.001	0.0068
rs34769775	15	80989172	C	T	0.702	0.018	0.0027	-0.006	0.0069
rs4572348	15	84540163	A	G	0.718	0.024	0.0027	-0.009	0.0068
rs56803094	15	99222509	A	G	0.773	0.020	0.0029	-0.004	0.0075
rs13330552	16	2170528	C	T	0.821	0.024	0.0032	-0.018	0.0085
rs760118	16	4940994	A	G	0.437	0.017	0.0025	-0.015	0.0069
rs12923476	16	24798079	G	A	0.745	0.022	0.0028	0.008	0.0071
rs7498665	16	28883241	G	A	0.403	0.032	0.0025	0.004	0.0064
rs4402589	16	29954654	G	T	0.553	0.027	0.0025	-0.003	0.0063
rs7187250	16	53810546	A	C	0.393	0.062	0.0025	-0.060	0.0063
rs11866219	16	69549749	A	C	0.417	0.019	0.0025	0.016	0.0066
rs747489841	16	73095430	AAC	A	0.356	0.018	0.0026	0.008	0.0074
rs55637757	16	89535888	C	T	0.868	0.025	0.0037	0.027	0.0098
rs546133832	17	1837168	T	TA	0.845	0.031	0.0034	-0.013	0.009
rs2306593	17	34866546	C	T	0.512	0.017	0.0025	0.006	0.007
rs67856160	17	42286541	TA	T	0.227	0.022	0.0030	-0.001	0.0076
rs113866544	17	46270606	C	T	0.068	0.037	0.0049	0.009	0.0116
rs55931203	17	65854602	T	C	0.188	0.032	0.0032	0.001	0.0082
rs4889867	17	78593058	C	T	0.554	0.017	0.0025	-0.009	0.0065
rs1652376	18	21109466	G	T	0.536	0.023	0.0025	0.006	0.0063
rs575818189	18	40749468	G	GT	0.626	0.019	0.0025	0.005	0.0065
rs58084604	18	57849429	T	C	0.234	0.048	0.0029	-0.023	0.0073
rs55714539	19	18207397	C	A	0.343	0.022	0.0026	0.011	0.0067
rs113230003	19	18460956	G	A	0.740	0.019	0.0028	0.000	0.0073
rs111640872	19	30290357	C	G	0.331	0.023	0.0026	0.023	0.0066
rs28483178	19	33977206	G	C	0.303	0.021	0.0027	-0.011	0.0069
rs10423928	19	46182304	T	A	0.806	0.031	0.0031	-0.047	0.008
rs112551143	19	47557971	G	A	0.755	0.022	0.0029	-0.013	0.0076
rs35679975	20	51194941	T	C	0.808	0.024	0.0031	0.025	0.0084
rs76040172	21	46488959	G	A	0.945	0.041	0.0054	0.007	0.0144
rs13056506	22	38580917	G	T	0.401	0.020	0.0025	-0.040	0.0063
Body fat measure trait – Trunk fat percentage									
rs5773757	1	42473492	T	TA	0.285	0.019	0.0027	0.002	0.0068
rs7536940	1	50251567	T	A	0.385	0.017	0.0025	-0.008	0.0066

rs61765651	1	72754314	C	T	0.807	0.024	0.0031	-0.009	0.0082
rs3104464	1	77966230	A	G	0.225	0.022	0.0029	0.008	0.0075
rs2306937	1	113246506	C	T	0.797	0.022	0.0031	0.006	0.0077
rs115584674	1	150346106	A	G	0.941	0.045	0.0052	0.027	0.014
rs35154152	1	155172725	T	C	0.893	0.027	0.0040	0.011	0.0103
rs543874	1	177889480	G	A	0.208	0.034	0.0030	-0.030	0.0079
rs2678204	1	201800511	G	T	0.342	0.018	0.0026	-0.007	0.0066
rs2494196	1	219762581	A	C	0.288	0.032	0.0027	-0.019	0.007
rs6751993	2	635864	G	A	0.828	0.033	0.0033	-0.038	0.0082
rs10203386	2	25136866	A	T	0.452	0.028	0.0025	-0.043	0.0067
rs10084382	2	36768447	T	C	0.312	0.019	0.0027	-0.001	0.0068
rs6545714	2	59307725	G	A	0.399	0.019	0.0025	0.004	0.0064
rs58300328	2	69646357	G	A	0.591	0.018	0.0025	-0.004	0.0062
rs13391980	2	165504841	A	G	0.119	0.038	0.0038	0.008	0.0093
rs2043016	2	198146381	T	C	0.376	0.018	0.0025	0.009	0.0068
rs2943653	2	227047771	C	T	0.327	0.024	0.0026	0.001	0.0066
rs62190394	2	230624929	T	C	0.314	0.020	0.0027	-0.012	0.0066
rs7649970	3	12392272	T	C	0.121	0.041	0.0038	-0.018	0.0093
3:49959570	3	49959570	C	CA	0.525	0.020	0.0025	0.017	0.0063
rs3911063	3	85906928	T	C	0.677	0.019	0.0026	0.004	0.0066
rs4857330	3	94037499	T	C	0.448	0.018	0.0025	-0.001	0.0062
rs2312193	3	141188399	C	T	0.389	0.019	0.0025	0.033	0.0064
rs2192527	4	18329824	G	A	0.465	0.020	0.0025	0.003	0.0062
rs10938398	4	45186139	A	G	0.433	0.024	0.0025	-0.014	0.0063
rs58083390	4	73549559	T	C	0.070	0.037	0.0049	-0.001	0.0137
rs58383713	4	80796055	A	C	0.196	0.021	0.0031	0.004	0.0078
rs987469	4	89706643	C	G	0.539	0.020	0.0025	-0.004	0.0062
rs13107325	4	103188709	T	C	0.075	0.047	0.0047	0.017	0.0125
rs6893495	5	64409378	T	C	0.214	0.022	0.0030	-0.003	0.0079
rs2112347	5	75015242	T	G	0.641	0.022	0.0026	-0.018	0.0064
rs34483452	5	87986314	A	C	0.135	0.032	0.0036	-0.003	0.009
rs17055653	5	157918528	A	C	0.312	0.021	0.0027	0.017	0.0069
rs245775	5	170532105	G	A	0.729	0.020	0.0028	0.000	0.0069
rs4412193	6	26338056	A	G	0.636	0.030	0.0026	-0.014	0.0064
rs2178899	6	31606756	A	T	0.870	0.028	0.0037	-0.005	0.0096
rs3736896	6	34735883	C	T	0.204	0.035	0.0030	-0.008	0.0075
rs9471333	6	40362023	C	T	0.450	0.020	0.0025	0.001	0.0068
rs145101485	6	50886236	A	G	0.168	0.029	0.0033	0.011	0.0082
rs9320823	6	98429337	C	T	0.602	0.021	0.0025	0.011	0.0063
rs72995085	6	143193971	T	C	0.823	0.022	0.0032	0.011	0.0084
rs1182199	7	2862542	C	A	0.695	0.021	0.0027	-0.017	0.0067
rs10259620	7	27202289	A	G	0.213	0.021	0.0030	0.019	0.0076
rs4549685	7	39326478	C	T	0.670	0.019	0.0026	0.012	0.0066
rs4718964	7	70038969	T	G	0.412	0.017	0.0025	0.002	0.0063

7:130438531	7	130438531	C	CTTTTTT	0.517	0.018	0.0025	0.023	0.0067
rs7845090	8	73449940	G	A	0.289	0.023	0.0027	0.012	0.0072
rs200119412	8	77224420	C	T	0.559	0.019	0.0025	-0.014	0.0062
rs4876611	8	116671848	G	A	0.716	0.023	0.0027	0.011	0.0069
rs377741138	9	28412183	G	GAAAA	0.342	0.019	0.0026	-0.002	0.0067
rs11012732	10	21830104	G	A	0.331	0.022	0.0026	0.042	0.0066
rs10999460	10	72428283	T	C	0.266	0.025	0.0028	0.000	0.0071
rs57866767	10	96023077	T	C	0.568	0.022	0.0025	0.006	0.0063
rs12357890	10	99762693	G	A	0.560	0.018	0.0025	0.002	0.0067
rs41310284	10	102447647	C	A	0.898	0.029	0.0041	0.004	0.0112
rs61888762	11	27709630	G	C	0.322	0.025	0.0026	-0.005	0.0067
rs60572790	11	43692383	C	T	0.317	0.022	0.0027	0.010	0.0067
rs11270408	11	47818703	ATTCACT	A	0.545	0.028	0.0025	-0.002	0.0064
rs801732	11	65935502	T	A	0.642	0.019	0.0026	0.024	0.0066
rs73041988	11	134517234	T	G	0.834	0.023	0.0033	0.002	0.0093
rs12367809	12	50256063	T	C	0.368	0.025	0.0026	-0.004	0.0065
rs704061	12	89771903	C	T	0.453	0.020	0.0025	0.000	0.007
rs7980305	12	108098039	C	T	0.395	0.020	0.0025	0.016	0.0066
rs80272996	12	121994892	G	A	0.944	0.038	0.0056	0.037	0.0159
rs147730268	12	123024476	G	T	0.912	0.044	0.0044	0.029	0.0118
rs12311848	12	124486851	G	A	0.334	0.028	0.0026	0.002	0.0069
rs7982447	13	54453811	C	T	0.206	0.021	0.0030	-0.004	0.0077
rs4898973	14	59379512	T	C	0.832	0.023	0.0033	-0.006	0.0081
rs2370982	14	79890677	T	C	0.215	0.026	0.0030	0.011	0.0076
rs6575340	14	94023972	A	G	0.637	0.017	0.0026	-0.002	0.0065
rs2289791	15	67476952	G	T	0.754	0.024	0.0029	0.013	0.0073
rs7171864	15	73227249	A	G	0.661	0.020	0.0026	0.001	0.0068
rs4572348	15	84540163	A	G	0.718	0.031	0.0027	-0.009	0.0068
rs1879529	15	89414295	G	T	0.735	0.024	0.0028	-0.012	0.0082
rs72755233	15	100692953	G	A	0.887	0.026	0.0039	-0.004	0.0127
rs12923476	16	24798079	G	A	0.745	0.020	0.0028	0.008	0.0071
rs8049439	16	28837515	C	T	0.406	0.034	0.0025	0.006	0.0064
rs4402589	16	29954654	G	T	0.553	0.019	0.0025	-0.003	0.0063
rs9972653	16	53814363	T	G	0.398	0.048	0.0025	-0.060	0.0063
rs11866219	16	69549749	A	C	0.417	0.023	0.0025	0.016	0.0066
rs55637757	16	89535888	C	T	0.868	0.027	0.0037	0.027	0.0098
rs546133832	17	1837168	T	TA	0.845	0.029	0.0034	-0.013	0.009
rs67856160	17	42286541	TA	T	0.227	0.025	0.0030	-0.001	0.0076
rs208015	17	46252346	T	C	0.068	0.034	0.0049	0.008	0.0116
rs55931203	17	65854602	T	C	0.188	0.033	0.0032	0.001	0.0082
rs303754	18	21076764	T	G	0.531	0.020	0.0025	0.008	0.0063
rs2052607	18	40788387	G	A	0.655	0.021	0.0026	0.009	0.0066
rs538656	18	57850422	T	G	0.235	0.029	0.0029	-0.023	0.0073

rs11666808	19	18383506	T	C	0.374	0.025	0.0025	0.009	0.0066
rs113696534	19	30286037	GCCTGT AATC	G	0.330	0.020	0.0026	0.024	0.0066
rs731839	19	33899065	A	G	0.667	0.024	0.0026	-0.017	0.0067
rs10423928	19	46182304	T	A	0.806	0.027	0.0031	-0.047	0.008
rs394608	21	46581798	C	T	0.539	0.017	0.0025	-0.003	0.0063
rs55951234	22	38601430	C	CCT	0.419	0.025	0.0025	-0.040	0.0063
rs764034945	22	41806642	TGTGTG TGC	T	0.220	0.021	0.0030	-0.004	0.0076
Body fat measure trait – Trunk fat mass									
rs4660586	1	42407229	C	T	0.261	0.021	0.0028	-0.002	0.007
rs7536940	1	50251567	T	A	0.385	0.019	0.0025	-0.008	0.0066
rs12140153	1	62579891	G	T	0.903	0.032	0.0043	-0.012	0.0116
rs61765651	1	72754314	C	T	0.807	0.027	0.0031	-0.009	0.0082
rs3104464	1	77966230	A	G	0.225	0.027	0.0029	0.008	0.0075
rs115584674	1	150346106	A	G	0.941	0.040	0.0052	0.027	0.014
rs543874	1	177889480	G	A	0.208	0.041	0.0030	-0.030	0.0079
rs2678204	1	201800511	G	T	0.342	0.022	0.0026	-0.007	0.0066
rs2494196	1	219762581	A	C	0.288	0.026	0.0027	-0.019	0.007
rs6751993	2	635864	G	A	0.828	0.043	0.0033	0.042	0.0066
rs76286777	2	25195577	C	T	0.219	0.029	0.0030	0.000	0.0071
rs10084382	2	36768447	T	C	0.312	0.020	0.0027	0.002	0.0067
rs6545714	2	59307725	G	A	0.399	0.021	0.0025	0.004	0.0112
rs58300328	2	69646357	G	A	0.591	0.017	0.0025	-0.001	0.0069
rs78343493	2	165502911	A	G	0.119	0.030	0.0038	-0.004	0.0069
rs62190394	2	230624929	T	C	0.314	0.021	0.0027	0.010	0.0067
rs7649970	3	12392272	T	C	0.121	0.034	0.0038	-0.002	0.0064
rs9813198	3	41258048	G	A	0.493	0.017	0.0025	0.024	0.0066
3:49959570	3	49959570	C	CA	0.525	0.025	0.0025	0.012	0.0143
rs62261725	3	85898626	A	G	0.673	0.021	0.0026	0.002	0.0093
rs4857330	3	94037499	T	C	0.448	0.020	0.0025	0.012	0.0076
rs10662785	3	131620696	GTTT	G	0.273	0.021	0.0028	-0.004	0.0065
rs9858603	3	141095949	G	A	0.346	0.027	0.0026	0.000	0.007
rs3063380	3	153688656	G	GGT	0.571	0.017	0.0025	0.016	0.0066
rs66679256	4	18351898	T	C	0.446	0.021	0.0025	0.029	0.0118
rs10938398	4	45186139	A	G	0.433	0.026	0.0025	0.019	0.0064
rs13135092	4	103198082	G	A	0.083	0.042	0.0045	0.010	0.0099
rs1355603	4	145566477	C	T	0.831	0.026	0.0033	-0.001	0.0075
rs2112347	5	75015242	T	G	0.641	0.027	0.0026	0.011	0.0076
rs2052478	5	77437291	C	T	0.764	0.022	0.0029	-0.002	0.0065
rs1477290	5	87988934	C	T	0.136	0.032	0.0036	-0.021	0.0065
rs2012027	5	139086415	C	T	0.286	0.019	0.0027	0.001	0.0071
rs245775	5	170532105	G	A	0.729	0.020	0.0028	0.001	0.0068
rs2183947	6	26159356	G	A	0.776	0.040	0.0029	-0.009	0.0068
6:28405892	6	28405892	G	GAGA	0.366	0.019	0.0026	-0.012	0.0082

rs2248162	6	29915061	T	C	0.362	0.018	0.0026	-0.011	0.0071
rs2178899	6	31606756	A	T	0.870	0.030	0.0037	-0.004	0.0127
rs9277988	6	33306235	C	T	0.196	0.021	0.0031	-0.018	0.0085
rs9471333	6	40362023	C	T	0.450	0.021	0.0025	-0.015	0.0069
rs16895130	6	41924931	G	A	0.269	0.020	0.0028	0.008	0.0071
rs145101485	6	50886236	A	G	0.168	0.034	0.0033	0.006	0.0064
rs9320823	6	98429337	C	T	0.602	0.020	0.0025	-0.003	0.0063
rs314279	6	105402083	C	A	0.116	0.028	0.0038	-0.060	0.0063
rs6927268	6	108865663	T	G	0.795	0.022	0.0030	0.013	0.0063
rs7774095	6	142670862	C	A	0.717	0.019	0.0027	0.008	0.0074
rs1182199	7	2862542	C	A	0.695	0.028	0.0027	0.027	0.0098
rs4718964	7	70038969	T	G	0.412	0.019	0.0025	-0.013	0.009
rs10269774	7	92253972	A	G	0.324	0.021	0.0026	-0.001	0.0076
rs10237306	7	121955981	T	G	0.380	0.018	0.0025	0.009	0.0116
rs11779446	8	23388326	A	G	0.839	0.023	0.0034	0.001	0.0082
rs7845090	8	73449940	G	A	0.289	0.025	0.0027	0.006	0.0063
rs200119412	8	77224420	C	T	0.559	0.020	0.0025	0.005	0.0065
rs4876611	8	116671848	G	A	0.716	0.023	0.0027	-0.023	0.0073
rs2954021	8	126482077	G	A	0.506	0.017	0.0025	0.011	0.0067
rs9776097	9	15647348	G	T	0.559	0.023	0.0025	0.000	0.0073
rs16912921	9	28413461	A	C	0.325	0.021	0.0026	0.025	0.0066
rs35344761	9	78510823	C	A	0.878	0.026	0.0038	-0.011	0.0069
rs11012732	10	21830104	G	A	0.331	0.023	0.0026	-0.047	0.008
rs10999460	10	72428283	T	C	0.266	0.019	0.0028	-0.013	0.0076
rs12357890	10	99762693	G	A	0.560	0.019	0.0025	-0.038	0.0082
rs41310284	10	102447647	C	A	0.898	0.031	0.0041	-0.038	0.0078
rs11042030	11	8690718	T	C	0.726	0.020	0.0028	-0.001	0.0068
rs11030119	11	27728102	A	G	0.309	0.030	0.0027	0.004	0.0064
rs60572790	11	43692383	C	T	0.317	0.024	0.0027	-0.004	0.0062
rs11270408	11	47818703	ATTCACT	A	0.545	0.025	0.0025	0.009	0.0093
rs801732	11	65935502	T	A	0.642	0.020	0.0026	-0.012	0.0066
rs7952436	11	67024534	C	T	0.917	0.038	0.0045	0.010	0.0078
rs73041988	11	134517234	T	G	0.834	0.023	0.0033	0.012	0.0069
rs57307148	12	1033183	A	C	0.214	0.021	0.0030	0.025	0.0084
rs12367809	12	50256063	T	C	0.368	0.029	0.0026	0.007	0.0144
rs704061	12	89771903	C	T	0.453	0.020	0.0025	-0.040	0.0063
rs7980305	12	108098039	C	T	0.395	0.020	0.0025	-0.018	0.0093
rs147730268	12	123024476	G	T	0.912	0.048	0.0044	0.005	0.0062
rs825453	12	124508758	A	T	0.393	0.021	0.0025	0.017	0.0063
rs4477562	13	54104968	T	C	0.129	0.027	0.0037	0.005	0.0066
rs4981693	14	29680331	A	G	0.773	0.021	0.0029	-0.001	0.0062
rs2370982	14	79890677	T	C	0.215	0.029	0.0030	-0.003	0.0073
rs6575340	14	94023972	A	G	0.637	0.019	0.0026	0.042	0.0065
rs4906263	14	103249127	G	C	0.346	0.017	0.0026	-0.002	0.0064

rs28399271	15	67710011	G	A	0.737	0.022	0.0028	0.003	0.0063
rs7171864	15	73227249	A	G	0.661	0.019	0.0026	-0.014	0.0063
rs4572348	15	84540163	A	G	0.718	0.029	0.0027	0.018	0.0121
rs1879529	15	89414295	G	T	0.735	0.022	0.0028	-0.001	0.0084
rs12591120	15	99236869	T	C	0.742	0.019	0.0028	-0.018	0.0064
rs72755233	15	100692953	G	A	0.887	0.031	0.0039	0.005	0.0083
rs13330552	16	2170528	C	T	0.821	0.025	0.0032	-0.002	0.009
rs760118	16	4940994	A	G	0.437	0.018	0.0025	0.021	0.0077
rs12923476	16	24798079	G	A	0.745	0.022	0.0028	0.000	0.0069
rs8049439	16	28837515	C	T	0.406	0.033	0.0025	-0.004	0.0075
rs4402589	16	29954654	G	T	0.553	0.026	0.0025	-0.016	0.0071
rs9972653	16	53814363	T	G	0.398	0.058	0.0025	-0.016	0.0068
rs10530053	16	69686676	CTTTTT	C	0.590	0.019	0.0025	-0.005	0.0096
rs747489841	16	73095430	AAC	A	0.356	0.019	0.0026	0.004	0.0079
rs55637757	16	89535888	C	T	0.868	0.028	0.0037	0.001	0.0068
rs546133832	17	1837168	T	TA	0.845	0.030	0.0034	0.005	0.0071
rs67856160	17	42286541	TA	T	0.227	0.023	0.0030	0.011	0.0082
rs113866544	17	46270606	C	T	0.068	0.037	0.0049	0.011	0.0063
rs55931203	17	65854602	T	C	0.188	0.034	0.0032	0.004	0.0098
rs1652376	18	21109466	G	T	0.536	0.023	0.0025	0.007	0.0078
rs575818189	18	40749468	G	GT	0.626	0.020	0.0025	0.000	0.0069
rs6567160	18	57829135	C	T	0.234	0.045	0.0029	-0.017	0.0067
rs55714539	19	18207397	C	A	0.343	0.023	0.0026	0.002	0.0063
rs113230003	19	18460956	G	A	0.740	0.020	0.0028	0.019	0.0065
rs62104483	19	30300017	A	G	0.329	0.023	0.0026	0.014	0.0068
rs28483178	19	33977206	G	C	0.303	0.021	0.0027	0.023	0.0086
rs10423928	19	46182304	T	A	0.806	0.030	0.0031	0.012	0.0072
rs112551143	19	47557971	G	A	0.755	0.021	0.0029	-0.014	0.0062
rs34298551	20	34030606	A	G	0.212	0.022	0.0030	0.011	0.0069
rs8356	20	43536455	T	C	0.267	0.019	0.0028	0.013	0.0063
rs35679975	20	51194941	T	C	0.808	0.023	0.0031	0.007	0.0063
rs76040172	21	46488959	G	A	0.945	0.039	0.0054	-0.003	0.0067
rs55951234	22	38601430	C	CCT	0.419	0.022	0.0025	-0.010	0.0106
Body fat measure trait – Body fat percentage adjusted for BMI									
rs1763838	1	8473331	A	G	0.342	0.018	0.0026	0.008	0.0071
rs9442571	1	9349611	A	T	0.130	0.029	0.0037	-0.005	0.0102
rs11121542	1	10393920	A	G	0.122	0.032	0.0038	-0.002	0.0093
rs2311528	1	17309540	G	A	0.730	0.020	0.0028	0.009	0.0073
rs10888851	1	54893163	C	G	0.876	0.026	0.0038	0.002	0.0102
rs3102053	1	103422730	C	T	0.271	0.020	0.0028	0.000	0.007
rs2303875	1	109955010	A	C	0.717	0.019	0.0027	-0.012	0.007
rs17030651	1	113239382	G	A	0.796	0.028	0.0031	0.006	0.0077
rs6428789	1	119550480	C	A	0.571	0.017	0.0025	0.004	0.0064
rs12058281	1	149928679	A	G	0.775	0.031	0.0029	0.028	0.0074

1:170705685	1	170705685	C	CTATATATATA	0.620	0.027	0.0026	0.007	0.0068
rs1926874	1	184009788	T	C	0.350	0.018	0.0026	0.010	0.0066
rs749853052	1	219747226	T	TG	0.300	0.034	0.0027	-0.019	0.007
rs10779426	1	221323432	A	T	0.415	0.023	0.0025	0.013	0.0065
rs2777832	1	227168555	G	A	0.786	0.023	0.0030	0.005	0.0075
rs750801245	2	27674931	AAAC	A	0.840	0.029	0.0034	-0.006	0.0089
rs73924573	2	40425793	A	C	0.872	0.028	0.0037	-0.020	0.0093
rs113542380	2	43464818	A	G	0.076	0.041	0.0047	0.001	0.0119
rs4671947	2	54746366	G	T	0.270	0.019	0.0028	0.026	0.0072
rs376096585	2	56094578	C	CT	0.777	0.028	0.0030	-0.001	0.0076
rs10172212	2	58379496	C	A	0.661	0.021	0.0026	-0.007	0.0066
rs75297654	2	165545615	T	C	0.119	0.034	0.0038	0.009	0.0093
rs7585974	2	172377212	C	G	0.190	0.025	0.0031	0.024	0.0081
rs1026027	2	177070920	T	C	0.945	0.043	0.0054	-0.004	0.0144
rs55696134	2	198821569	A	G	0.523	0.025	0.0025	-0.010	0.0062
rs6715398	2	207069563	A	G	0.487	0.017	0.0025	-0.007	0.0065
rs1047891	2	211540507	C	A	0.684	0.018	0.0026	-0.011	0.007
rs60214611	2	217674017	C	CTCACAT	0.422	0.026	0.0025	0.013	0.0064
rs2943653	2	227047771	C	T	0.327	0.035	0.0026	0.001	0.0066
rs55940205	2	242065304	A	G	0.080	0.035	0.0045	-0.004	0.0123
rs13085211	3	12383265	A	G	0.121	0.049	0.0038	-0.018	0.0093
3:13596447	3	13596447	CTTTTTTT	C	0.177	0.026	0.0032	-0.003	0.0084
rs9838614	3	38537671	G	T	0.387	0.023	0.0025	-0.002	0.0069
rs339661	3	42753904	A	G	0.743	0.021	0.0028	-0.005	0.0071
3:48876040	3	48876040	T	TA	0.660	0.021	0.0026	0.004	0.0066
rs11130274	3	51163896	G	A	0.108	0.039	0.0040	0.018	0.0101
rs772585020	3	52725718	ATT	A	0.510	0.022	0.0025	0.012	0.0063
rs71298348	3	70661805	A	C	0.287	0.022	0.0027	0.010	0.0069
rs12488245	3	99835254	C	T	0.418	0.017	0.0025	0.033	0.0063
rs745372859	3	124482494	T	TTTGTTGAAC	0.130	0.026	0.0037	0.028	0.0095
rs201219764	3	133923423	A	ACACAGC	0.883	0.028	0.0038	0.019	0.0099
rs6807935	3	141114293	G	A	0.346	0.019	0.0026	0.044	0.0065
rs62271373	3	150066540	T	A	0.940	0.047	0.0053	0.012	0.0164
rs34390533	3	184030838	A	C	0.249	0.020	0.0029	-0.021	0.0074
rs6821714	4	26463980	G	A	0.141	0.027	0.0036	-0.010	0.0094
rs1047354	4	56295583	G	A	0.366	0.020	0.0026	0.001	0.0064
rs61580113	4	73543505	A	G	0.063	0.076	0.0050	-0.004	0.0141
rs710840	4	82135230	A	G	0.241	0.022	0.0029	-0.014	0.0073
4:83240238	4	83240238	TAAAAC	T	0.783	0.025	0.0030	-0.007	0.0084
rs3822072	4	89741269	G	A	0.552	0.020	0.0025	-0.001	0.0063

rs112217694	4	104641064	C	G	0.058	0.036	0.0053	-0.012	0.0134
rs70944858	4	120249383	G	GT	0.663	0.022	0.0026	0.003	0.0068
rs11727676	4	145659064	C	T	0.096	0.037	0.0042	-0.016	0.0116
4:157456418	4	157456418	AT	A	0.740	0.019	0.0028	-0.008	0.0072
rs2062708	5	32753672	C	T	0.161	0.023	0.0033	-0.001	0.009
rs256112	5	52880175	G	A	0.231	0.027	0.0029	-0.023	0.0072
rs588898	5	55797382	A	G	0.124	0.030	0.0037	0.003	0.0097
rs16893612	5	64551463	T	C	0.227	0.030	0.0029	-0.002	0.0077
5:71732116	5	71732116	TTA	T	0.250	0.022	0.0029	0.026	0.0074
rs12515004	5	88746865	C	T	0.635	0.018	0.0026	0.003	0.0068
rs5019041	5	108179863	G	A	0.238	0.022	0.0029	0.006	0.0074
rs11403418	5	115041970	CT	C	0.271	0.020	0.0028	-0.004	0.0072
rs3812049	5	127418850	G	C	0.741	0.034	0.0028	-0.032	0.0073
rs13170063	5	157895013	A	G	0.593	0.025	0.0025	0.012	0.0065
rs351855	5	176520243	G	A	0.704	0.027	0.0027	-0.019	0.0068
rs76088637	5	178507756	C	T	0.348	0.019	0.0026	0.006	0.0068
rs668674	6	2054847	A	G	0.663	0.023	0.0026	0.011	0.0068
rs4412193	6	26338056	A	G	0.636	0.031	0.0026	-0.014	0.0064
rs7766862	6	32033007	A	G	0.295	0.023	0.0027	-0.003	0.0067
6:34272180	6	34272180	GAAGGA	G	0.862	0.026	0.0036	0.008	0.0089
rs2766535	6	35691782	A	G	0.467	0.017	0.0025	-0.009	0.0062
rs6937133	6	39800014	G	A	0.241	0.021	0.0029	-0.012	0.0081
rs368393805	6	98584711	T	TAA	0.516	0.017	0.0025	0.002	0.0065
6:105373111	6	105373111	C	CT	0.321	0.032	0.0026	-0.001	0.0067
rs375609013	6	142795068	C	CT	0.721	0.023	0.0028	0.000	0.0072
rs10229964	7	1051776	G	A	0.430	0.018	0.0025	-0.010	0.0063
rs1182199	7	2862542	C	A	0.695	0.020	0.0027	-0.017	0.0067
rs12533489	7	19016933	G	C	0.844	0.026	0.0034	0.001	0.0084
rs73086541	7	20376103	C	A	0.605	0.019	0.0025	0.003	0.0063
rs2067087	7	27241660	G	C	0.285	0.026	0.0027	0.002	0.0072
rs2345701	7	46634598	G	C	0.562	0.025	0.0025	0.005	0.0064
rs2529414	7	50737831	G	A	0.224	0.022	0.0030	-0.001	0.0078
rs199980439	7	73007087	C	CA	0.876	0.025	0.0037	-0.034	0.0108
rs3763469	7	94021475	T	C	0.777	0.023	0.0030	0.014	0.0076
7:130438531	7	130438531	C	CTTTTTT	0.517	0.018	0.0025	0.023	0.0067
rs13275541	8	10541179	G	A	0.267	0.020	0.0028	0.018	0.0079
rs2645429	8	11660051	A	G	0.243	0.020	0.0029	-0.008	0.0076
rs2134964	8	89397637	A	G	0.300	0.025	0.0027	0.000	0.0068
rs7838996	8	122669480	T	C	0.506	0.018	0.0025	0.011	0.0066
rs10810471	9	15906776	C	A	0.581	0.019	0.0025	0.009	0.0063
rs35307904	9	78511889	G	A	0.878	0.040	0.0038	-0.012	0.0105
rs10124390	9	86549939	A	C	0.505	0.020	0.0025	0.012	0.0062
9:94970162	9	94970162	CT	C	0.664	0.023	0.0026	0.009	0.0069

rs8176741	9	136131461	A	G	0.060	0.040	0.0052	-0.039	0.0115
rs1414459	10	25028792	C	A	0.664	0.018	0.0026	-0.004	0.0068
rs2435382	10	43677099	T	A	0.280	0.019	0.0028	-0.010	0.0072
rs10509108	10	61340890	G	A	0.204	0.021	0.0031	0.019	0.0079
rs10998338	10	70382179	A	G	0.454	0.018	0.0025	0.006	0.0066
rs68049170	10	72432047	A	G	0.277	0.038	0.0028	0.001	0.007
rs1897191	10	77143467	G	A	0.617	0.018	0.0025	0.008	0.0067
rs11187838	10	96038686	G	A	0.568	0.046	0.0025	0.006	0.0063
rs10749052	10	112527532	G	A	0.435	0.017	0.0025	0.020	0.0062
rs74501871	11	2665357	G	A	0.093	0.029	0.0042	-0.006	0.0114
rs12419064	11	10320608	G	A	0.492	0.028	0.0025	0.025	0.0062
rs10765992	11	12843878	C	A	0.320	0.020	0.0026	0.008	0.0069
rs11029806	11	27075050	C	T	0.632	0.017	0.0026	-0.021	0.0067
rs4752860	11	47705015	A	C	0.551	0.018	0.0025	0.002	0.0063
rs35904570	11	62381703	C	CT	0.717	0.023	0.0027	-0.010	0.0075
rs7952436	11	67024534	C	T	0.917	0.044	0.0045	0.012	0.0143
rs10894192	11	130266117	A	T	0.569	0.018	0.0025	0.003	0.007
12:3346767	12	3346767	CTCT	C	0.903	0.039	0.0042	0.036	0.0121
rs3782904	12	46757985	T	C	0.393	0.021	0.0025	-0.002	0.0063
rs12228854	12	48396920	T	G	0.222	0.029	0.0030	-0.009	0.0077
rs762625671	12	51116036	G	GTTTA TTTTAT TTTAT	0.315	0.026	0.0026	0.000	0.0067
rs12426399	12	54419910	T	G	0.362	0.024	0.0026	-0.018	0.0067
rs11105468	12	90328833	A	T	0.278	0.019	0.0027	-0.004	0.0074
rs10861879	12	108609634	G	A	0.694	0.023	0.0027	0.002	0.0079
rs3847968	12	120730869	G	A	0.942	0.041	0.0053	0.033	0.0142
rs9971695	12	124413491	A	G	0.336	0.024	0.0026	0.002	0.0068
rs4759850	12	131618745	G	C	0.404	0.017	0.0025	0.000	0.0066
rs797472	13	51237659	G	T	0.401	0.017	0.0025	0.005	0.0066
rs7982613	13	76170513	G	A	0.535	0.019	0.0025	0.005	0.0062
rs12881869	14	50923249	T	C	0.071	0.033	0.0048	0.025	0.012
rs768118380	14	59385154	TAGTCT CA	T	0.837	0.030	0.0033	-0.004	0.0082
14:74988127	14	74988127	C	CCACA T	0.637	0.018	0.0026	0.001	0.0067
rs398043971	14	93112310	AG	A	0.812	0.036	0.0032	0.060	0.0084
rs4775762	15	48744005	C	T	0.775	0.025	0.0029	-0.025	0.0083
15:67366002	15	67366002	C	CATTTT	0.463	0.025	0.0025	0.016	0.0063
rs4337252	15	74226765	C	G	0.495	0.024	0.0025	-0.015	0.0062
rs17466257	15	77376183	C	A	0.604	0.022	0.0025	-0.006	0.0065
rs768397327	15	84575367	C	CCACA CACCA	0.514	0.056	0.0025	-0.007	0.0062
rs1879529	15	89414295	G	T	0.735	0.046	0.0028	-0.012	0.0082
rs72755233	15	100692953	G	A	0.887	0.059	0.0039	-0.004	0.0127
rs72761142	16	1663250	T	A	0.909	0.030	0.0043	-0.022	0.0112

rs12928404	16	28847246	C	T	0.410	0.019	0.0025	0.008	0.0064
rs3814283	16	50268817	G	T	0.261	0.022	0.0028	0.003	0.0074
rs7187250	16	53810546	C	A	0.607	0.019	0.0025	0.060	0.0063
16:68305708	16	68305708	T	TTTTC	0.099	0.029	0.0042	0.017	0.0102
rs7197999	16	75278920	T	C	0.524	0.018	0.0025	-0.011	0.0064
rs4888156	16	81604256	T	C	0.340	0.021	0.0026	0.007	0.0071
rs4328458	16	86424293	A	G	0.443	0.020	0.0025	0.002	0.0065
rs7200366	16	89679266	A	C	0.865	0.029	0.0036	0.017	0.01
rs2447091	17	2296014	C	T	0.390	0.019	0.0025	-0.006	0.007
rs78744936	17	7461343	A	G	0.268	0.019	0.0028	-0.003	0.0071
rs9893756	17	42321109	T	C	0.295	0.026	0.0027	-0.001	0.0069
rs59435462	17	43750921	TA	T	0.758	0.029	0.0029	0.040	0.0074
rs199440	17	44781030	G	C	0.798	0.028	0.0031	0.041	0.008
rs558985606	17	46388141	T	TA	0.766	0.020	0.0029	-0.011	0.0074
17:47423912	17	47423912	TCAAA	T	0.631	0.031	0.0026	-0.014	0.0065
rs28855509	17	65998167	C	T	0.221	0.023	0.0030	0.007	0.0078
rs12979274	19	10000925	T	C	0.486	0.022	0.0025	-0.011	0.0062
rs11666569	19	17214073	T	C	0.285	0.023	0.0027	-0.026	0.0068
rs7247222	19	18392873	C	A	0.367	0.031	0.0026	0.007	0.0066
rs62102718	19	33891013	A	T	0.715	0.030	0.0027	-0.019	0.0072
rs1884762	20	21124667	C	G	0.662	0.019	0.0026	0.003	0.0067
rs61734651	20	61451332	T	C	0.072	0.048	0.0050	-0.014	0.0147
rs9985046	21	18074927	A	T	0.701	0.020	0.0027	-0.004	0.0069
rs4820325	22	38599978	G	A	0.419	0.030	0.0025	-0.040	0.0063
rs5995843	22	40697377	G	A	0.349	0.019	0.0026	0.039	0.0065
rs28638318	22	41753059	A	G	0.234	0.027	0.0029	-0.005	0.0075
rs9614667	22	45830049	A	G	0.163	0.023	0.0033	0.008	0.0087
Body fat measure trait – Whole body fat mass adjusted for BMI									
rs9442571	1	9349611	A	T	0.130	0.045	0.0037	-0.005	0.0102
rs2311528	1	17309540	G	A	0.730	0.033	0.0028	0.009	0.0073
rs57707706	1	41742155	A	G	0.218	0.021	0.0030	-0.010	0.0075
1:47905555	1	47905555	AG	A	0.403	0.017	0.0025	-0.007	0.0065
rs797906	1	54190695	A	C	0.342	0.019	0.0026	0.008	0.0065
rs10888851	1	54893163	C	G	0.876	0.035	0.0038	0.002	0.0102
rs3104464	1	77966230	A	G	0.225	0.021	0.0029	0.008	0.0075
rs10922478	1	89144053	G	A	0.563	0.021	0.0025	0.017	0.0063
rs111866095	1	93074952	TTGCTC AGGCTG GAG	T	0.894	0.030	0.0040	0.006	0.0102
rs2061708	1	103417203	G	C	0.409	0.027	0.0025	-0.002	0.0063
rs6680912	1	110054361	T	A	0.759	0.021	0.0029	-0.016	0.0072
rs1106287	1	113242122	T	G	0.795	0.036	0.0030	0.006	0.0076
rs7534091	1	118864616	A	G	0.740	0.037	0.0028	0.015	0.0073
rs12121447	1	120216971	C	T	0.860	0.027	0.0036	0.023	0.0092
rs72692823	1	149910775	T	C	0.854	0.049	0.0035	0.035	0.0087

rs11584388	1	151169752	G	T	0.834	0.031	0.0033	0.021	0.0083
rs10918158	1	165350347	G	C	0.621	0.018	0.0025	0.005	0.0065
rs4656794	1	170649279	A	G	0.371	0.028	0.0026	-0.003	0.0068
rs55656112	1	172189764	C	A	0.212	0.042	0.0030	-0.007	0.0076
rs1327124	1	184014199	G	A	0.360	0.041	0.0026	0.010	0.0066
rs533867335	1	212516190	CT	C	0.213	0.023	0.0030	-0.008	0.0076
rs6683598	1	218617900	T	C	0.286	0.029	0.0027	0.004	0.0068
rs2494196	1	219762581	A	C	0.288	0.037	0.0027	-0.019	0.007
rs10779426	1	221323432	A	T	0.415	0.028	0.0025	0.013	0.0065
rs7540754	1	227850588	T	A	0.827	0.042	0.0033	0.007	0.0085
rs60843830	2	286756	G	C	0.348	0.020	0.0026	0.017	0.0066
rs66753271	2	1642790	C	T	0.080	0.035	0.0045	0.003	0.0124
rs1369703	2	25481898	C	T	0.417	0.033	0.0025	0.035	0.0066
rs1010644	2	33288414	G	C	0.781	0.024	0.0030	0.003	0.0074
rs4670893	2	33360848	C	G	0.707	0.026	0.0027	-0.006	0.0068
rs848606	2	36770736	G	T	0.672	0.026	0.0026	0.005	0.0067
rs746060063	2	38006242	A	AAGAC	0.500	0.022	0.0025	-0.009	0.0077
rs440056	2	40393223	C	G	0.794	0.023	0.0031	-0.012	0.0078
rs149290349	2	43451957	A	G	0.075	0.041	0.0047	0.001	0.012
rs4671222	2	54741020	C	A	0.270	0.020	0.0028	0.025	0.0072
rs376096585	2	56094578	C	CT	0.777	0.063	0.0030	-0.001	0.0076
rs10641725	2	58385305	T	TCTTA	0.658	0.021	0.0026	-0.007	0.0066
rs112210761	2	69318443	C	G	0.749	0.025	0.0029	0.004	0.0072
rs35826222	2	69450314	A	C	0.417	0.020	0.0025	0.023	0.0067
rs6731022	2	88917035	C	G	0.342	0.023	0.0026	0.024	0.0065
rs66989638	2	106689736	A	G	0.120	0.030	0.0038	0.006	0.0104
rs4848125	2	121620096	G	A	0.495	0.017	0.0025	0.004	0.0067
rs3835930	2	165659058	GT	G	0.621	0.020	0.0026	-0.005	0.0066
rs1026027	2	177070920	T	C	0.945	0.039	0.0054	-0.004	0.0144
rs57669318	2	198823642	A	C	0.524	0.024	0.0025	-0.010	0.0062
rs60214611	2	217674017	C	CTCAC AT	0.422	0.023	0.0025	0.013	0.0064
rs13029742	2	220035118	C	A	0.696	0.030	0.0027	-0.013	0.0068
rs6761041	2	225030129	T	C	0.556	0.020	0.0025	0.002	0.0062
rs2943653	2	227047771	C	T	0.327	0.031	0.0026	0.001	0.0066
rs3100618	2	232916347	C	A	0.916	0.046	0.0044	0.024	0.0115
rs62187373	2	242028406	A	G	0.088	0.038	0.0043	-0.003	0.0118
rs7647481	3	12391813	A	G	0.121	0.048	0.0038	-0.018	0.0093
rs2731341	3	13562575	C	G	0.104	0.046	0.0041	-0.009	0.0107
rs9835390	3	25401189	T	G	0.509	0.017	0.0025	-0.006	0.0066
rs773291508	3	38044996	C	CTCA	0.162	0.027	0.0034	-0.002	0.009
rs5743395	3	41269152	T	A	0.475	0.018	0.0025	0.005	0.0062
rs12492075	3	43068569	A	G	0.830	0.024	0.0033	-0.003	0.0084
rs62260708	3	47553806	C	T	0.809	0.028	0.0031	-0.016	0.008
rs35351750	3	49128061	CA	C	0.651	0.025	0.0026	0.003	0.0067

rs11130252	3	50591727	A	G	0.125	0.047	0.0037	0.026	0.0095
rs4355273	3	51706179	C	G	0.143	0.037	0.0035	0.009	0.0092
rs11130321	3	52762698	C	T	0.596	0.028	0.0025	0.008	0.0063
rs7641375	3	57568444	A	C	0.374	0.020	0.0025	-0.004	0.0064
rs73093079	3	61547274	G	A	0.894	0.034	0.0040	-0.013	0.0111
rs6793260	3	70705096	G	A	0.287	0.024	0.0027	0.007	0.0069
rs9821691	3	72396902	G	T	0.571	0.029	0.0025	0.016	0.0066
3:99298043	3	99298043	C	CT	0.366	0.022	0.0026	0.022	0.0066
rs17282078	3	124481760	A	T	0.131	0.028	0.0036	0.027	0.0093
rs6762578	3	128992047	A	G	0.778	0.028	0.0030	0.005	0.0085
rs201219764	3	133923423	A	ACACAGC	0.883	0.030	0.0038	0.019	0.0099
rs35320690	3	135932494	T	C	0.725	0.031	0.0028	-0.004	0.0069
rs6440008	3	141154542	C	T	0.387	0.054	0.0025	0.042	0.0065
rs1996711	3	146980646	T	C	0.504	0.017	0.0025	0.004	0.0062
rs62271373	3	150066540	T	A	0.940	0.048	0.0053	0.012	0.0164
rs59833847	3	156942911	T	TA	0.750	0.022	0.0029	0.001	0.0074
3:171924883	3	171924883	TG	T	0.517	0.024	0.0025	-0.003	0.0066
rs2194411	3	185548663	A	G	0.128	0.041	0.0037	0.000	0.0103
rs61732778	3	187443314	A	G	0.071	0.038	0.0048	-0.018	0.0128
rs62288581	4	8609848	G	A	0.581	0.020	0.0025	0.012	0.0064
rs33935568	4	12965756	A	AC	0.545	0.022	0.0025	0.010	0.0066
rs2610989	4	18022834	T	C	0.261	0.034	0.0028	0.012	0.0072
rs10018344	4	48498670	G	C	0.503	0.021	0.0025	0.024	0.0062
rs200697317	4	56291620	C	CAA	0.305	0.025	0.0027	0.007	0.0067
rs12645070	4	57770106	A	G	0.183	0.026	0.0032	0.020	0.0078
rs4694504	4	73496691	G	A	0.474	0.044	0.0025	0.007	0.0065
rs61371439	4	82195349	C	T	0.312	0.041	0.0027	-0.011	0.0068
rs3822076	4	89709908	T	A	0.540	0.017	0.0025	-0.003	0.0062
rs17600719	4	100563999	A	G	0.160	0.024	0.0034	-0.008	0.0087
rs2086646	4	104585957	T	C	0.151	0.027	0.0034	-0.017	0.0091
rs10010325	4	106106353	A	C	0.483	0.022	0.0025	0.031	0.0062
rs10029669	4	120619666	C	T	0.656	0.024	0.0026	-0.004	0.0066
rs7680661	4	145565116	A	G	0.831	0.065	0.0033	-0.001	0.0084
rs62330032	5	330557	C	T	0.058	0.042	0.0053	0.066	0.0141
rs3792752	5	32768634	G	A	0.259	0.034	0.0028	0.004	0.0076
rs10072767	5	53118818	A	G	0.399	0.022	0.0025	-0.014	0.0063
rs25757	5	55804204	G	C	0.124	0.035	0.0037	0.002	0.0097
rs6449778	5	64563813	A	G	0.537	0.024	0.0025	-0.019	0.0066
rs72776486	5	77515056	C	A	0.766	0.020	0.0029	0.005	0.0084
rs10065531	5	88744406	A	T	0.635	0.025	0.0026	0.002	0.0068
rs62361342	5	108120115	A	G	0.227	0.033	0.0029	0.005	0.0074
rs11403418	5	115041970	CT	C	0.271	0.031	0.0028	-0.004	0.0072
rs154001	5	127685135	T	C	0.676	0.021	0.0026	0.003	0.0067
rs157577	5	131563571	C	G	0.721	0.024	0.0028	0.016	0.0071

rs578475	5	134354896	C	G	0.695	0.021	0.0027	0.009	0.0069
rs6881817	5	157887966	C	T	0.742	0.021	0.0028	0.007	0.0072
rs112851629	5	170870505	A	T	0.766	0.025	0.0029	0.000	0.0078
rs702101	5	171276393	A	G	0.597	0.028	0.0025	-0.014	0.0076
rs10866665	5	172975691	C	T	0.406	0.018	0.0025	0.009	0.0064
rs6556301	5	176527577	T	G	0.372	0.037	0.0026	-0.010	0.0065
rs888762	5	178547313	C	A	0.334	0.026	0.0026	0.009	0.0069
rs34704166	5	179740398	T	C	0.670	0.020	0.0026	0.009	0.0072
rs501038	6	2056603	C	G	0.664	0.028	0.0026	0.011	0.0068
rs876122	6	6886297	G	A	0.879	0.028	0.0038	0.020	0.0104
rs9392172	6	7723962	G	C	0.470	0.025	0.0025	-0.001	0.0062
rs62390280	6	14836562	C	G	0.084	0.031	0.0044	0.012	0.0113
rs4412193	6	26338056	A	G	0.636	0.053	0.0026	-0.014	0.0064
rs2263297	6	30441652	C	T	0.857	0.027	0.0035	0.005	0.0089
rs28732146	6	31561353	T	A	0.803	0.028	0.0031	0.011	0.0078
rs112540634	6	34623905	T	C	0.136	0.053	0.0036	-0.011	0.0089
rs1319012	6	41852616	T	A	0.074	0.034	0.0048	-0.001	0.0125
rs6938592	6	45097503	T	A	0.743	0.022	0.0028	-0.010	0.007
rs7745990	6	47488387	A	G	0.689	0.027	0.0027	0.001	0.0067
rs10943249	6	76199219	T	C	0.114	0.034	0.0039	0.019	0.0102
rs4639293	6	81757092	T	C	0.799	0.027	0.0031	-0.001	0.0081
6:105373111	6	105373111	C	CT	0.321	0.055	0.0026	-0.001	0.0067
rs1931897	6	116440007	C	A	0.282	0.027	0.0027	-0.010	0.0071
6:131317527	6	131317527	G	GC	0.386	0.024	0.0025	-0.009	0.0065
rs7764488	6	133812872	A	G	0.320	0.019	0.0026	0.005	0.0072
rs7774095	6	142670862	C	A	0.717	0.052	0.0027	0.000	0.0069
rs3020434	6	152358940	T	C	0.168	0.030	0.0033	0.002	0.0082
rs10622588	6	164122040	CCATG	C	0.132	0.028	0.0036	0.013	0.0104
rs2763265	6	168814600	A	G	0.757	0.029	0.0029	-0.012	0.0072
rs10229964	7	1051776	G	A	0.430	0.017	0.0025	-0.010	0.0063
rs798488	7	2802522	T	C	0.700	0.050	0.0027	-0.014	0.0068
rs141773762	7	5366653	G	A	0.885	0.028	0.0039	0.011	0.0116
rs1178142	7	18773635	T	C	0.202	0.022	0.0031	0.003	0.0077
rs113657755	7	19638940	TG	T	0.184	0.022	0.0032	0.013	0.0082
rs34134267	7	20417034	C	A	0.575	0.029	0.0025	0.003	0.0062
rs11769806	7	23480132	A	T	0.754	0.022	0.0029	-0.021	0.0073
rs849141	7	28185091	A	G	0.291	0.046	0.0027	-0.009	0.0069
rs17157112	7	28779946	T	G	0.529	0.019	0.0025	-0.006	0.0062
rs28844277	7	35233589	C	T	0.628	0.019	0.0026	-0.004	0.0067
rs5883629	7	38099909	CT	C	0.652	0.021	0.0026	-0.009	0.0067
rs1007358	7	46201355	G	A	0.213	0.028	0.0030	0.000	0.0079
rs2529414	7	50737831	G	A	0.224	0.026	0.0030	-0.001	0.0078
rs2946580	7	65531842	G	A	0.260	0.021	0.0028	0.003	0.0071
7:72692718	7	72692718	T	TAC	0.871	0.026	0.0038	-0.021	0.011

rs7804293	7	92287849	G	T	0.269	0.037	0.0028	0.026	0.0069
rs3763469	7	94021475	T	C	0.777	0.022	0.0030	0.014	0.0076
rs4730073	7	104855871	C	A	0.359	0.019	0.0026	-0.004	0.0067
rs1404264	7	120788347	C	A	0.610	0.019	0.0025	0.001	0.0064
rs3812277	7	135067234	C	T	0.651	0.018	0.0026	0.006	0.0069
rs273958	7	137599375	C	T	0.595	0.021	0.0025	0.003	0.0065
rs822530	7	148631555	T	A	0.795	0.037	0.0031	0.005	0.0081
8:8661026	8	8661026	CA	C	0.512	0.019	0.0025	0.019	0.0075
rs4368940	8	10526742	T	C	0.410	0.021	0.0025	0.014	0.007
rs10903343	8	11695872	T	C	0.464	0.018	0.0025	0.008	0.0071
rs76289108	8	13218849	A	G	0.266	0.021	0.0028	0.010	0.0071
rs62501195	8	24041988	A	C	0.828	0.030	0.0033	0.003	0.0089
rs1506871	8	25314571	G	C	0.642	0.017	0.0026	-0.005	0.0064
rs62515432	8	57123523	C	T	0.209	0.028	0.0030	0.002	0.0079
rs2925155	8	75886297	C	T	0.739	0.021	0.0028	-0.006	0.0072
rs6473015	8	78178485	C	A	0.286	0.019	0.0027	0.021	0.0068
rs2134964	8	89397637	A	G	0.300	0.021	0.0027	0.000	0.0068
rs4876361	8	117566387	G	A	0.276	0.021	0.0028	0.011	0.0068
rs2249015	8	120605652	A	G	0.242	0.020	0.0029	0.004	0.0074
rs10088006	8	122665121	A	G	0.507	0.018	0.0025	0.009	0.0066
rs4501553	8	130718314	G	A	0.674	0.020	0.0026	0.005	0.0067
rs28716235	8	135602976	A	C	0.628	0.020	0.0026	0.012	0.0064
rs4961303	8	141950320	T	A	0.706	0.020	0.0027	0.005	0.0068
rs4072020	8	143997415	C	T	0.448	0.018	0.0025	0.012	0.0069
rs6988451	8	145247168	G	A	0.602	0.023	0.0025	-0.009	0.0074
rs539864802	9	17023805	G	GA	0.846	0.028	0.0035	0.009	0.0089
rs35307904	9	78511889	G	A	0.878	0.066	0.0038	-0.012	0.0105
rs796007	9	86577541	A	G	0.251	0.030	0.0028	0.010	0.007
rs461289	9	89052563	T	C	0.711	0.022	0.0027	0.013	0.0068
rs277742	9	89745271	G	T	0.452	0.022	0.0025	0.004	0.0062
rs734765	9	90852610	C	T	0.212	0.025	0.0030	-0.007	0.0084
9:94970162	9	94970162	CT	C	0.664	0.027	0.0026	0.009	0.0069
rs1984119	9	98368761	T	C	0.742	0.032	0.0028	0.013	0.0074
rs34575265	9	108943801	C	T	0.721	0.029	0.0027	-0.012	0.0068
rs953489	9	114188671	T	C	0.427	0.017	0.0025	-0.012	0.0063
rs10797291	9	127016044	T	C	0.388	0.017	0.0025	0.018	0.0065
rs10901208	9	133462640	T	C	0.647	0.027	0.0026	0.004	0.0068
rs8176741	9	136131461	A	G	0.060	0.038	0.0052	-0.039	0.0115
rs3824359	9	139105229	C	T	0.142	0.034	0.0035	0.017	0.0097
rs72775768	9	139324574	T	C	0.290	0.019	0.0027	0.016	0.0069
rs1251015	10	12974824	A	G	0.648	0.021	0.0026	-0.008	0.0067
rs6481490	10	28197441	G	C	0.527	0.017	0.0025	0.000	0.0062
rs113059026	10	32158478	C	A	0.689	0.020	0.0027	0.021	0.0068
rs2435373	10	43693727	A	G	0.277	0.021	0.0028	-0.010	0.0072

rs10509108	10	61340890	G	A	0.204	0.023	0.0031	0.019	0.0079
rs7924036	10	65191645	T	G	0.503	0.019	0.0025	-0.025	0.0062
rs11818897	10	70616199	G	A	0.924	0.038	0.0047	0.006	0.0119
10:72431265	10	72431265	G	GAATA T	0.277	0.033	0.0028	0.000	0.0071
rs1628023	10	80924258	G	T	0.566	0.028	0.0025	-0.013	0.0063
rs2631676	10	93037409	G	A	0.190	0.027	0.0031	0.000	0.008
rs11187838	10	96038686	G	A	0.568	0.036	0.0025	0.006	0.0063
rs7913418	10	97808509	A	G	0.641	0.025	0.0026	0.013	0.0068
rs4604804	10	99878997	A	G	0.428	0.021	0.0025	0.003	0.0062
rs3839934	10	104352124	C	CCATT T	0.569	0.024	0.0025	0.005	0.0063
rs12220358	10	105481068	G	T	0.244	0.021	0.0029	0.006	0.0072
rs11198821	10	120965341	G	A	0.104	0.033	0.0040	0.013	0.0105
rs7079914	10	123393509	G	C	0.811	0.026	0.0031	0.010	0.008
rs11245321	10	126323279	T	C	0.304	0.023	0.0027	0.022	0.0067
rs496298	10	131355130	G	A	0.657	0.021	0.0026	0.003	0.0066
rs4244808	11	2163110	G	T	0.460	0.018	0.0025	0.016	0.0062
rs149419928	11	2813004	TG	T	0.113	0.037	0.0040	-0.019	0.0108
rs4757060	11	12842990	G	A	0.424	0.027	0.0025	0.003	0.0063
rs61885960	11	14819828	A	T	0.055	0.039	0.0055	0.031	0.0146
rs7130826	11	17037793	G	T	0.273	0.022	0.0028	0.005	0.0073
rs11029806	11	27075050	C	T	0.632	0.018	0.0026	-0.021	0.0067
rs7943600	11	28887217	G	A	0.568	0.017	0.0025	-0.007	0.0063
rs2863714	11	45952311	G	A	0.912	0.032	0.0044	0.007	0.0109
rs603061	11	61018328	C	A	0.163	0.024	0.0034	-0.002	0.0094
rs11231172	11	62412944	C	T	0.690	0.020	0.0027	-0.014	0.0072
rs56223081	11	65961498	G	T	0.946	0.058	0.0056	0.034	0.0159
rs7952436	11	67024534	C	T	0.917	0.090	0.0045	0.012	0.0143
rs72940413	11	69202148	C	T	0.907	0.031	0.0043	0.023	0.0104
rs584961	11	75277628	A	G	0.115	0.046	0.0039	0.035	0.0108
11:77968055	11	77968055	G	GT	0.159	0.023	0.0034	-0.010	0.0086
rs610476	11	86184102	A	G	0.411	0.017	0.0025	0.000	0.0063
rs6589961	11	122820281	T	C	0.568	0.020	0.0025	-0.011	0.0063
rs10893812	11	127932610	G	C	0.814	0.022	0.0032	-0.011	0.0085
rs10894192	11	130266117	A	T	0.569	0.020	0.0025	0.003	0.007
rs215226	12	591300	G	A	0.402	0.022	0.0025	-0.007	0.0063
rs7139060	12	28693144	A	G	0.670	0.036	0.0026	0.047	0.0066
rs12228854	12	48396920	T	G	0.222	0.030	0.0030	-0.009	0.0077
rs762625671	12	51116036	G	GTTTA TTTTAT TTTAT	0.315	0.031	0.0026	0.000	0.0067
rs894736	12	54418166	G	A	0.363	0.020	0.0026	-0.020	0.0067
rs703842	12	58162739	A	G	0.671	0.023	0.0026	-0.009	0.0066
rs6581627	12	65719229	G	C	0.478	0.022	0.0025	-0.006	0.0062
rs8756	12	66359752	C	A	0.484	0.030	0.0025	-0.006	0.0062

rs11177668	12	69828528	G	T	0.259	0.022	0.0028	0.004	0.0077
rs9705466	12	77654536	A	G	0.751	0.020	0.0029	-0.002	0.0073
rs17018712	12	91496137	C	T	0.138	0.029	0.0036	-0.013	0.0095
rs11107120	12	93985482	C	T	0.222	0.027	0.0030	0.010	0.0075
rs10777561	12	94331007	G	A	0.594	0.020	0.0025	-0.007	0.0067
rs11111109	12	102366156	T	C	0.504	0.017	0.0025	0.002	0.0067
rs7980305	12	108098039	C	T	0.395	0.021	0.0025	0.016	0.0066
rs2062506	12	123084836	G	A	0.736	0.026	0.0028	0.016	0.0071
rs12305360	12	124804566	A	G	0.127	0.031	0.0038	0.006	0.0096
rs7995591	13	91991743	A	G	0.223	0.028	0.0030	0.012	0.0075
rs76140469	13	114749713	T	A	0.903	0.032	0.0042	-0.011	0.0108
rs4898855	14	55268319	T	G	0.554	0.019	0.0025	0.000	0.0068
rs10131381	14	59278143	T	C	0.833	0.032	0.0033	-0.004	0.0081
rs28711886	14	61072658	G	A	0.320	0.020	0.0027	0.004	0.0067
rs862048	14	74982149	G	A	0.657	0.032	0.0026	-0.001	0.0066
rs11466414	14	76447850	G	A	0.930	0.040	0.0048	-0.005	0.0132
rs76497846	14	92531888	G	A	0.635	0.027	0.0026	-0.008	0.0064
rs117068593	14	93118229	C	T	0.811	0.022	0.0032	0.059	0.0083
rs4775762	15	48744005	C	T	0.775	0.033	0.0029	-0.025	0.0083
rs73408568	15	51379196	C	T	0.783	0.021	0.0030	0.021	0.0075
rs35874463	15	67457698	G	A	0.058	0.085	0.0053	0.067	0.0142
rs7177657	15	70041693	T	C	0.896	0.044	0.0040	-0.002	0.0106
rs8039718	15	70356150	T	C	0.179	0.028	0.0032	0.016	0.0084
rs4886778	15	74225388	A	C	0.495	0.036	0.0025	-0.015	0.0062
15:75786472	15	75786472	C	CATAT	0.510	0.019	0.0025	-0.003	0.0063
rs17466257	15	77376183	C	A	0.604	0.026	0.0025	-0.006	0.0065
rs768397327	15	84575367	C	CCACA CACCA	0.514	0.075	0.0025	-0.007	0.0062
rs1879529	15	89414295	G	T	0.735	0.060	0.0028	-0.012	0.0082
rs72755233	15	100692953	G	A	0.887	0.096	0.0039	-0.004	0.0127
rs62621400	15	101718239	C	G	0.943	0.058	0.0053	0.022	0.0138
rs75516813	16	2179719	G	A	0.928	0.044	0.0048	-0.025	0.0126
rs59945160	16	4356206	G	C	0.231	0.022	0.0030	0.009	0.0078
16:19707417	16	19707417	A	AG	0.131	0.026	0.0037	0.010	0.0098
rs12103006	16	24726237	G	A	0.571	0.021	0.0025	0.001	0.0063
rs11642449	16	28896015	T	C	0.358	0.023	0.0026	0.000	0.0066
rs3814283	16	50268817	G	T	0.261	0.022	0.0028	0.003	0.0074
16:68305708	16	68305708	T	TTTTC	0.099	0.031	0.0042	0.017	0.0102
rs7197999	16	75278920	T	C	0.524	0.017	0.0025	-0.011	0.0064
rs4569296	16	78331032	A	G	0.361	0.018	0.0026	-0.013	0.0066
rs62046625	16	81578706	A	G	0.116	0.031	0.0038	0.006	0.0106
rs12928375	16	82200011	T	C	0.132	0.025	0.0036	-0.017	0.0103
rs75309741	16	84893698	CCTTCC TCT	C	0.789	0.024	0.0031	0.002	0.0083
rs4843585	16	87320279	C	A	0.758	0.022	0.0029	-0.004	0.0075

rs7191697	16	89678165	G	A	0.900	0.043	0.0041	0.018	0.0115
rs77612020	17	400799	G	A	0.892	0.028	0.0040	-0.010	0.0102
rs4790812	17	1618135	G	A	0.711	0.022	0.0027	-0.001	0.0071
rs2605134	17	18130144	C	T	0.394	0.021	0.0025	-0.010	0.0064
rs542939	17	27889986	C	T	0.656	0.023	0.0026	0.019	0.0073
rs7223535	17	29211667	G	A	0.730	0.033	0.0028	0.044	0.007
rs11656316	17	42313644	G	A	0.293	0.020	0.0027	0.000	0.0069
rs552290972	17	43947883	T	G	0.786	0.030	0.0030	0.048	0.008
rs35701113	17	45882237	G	T	0.816	0.031	0.0032	0.004	0.0083
rs521833	17	46892436	G	A	0.640	0.023	0.0026	-0.001	0.0064
17:47423912	17	47423912	TCAAA	T	0.631	0.038	0.0026	-0.014	0.0065
rs1401795	17	54839652	A	G	0.500	0.024	0.0025	0.000	0.0068
rs7214743	17	59498052	A	G	0.330	0.027	0.0026	0.011	0.0066
rs2006122	17	61987405	T	A	0.271	0.025	0.0028	0.009	0.007
rs72856681	17	63551948	G	A	0.891	0.030	0.0040	0.002	0.0106
17:65822573	17	65822573	C	CAG	0.196	0.031	0.0031	0.002	0.0079
rs12602679	17	68064408	T	C	0.353	0.018	0.0026	0.011	0.0065
rs12607903	18	3817134	C	T	0.278	0.019	0.0027	-0.009	0.0068
rs7238093	18	20728158	T	A	0.787	0.048	0.0030	-0.015	0.0077
rs62102900	18	46960814	T	C	0.664	0.024	0.0026	0.007	0.0065
rs76858784	18	53184787	G	A	0.799	0.021	0.0031	0.009	0.0081
rs11659752	18	77222862	T	G	0.687	0.020	0.0027	-0.008	0.0069
rs7249081	19	2157167	C	T	0.477	0.022	0.0025	0.015	0.0062
rs35533339	19	3438636	T	C	0.320	0.022	0.0026	0.011	0.0068
rs10853981	19	4965064	G	A	0.668	0.023	0.0026	0.024	0.0066
rs6510959	19	7184238	A	G	0.167	0.027	0.0033	-0.003	0.0084
rs8104651	19	9950127	T	C	0.562	0.020	0.0025	-0.009	0.0063
rs2305769	19	17264961	G	C	0.769	0.022	0.0029	-0.002	0.0074
rs4531856	19	18388383	C	T	0.367	0.021	0.0026	0.008	0.0066
rs8103992	19	19665643	A	C	0.199	0.030	0.0031	0.022	0.0077
rs62102718	19	33891013	A	T	0.715	0.030	0.0027	-0.019	0.0072
rs284661	19	41932120	C	T	0.388	0.022	0.0025	0.006	0.0067
rs57674902	20	4096741	T	C	0.346	0.027	0.0026	0.008	0.0071
rs1321432	20	6614691	A	C	0.371	0.039	0.0026	0.006	0.0066
rs6087571	20	32912091	G	A	0.138	0.037	0.0036	-0.002	0.0096
rs224331	20	34022387	C	A	0.342	0.037	0.0026	0.006	0.0065
rs151144289	20	39837755	T	C	0.157	0.026	0.0034	0.029	0.0086
rs73113648	20	48598974	C	T	0.896	0.027	0.0040	0.005	0.0104
rs6026704	20	57684145	C	G	0.134	0.025	0.0036	0.009	0.009
rs61734651	20	61451332	T	C	0.072	0.066	0.0050	-0.014	0.0147
rs2823991	21	18082592	T	G	0.740	0.019	0.0028	0.005	0.0072
rs229048	21	28314030	G	A	0.772	0.022	0.0029	0.002	0.0081
rs2834457	21	35712214	A	T	0.620	0.023	0.0025	0.006	0.0065
rs877382	21	38076278	T	C	0.735	0.020	0.0028	0.011	0.0071

rs11450220	22	38607534	T	TG	0.448	0.033	0.0025	-0.036	0.0063
rs3830738	22	40711227	AT	A	0.213	0.021	0.0030	0.054	0.0076
rs28638318	22	41753059	A	G	0.234	0.025	0.0029	-0.005	0.0075
rs6007043	22	45838646	C	T	0.200	0.030	0.0031	0.011	0.0079
rs4253755	22	46615376	A	G	0.129	0.028	0.0037	-0.007	0.0096
Body fat measure trait – Trunk fat percentage adjusted for BMI									
rs17400878	1	10316729	G	A	0.127	0.034	0.0037	-0.004	0.0091
rs2311528	1	17309540	G	A	0.730	0.020	0.0028	0.009	0.0073
rs3102053	1	103422730	C	T	0.271	0.021	0.0028	0.000	0.007
rs12406282	1	113238593	G	A	0.795	0.027	0.0030	0.006	0.0076
rs12058281	1	149928679	A	G	0.775	0.033	0.0029	0.028	0.0074
1:170705685	1	170705685	C	CTATATATATA	0.620	0.027	0.0026	0.007	0.0068
rs1926874	1	184009788	T	C	0.350	0.020	0.0026	0.010	0.0066
rs79112217	1	218622949	C	T	0.107	0.028	0.0040	0.011	0.0105
rs749853052	1	219747226	T	TG	0.299	0.035	0.0027	-0.019	0.007
rs10779426	1	221323432	A	T	0.415	0.022	0.0025	0.013	0.0065
rs2777832	1	227168555	G	A	0.786	0.023	0.0030	0.005	0.0075
rs12991495	2	25486770	T	C	0.689	0.019	0.0027	0.021	0.0071
rs750801245	2	27674931	AAAC	A	0.840	0.026	0.0034	-0.006	0.0089
rs73924573	2	40425793	A	C	0.872	0.026	0.0037	-0.020	0.0093
rs113542380	2	43464818	A	G	0.075	0.039	0.0047	0.001	0.0119
rs376096585	2	56094578	C	CT	0.777	0.033	0.0030	-0.001	0.0076
rs10172212	2	58379496	C	A	0.661	0.019	0.0026	-0.007	0.0066
rs35826222	2	69450314	A	C	0.417	0.018	0.0025	0.023	0.0067
rs75265117	2	165518799	G	C	0.119	0.035	0.0038	0.009	0.0093
rs1026027	2	177070920	T	C	0.945	0.041	0.0054	-0.004	0.0144
rs55696134	2	198821569	A	G	0.523	0.025	0.0025	-0.010	0.0062
rs60214611	2	217674017	C	CTCACAT	0.422	0.026	0.0025	0.013	0.0064
rs13029742	2	220035118	C	A	0.696	0.018	0.0027	-0.013	0.0068
rs2943653	2	227047771	C	T	0.327	0.033	0.0026	0.001	0.0066
rs56288586	2	242065020	C	A	0.079	0.034	0.0046	-0.004	0.0123
rs7647481	3	12391813	A	G	0.121	0.044	0.0038	-0.018	0.0093
rs2607767	3	14180552	A	G	0.377	0.018	0.0025	0.010	0.0065
rs9838614	3	38537671	G	T	0.387	0.022	0.0025	-0.002	0.0069
rs339661	3	42753904	A	G	0.743	0.020	0.0028	-0.005	0.0071
3:48876040	3	48876040	T	TA	0.660	0.022	0.0026	0.004	0.0066
rs62262097	3	49970310	G	A	0.879	0.026	0.0038	0.002	0.0105
rs11130274	3	51163896	G	A	0.108	0.036	0.0040	0.018	0.0101
rs772585020	3	52725718	ATT	A	0.510	0.022	0.0025	0.012	0.0063
rs71298348	3	70661805	A	C	0.287	0.023	0.0027	0.010	0.0069
rs12488245	3	99835254	C	T	0.418	0.017	0.0025	0.033	0.0063
rs745372859	3	124482494	T	TTTGTTGAAC	0.130	0.025	0.0037	0.028	0.0095

rs201219764	3	133923423	A	ACACA GC	0.883	0.029	0.0038	0.019	0.0099
rs56398805	3	135932400	A	G	0.724	0.020	0.0028	-0.004	0.0069
rs9866391	3	141076084	C	T	0.392	0.023	0.0025	0.045	0.0063
rs62271373	3	150066540	T	A	0.940	0.046	0.0053	0.012	0.0164
rs2048564	4	56274132	A	G	0.305	0.021	0.0027	0.006	0.0067
rs2140147	4	57792682	A	G	0.567	0.017	0.0025	0.013	0.0063
rs61580113	4	73543505	A	G	0.063	0.073	0.0050	-0.004	0.0141
rs137988704	4	82195772	CACTTC CTGATT	C	0.308	0.023	0.0027	-0.012	0.0068
4:83240238	4	83240238	TAAAAC	T	0.783	0.023	0.0030	-0.007	0.0084
rs3822076	4	89709908	T	A	0.540	0.021	0.0025	-0.003	0.0062
rs70944858	4	120249383	G	GT	0.663	0.019	0.0026	0.003	0.0068
rs11727676	4	145659064	C	T	0.096	0.038	0.0042	-0.016	0.0116
rs17035181	4	157678511	G	T	0.145	0.024	0.0035	0.003	0.0092
rs2062708	5	32753672	C	T	0.161	0.024	0.0033	-0.001	0.009
rs4501300	5	53137505	T	A	0.356	0.023	0.0026	-0.013	0.0064
rs455660	5	55816888	T	C	0.186	0.027	0.0032	-0.003	0.0082
rs1423427	5	64560698	A	G	0.227	0.029	0.0029	-0.003	0.0076
rs448809	5	88005828	G	T	0.419	0.017	0.0025	0.008	0.0063
rs5019041	5	108179863	G	A	0.238	0.023	0.0029	0.006	0.0074
rs11403418	5	115041970	CT	C	0.271	0.021	0.0028	-0.004	0.0072
rs13170063	5	157895013	A	G	0.593	0.024	0.0025	0.012	0.0065
rs351855	5	176520243	G	A	0.704	0.024	0.0027	-0.019	0.0068
rs76088637	5	178507756	C	T	0.348	0.021	0.0026	0.006	0.0068
rs668674	6	2054847	A	G	0.663	0.023	0.0026	0.011	0.0068
rs4412193	6	26338056	A	G	0.636	0.034	0.0026	-0.014	0.0064
rs7766862	6	32033007	A	G	0.295	0.019	0.0027	-0.003	0.0067
6:34272180	6	34272180	GAAGG A	G	0.862	0.026	0.0036	0.008	0.0089
rs6937133	6	39800014	G	A	0.241	0.020	0.0029	-0.012	0.0081
6:105373111	6	105373111	C	CT	0.321	0.035	0.0026	-0.001	0.0067
rs7774095	6	142670862	C	A	0.717	0.026	0.0027	0.000	0.0069
rs10229964	7	1051776	G	A	0.430	0.018	0.0025	-0.010	0.0063
rs798488	7	2802522	T	C	0.700	0.026	0.0027	-0.014	0.0068
rs12533489	7	19016933	G	C	0.844	0.026	0.0034	0.001	0.0084
rs73086541	7	20376103	C	A	0.605	0.020	0.0025	0.003	0.0063
rs2067087	7	27241660	G	C	0.285	0.026	0.0027	0.002	0.0072
rs2060186	7	46657838	T	A	0.520	0.021	0.0025	0.001	0.0065
rs2529414	7	50737831	G	A	0.224	0.024	0.0030	-0.001	0.0078
rs3763469	7	94021475	T	C	0.777	0.021	0.0030	0.014	0.0076
7:130438531	7	130438531	C	CTTTTT T	0.517	0.017	0.0025	0.023	0.0067
rs4368940	8	10526742	T	C	0.410	0.019	0.0025	0.014	0.007
rs2134964	8	89397637	A	G	0.300	0.021	0.0027	0.000	0.0068
rs7838996	8	122669480	T	C	0.506	0.019	0.0025	0.011	0.0066

rs10810471	9	15906776	C	A	0.581	0.017	0.0025	0.009	0.0063
rs35307904	9	78511889	G	A	0.878	0.042	0.0038	-0.012	0.0105
rs10124390	9	86549939	A	C	0.505	0.021	0.0025	0.012	0.0062
9:94970162	9	94970162	CT	C	0.664	0.025	0.0026	0.009	0.0069
rs505922	9	136149229	C	T	0.318	0.019	0.0026	0.016	0.0065
rs12378391	9	139086666	A	C	0.166	0.024	0.0033	0.010	0.0093
rs2435382	10	43677099	T	A	0.280	0.019	0.0028	-0.010	0.0072
rs10509108	10	61340890	G	A	0.204	0.022	0.0031	0.019	0.0079
rs767673767	10	72433203	G	GA	0.276	0.035	0.0028	0.001	0.0071
rs7910087	10	77209145	C	T	0.552	0.017	0.0025	0.009	0.0066
rs11187838	10	96038686	G	A	0.568	0.040	0.0025	0.006	0.0063
11:10366873	11	10366873	A	AAAAC	0.417	0.025	0.0025	0.024	0.0064
rs6486059	11	12824581	A	G	0.425	0.017	0.0025	0.000	0.0065
rs4752860	11	47705015	A	C	0.551	0.019	0.0025	0.002	0.0063
rs35904570	11	62381703	C	CT	0.717	0.023	0.0027	-0.010	0.0075
rs7952436	11	67024534	C	T	0.917	0.048	0.0045	0.012	0.0143
rs10894192	11	130266117	A	T	0.569	0.020	0.0025	0.003	0.007
12:3338920	12	3338920	GCACAGCTGGGGCTGA	G	0.786	0.024	0.0030	0.020	0.0089
rs11049368	12	28293114	C	A	0.251	0.019	0.0028	0.010	0.007
rs3782904	12	46757985	T	C	0.393	0.019	0.0025	-0.002	0.0063
rs12228854	12	48396920	T	G	0.222	0.027	0.0030	-0.009	0.0077
rs762625671	12	51116036	G	GTTTATTTTATTTTAT	0.315	0.026	0.0026	0.000	0.0067
rs765634	12	54432997	G	A	0.366	0.021	0.0026	-0.019	0.0067
rs703842	12	58162739	A	G	0.671	0.018	0.0026	-0.009	0.0066
rs7980305	12	108098039	C	T	0.395	0.019	0.0025	0.016	0.0066
rs3847968	12	120730869	G	A	0.942	0.040	0.0053	0.033	0.0142
rs11057397	12	124419728	T	C	0.336	0.025	0.0026	0.002	0.0068
rs7982613	13	76170513	G	A	0.535	0.018	0.0025	0.005	0.0062
rs12881869	14	50923249	T	C	0.071	0.036	0.0048	0.025	0.012
rs10138637	14	59310233	G	C	0.823	0.027	0.0032	-0.003	0.0079
14:74988127	14	74988127	C	CCACAT	0.637	0.019	0.0026	0.001	0.0067
rs11624512	14	93111120	C	T	0.810	0.029	0.0031	0.057	0.0082
rs4775762	15	48744005	C	T	0.775	0.026	0.0029	-0.025	0.0083
rs4776879	15	67364320	A	T	0.433	0.025	0.0025	0.016	0.0063
rs7181877	15	67476735	G	A	0.759	0.024	0.0029	0.013	0.0073
rs4337252	15	74226765	C	G	0.495	0.026	0.0025	-0.015	0.0062
rs17466257	15	77376183	C	A	0.604	0.020	0.0025	-0.006	0.0065
rs768397327	15	84575367	C	CCACACACCA	0.514	0.052	0.0025	-0.007	0.0062
rs1879529	15	89414295	G	T	0.735	0.046	0.0028	-0.012	0.0082
rs72755233	15	100692953	G	A	0.887	0.059	0.0039	-0.004	0.0127

rs8049439	16	28837515	C	T	0.406	0.022	0.0025	0.006	0.0064
rs3814283	16	50268817	G	T	0.261	0.022	0.0028	0.003	0.0074
rs4888156	16	81604256	T	C	0.340	0.021	0.0026	0.007	0.0071
rs4843367	16	86417890	T	C	0.334	0.018	0.0026	0.005	0.0069
rs7191697	16	89678165	G	A	0.900	0.033	0.0041	0.018	0.0115
rs4790812	17	1618135	G	A	0.711	0.019	0.0027	-0.001	0.0071
rs78744936	17	7461343	A	G	0.268	0.019	0.0028	-0.003	0.0071
rs9893756	17	42321109	T	C	0.295	0.024	0.0027	-0.001	0.0069
rs552290972	17	43947883	T	G	0.786	0.033	0.0030	0.048	0.008
rs35701113	17	45882237	G	T	0.816	0.023	0.0032	0.004	0.0083
17:47423912	17	47423912	TCAAA	T	0.631	0.030	0.0026	-0.014	0.0065
rs28855509	17	65998167	C	T	0.221	0.023	0.0030	0.007	0.0078
rs10419418	19	9994286	G	A	0.717	0.023	0.0027	-0.006	0.0069
rs11666569	19	17214073	T	C	0.285	0.021	0.0027	-0.026	0.0068
rs7247222	19	18392873	C	A	0.367	0.029	0.0026	0.007	0.0066
19:19498865	19	19498865	TC	T	0.169	0.024	0.0033	0.030	0.0084
rs731839	19	33899065	A	G	0.667	0.030	0.0026	-0.017	0.0067
rs6047271	20	21126194	G	C	0.662	0.018	0.0026	0.003	0.0067
rs61734651	20	61451332	T	C	0.072	0.049	0.0050	-0.014	0.0147
rs9985046	21	18074927	A	T	0.701	0.019	0.0027	-0.004	0.0069
rs4820325	22	38599978	G	A	0.419	0.030	0.0025	-0.040	0.0063
rs5995843	22	40697377	G	A	0.349	0.018	0.0026	0.039	0.0065
rs28638318	22	41753059	A	G	0.234	0.027	0.0029	-0.005	0.0075
rs9614667	22	45830049	A	G	0.163	0.024	0.0033	0.008	0.0087
Body fat measure trait – Trunk fat mass adjusted for BMI									
rs9442571	1	9349611	A	T	0.130	0.044	0.0037	-0.005	0.0102
rs761422	1	17301780	G	A	0.492	0.026	0.0025	0.009	0.0065
rs34975537	1	32313363	A	G	0.070	0.033	0.0048	-0.016	0.0133
rs797906	1	54190695	A	C	0.342	0.018	0.0026	0.008	0.0065
rs10888851	1	54893163	C	G	0.876	0.032	0.0038	0.002	0.0102
rs10922478	1	89144053	G	A	0.563	0.020	0.0025	0.017	0.0063
rs111866095	1	93074952	TTGCTC AGGCTG GAG	T	0.894	0.030	0.0040	0.006	0.0102
rs2061708	1	103417203	G	C	0.409	0.025	0.0025	-0.002	0.0063
rs34848593	1	113240106	A	T	0.795	0.034	0.0030	0.006	0.0076
rs7534091	1	118864616	A	G	0.740	0.029	0.0028	0.015	0.0073
rs12058281	1	149928679	A	G	0.775	0.040	0.0029	0.028	0.0074
rs11584388	1	151169752	G	T	0.834	0.030	0.0033	0.021	0.0083
rs4656794	1	170649279	A	G	0.371	0.027	0.0025	-0.003	0.0068
rs1317394	1	172208204	C	T	0.212	0.038	0.0030	-0.008	0.0076
rs1327124	1	184014199	G	A	0.360	0.037	0.0026	0.010	0.0066
rs533867335	1	212516190	CT	C	0.213	0.022	0.0030	-0.008	0.0076
rs79112217	1	218622949	C	T	0.107	0.039	0.0040	0.011	0.0105
rs2494196	1	219762581	A	C	0.288	0.036	0.0027	-0.019	0.007

rs10779426	1	221323432	A	T	0.415	0.026	0.0025	0.013	0.0065
rs7540754	1	227850588	T	A	0.827	0.038	0.0033	0.007	0.0085
rs60843830	2	286756	G	C	0.348	0.020	0.0026	0.017	0.0066
rs66753271	2	1642790	C	T	0.080	0.031	0.0045	0.003	0.0124
rs1369703	2	25481898	C	T	0.417	0.029	0.0025	0.035	0.0066
rs1010644	2	33288414	G	C	0.781	0.021	0.0030	0.003	0.0074
rs4670893	2	33360848	C	G	0.707	0.023	0.0027	-0.006	0.0068
rs848606	2	36770736	G	T	0.672	0.024	0.0026	0.005	0.0067
rs17511102	2	37960613	T	A	0.091	0.035	0.0043	0.000	0.0126
rs149290349	2	43451957	A	G	0.075	0.039	0.0047	0.001	0.012
rs4671222	2	54741020	C	A	0.270	0.019	0.0028	0.025	0.0072
rs376096585	2	56094578	C	CT	0.777	0.058	0.0030	-0.001	0.0076
rs10172212	2	58379496	C	A	0.661	0.020	0.0026	-0.007	0.0066
rs112210761	2	69318443	C	G	0.749	0.024	0.0029	0.004	0.0072
rs3890787	2	69370771	C	T	0.270	0.020	0.0028	-0.006	0.0076
rs35826222	2	69450314	A	C	0.417	0.020	0.0025	0.023	0.0067
rs6731022	2	88917035	C	G	0.342	0.021	0.0026	0.024	0.0065
rs66989638	2	106689736	A	G	0.120	0.028	0.0038	0.006	0.0104
rs7647481	3	12391813	A	G	0.121	0.043	0.0038	-0.018	0.0093
rs2731341	3	13562575	C	G	0.104	0.041	0.0041	-0.009	0.0107
rs773291508	3	38044996	C	CTCA	0.162	0.027	0.0034	-0.002	0.009
rs5743395	3	41269152	T	A	0.475	0.018	0.0025	0.005	0.0062
rs12492075	3	43068569	A	G	0.830	0.025	0.0033	-0.003	0.0084
rs62260708	3	47553806	C	T	0.809	0.022	0.0031	-0.016	0.008
rs35351750	3	49128061	CA	C	0.651	0.025	0.0026	0.003	0.0067
rs4289378	3	51180779	T	C	0.083	0.051	0.0046	0.020	0.0115
rs11130321	3	52762698	C	T	0.596	0.027	0.0025	0.008	0.0063
rs7641375	3	57568444	A	C	0.374	0.019	0.0025	-0.004	0.0064
rs73093079	3	61547274	G	A	0.894	0.029	0.0040	-0.013	0.0111
rs745673	3	70705246	T	A	0.287	0.023	0.0027	0.007	0.0069
rs9821691	3	72396902	G	T	0.571	0.026	0.0025	0.016	0.0066
3:99298043	3	99298043	C	CT	0.366	0.020	0.0026	0.022	0.0066
rs745372859	3	124482494	T	TTTGTT GAAC	0.130	0.028	0.0037	0.028	0.0095
rs6762578	3	128992047	A	G	0.778	0.028	0.0030	0.005	0.0085
rs201219764	3	133923423	A	ACACA GC	0.883	0.029	0.0038	0.019	0.0099
rs35320690	3	135932494	T	C	0.724	0.029	0.0028	-0.004	0.0069
rs6440008	3	141154542	C	T	0.386	0.048	0.0025	0.042	0.0065
rs62271373	3	150066540	T	A	0.940	0.047	0.0053	0.012	0.0164
rs4325879	3	156851984	C	T	0.741	0.020	0.0028	0.000	0.007
3:171924883	3	171924883	TG	T	0.517	0.020	0.0025	-0.003	0.0066
rs2194411	3	185548663	A	G	0.128	0.038	0.0037	0.000	0.0103
rs61732778	3	187443314	A	G	0.071	0.034	0.0048	-0.018	0.0128
rs62288581	4	8609848	G	A	0.581	0.020	0.0025	0.012	0.0064

rs33935568	4	12965756	A	AC	0.545	0.021	0.0025	0.010	0.0066
rs2610989	4	18022834	T	C	0.261	0.031	0.0028	0.012	0.0072
rs10018344	4	48498670	G	C	0.503	0.019	0.0025	0.024	0.0062
rs200697317	4	56291620	C	CAA	0.305	0.023	0.0027	0.007	0.0067
rs12645070	4	57770106	A	G	0.183	0.024	0.0032	0.020	0.0078
rs4694504	4	73496691	G	A	0.474	0.041	0.0025	0.007	0.0065
rs61371439	4	82195349	C	T	0.312	0.038	0.0027	-0.011	0.0068
4:83240238	4	83240238	TAAAAC	T	0.783	0.027	0.0030	-0.007	0.0084
rs3822076	4	89709908	T	A	0.540	0.018	0.0025	-0.003	0.0062
rs2086646	4	104585957	T	C	0.151	0.024	0.0034	-0.017	0.0091
rs10010325	4	106106353	A	C	0.483	0.018	0.0025	0.031	0.0062
rs10029669	4	120619666	C	T	0.656	0.022	0.0026	-0.004	0.0066
rs7680661	4	145565116	A	G	0.831	0.061	0.0033	-0.001	0.0084
rs17035181	4	157678511	G	T	0.145	0.025	0.0035	0.003	0.0092
rs55884613	5	264646	A	G	0.124	0.027	0.0038	0.034	0.0101
rs2062708	5	32753672	C	T	0.161	0.035	0.0033	-0.001	0.009
rs2457126	5	33029902	G	A	0.499	0.020	0.0025	-0.004	0.0068
rs10072767	5	53118818	A	G	0.399	0.022	0.0025	-0.014	0.0063
rs25757	5	55804204	G	C	0.124	0.034	0.0037	0.002	0.0097
rs16893612	5	64551463	T	C	0.227	0.029	0.0029	-0.002	0.0077
rs72776486	5	77515056	C	A	0.766	0.021	0.0029	0.005	0.0084
rs2011071	5	88741077	A	G	0.392	0.022	0.0025	0.002	0.0065
rs530644231	5	108169699	TTC	T	0.228	0.032	0.0029	0.006	0.0075
rs11403418	5	115041970	CT	C	0.271	0.028	0.0028	-0.004	0.0072
rs157577	5	131563571	C	G	0.721	0.021	0.0028	0.016	0.0071
rs72800392	5	134356061	C	T	0.696	0.019	0.0027	0.008	0.0069
rs2963468	5	158003020	A	G	0.767	0.022	0.0029	0.011	0.0075
rs4073717	5	170864021	G	T	0.799	0.025	0.0031	-0.003	0.008
rs111748972	5	171275948	ATTT	A	0.580	0.025	0.0025	-0.015	0.0076
rs7718768	5	178536089	A	G	0.335	0.024	0.0026	0.008	0.0068
rs34704166	5	179740398	T	C	0.670	0.018	0.0026	0.009	0.0072
rs501038	6	2056603	C	G	0.664	0.027	0.0026	0.011	0.0068
rs9392172	6	7723962	G	C	0.470	0.021	0.0025	-0.001	0.0062
rs4412193	6	26338056	A	G	0.636	0.050	0.0026	-0.014	0.0064
rs2263297	6	30441652	C	T	0.857	0.026	0.0035	0.005	0.0089
rs28732146	6	31561353	T	A	0.803	0.026	0.0031	0.011	0.0078
rs112540634	6	34623905	T	C	0.136	0.050	0.0036	-0.011	0.0089
rs1319012	6	41852616	T	A	0.074	0.033	0.0048	-0.001	0.0125
rs7745990	6	47488387	A	G	0.689	0.023	0.0027	0.001	0.0067
rs4639293	6	81757092	T	C	0.799	0.023	0.0031	-0.001	0.0081
6:105373111	6	105373111	C	CT	0.321	0.051	0.0026	-0.001	0.0067
rs1931897	6	116440007	C	A	0.282	0.025	0.0027	-0.010	0.0071
6:131317527	6	131317527	G	GC	0.386	0.022	0.0025	-0.009	0.0065
rs7774095	6	142670862	C	A	0.717	0.047	0.0027	0.000	0.0069

rs9397448	6	152161066	A	G	0.457	0.023	0.0025	-0.008	0.0062
rs3105752	6	160822925	A	G	0.504	0.017	0.0025	0.002	0.0062
rs10622588	6	164122040	CCATG	C	0.132	0.029	0.0036	0.013	0.0104
rs2763263	6	168814392	T	A	0.757	0.026	0.0029	-0.012	0.0072
rs62433138	7	1050877	C	T	0.429	0.017	0.0025	-0.009	0.0063
rs798488	7	2802522	T	C	0.700	0.049	0.0027	-0.014	0.0068
rs141773762	7	5366653	G	A	0.885	0.029	0.0039	0.011	0.0116
rs34134267	7	20417034	C	A	0.575	0.027	0.0025	0.003	0.0062
rs11769806	7	23480132	A	T	0.754	0.019	0.0029	-0.021	0.0073
rs481806	7	28207300	G	T	0.296	0.042	0.0027	-0.009	0.0068
rs34820887	7	28819213	T	C	0.652	0.019	0.0026	0.004	0.0065
rs28844277	7	35233589	C	T	0.627	0.018	0.0026	-0.004	0.0067
rs5883629	7	38099909	CT	C	0.652	0.020	0.0026	-0.009	0.0067
rs6978655	7	46171683	T	C	0.288	0.023	0.0027	-0.002	0.0073
rs2529414	7	50737831	G	A	0.224	0.026	0.0030	-0.001	0.0078
rs2946580	7	65531842	G	A	0.260	0.019	0.0028	0.003	0.0071
7:72692718	7	72692718	T	TAC	0.871	0.026	0.0038	-0.021	0.011
rs7804293	7	92287849	G	T	0.269	0.034	0.0028	0.026	0.0069
7:104885481	7	104885481	A	AACACAC	0.377	0.018	0.0025	-0.005	0.0066
rs1404264	7	120788347	C	A	0.610	0.018	0.0025	0.001	0.0064
7:130438531	7	130438531	C	CTTTTTT	0.517	0.017	0.0025	0.023	0.0067
rs273958	7	137599375	C	T	0.595	0.020	0.0025	0.003	0.0065
rs822530	7	148631555	T	A	0.795	0.032	0.0031	0.005	0.0081
8:8661026	8	8661026	CA	C	0.512	0.018	0.0025	0.019	0.0075
rs4368940	8	10526742	T	C	0.410	0.021	0.0025	0.014	0.007
rs10903343	8	11695872	T	C	0.464	0.017	0.0025	0.008	0.0071
rs76289108	8	13218849	A	G	0.266	0.020	0.0028	0.010	0.0071
rs4291276	8	23173591	A	G	0.236	0.024	0.0029	0.005	0.0074
rs62515432	8	57123523	C	T	0.209	0.024	0.0030	0.002	0.0079
rs2925155	8	75886297	C	T	0.739	0.020	0.0028	-0.006	0.0072
rs6473015	8	78178485	C	A	0.286	0.019	0.0027	0.021	0.0068
rs4876361	8	117566387	G	A	0.276	0.019	0.0028	0.011	0.0068
rs7838996	8	122669480	T	C	0.506	0.018	0.0025	0.011	0.0066
rs4501553	8	130718314	G	A	0.674	0.019	0.0026	0.005	0.0067
rs2585138	8	143808951	T	C	0.484	0.017	0.0025	0.010	0.0063
rs6988451	8	145247168	G	A	0.602	0.021	0.0025	-0.009	0.0074
rs79476472	9	17004288	T	C	0.886	0.029	0.0039	0.013	0.0102
rs35307904	9	78511889	G	A	0.878	0.061	0.0038	-0.012	0.0105
rs796007	9	86577541	A	G	0.251	0.031	0.0028	0.010	0.007
rs461289	9	89052563	T	C	0.711	0.021	0.0027	0.013	0.0068
rs278663	9	89794090	G	A	0.482	0.021	0.0025	-0.002	0.0062
rs734765	9	90852610	C	T	0.212	0.022	0.0030	-0.007	0.0084
9:94970162	9	94970162	CT	C	0.664	0.027	0.0026	0.009	0.0069

rs817300	9	98380222	G	A	0.925	0.044	0.0047	0.008	0.013
rs34575265	9	108943801	C	T	0.721	0.025	0.0027	-0.012	0.0068
rs10797291	9	127016044	T	C	0.388	0.017	0.0025	0.018	0.0065
rs7870114	9	133440976	C	T	0.656	0.025	0.0026	0.001	0.0069
rs3824359	9	139105229	C	T	0.142	0.034	0.0035	0.017	0.0097
rs1251015	10	12974824	A	G	0.649	0.019	0.0026	-0.008	0.0067
rs113059026	10	32158478	C	A	0.689	0.019	0.0027	0.021	0.0068
rs2435382	10	43677099	T	A	0.280	0.019	0.0028	-0.010	0.0072
rs10509108	10	61340890	G	A	0.204	0.021	0.0031	0.019	0.0079
rs10822143	10	64887856	T	C	0.504	0.017	0.0025	-0.019	0.0062
rs11818897	10	70616199	G	A	0.924	0.033	0.0047	0.006	0.0119
10:72431265	10	72431265	G	GAATAT	0.277	0.032	0.0028	0.000	0.0071
rs1628023	10	80924258	G	T	0.566	0.025	0.0025	-0.013	0.0063
rs11186507	10	92983831	G	A	0.199	0.025	0.0031	0.001	0.008
rs11187838	10	96038686	G	A	0.568	0.033	0.0025	0.006	0.0063
rs7913418	10	97808509	A	G	0.641	0.023	0.0026	0.013	0.0068
rs4604804	10	99878997	A	G	0.428	0.019	0.0025	0.003	0.0062
rs5870	10	104239100	C	T	0.540	0.019	0.0025	0.010	0.0062
rs11198821	10	120965341	G	A	0.104	0.029	0.0040	0.013	0.0105
rs7079914	10	123393509	G	C	0.811	0.024	0.0031	0.010	0.008
rs942015	10	126289932	G	T	0.399	0.020	0.0025	0.001	0.0063
rs496298	10	131355130	G	A	0.657	0.021	0.0026	0.003	0.0066
rs149419928	11	2813004	TG	T	0.113	0.034	0.0040	-0.019	0.0108
rs6486059	11	12824581	A	G	0.425	0.023	0.0025	0.000	0.0065
rs603061	11	61018328	C	A	0.163	0.023	0.0034	-0.002	0.0094
rs11553576	11	62378801	T	C	0.625	0.020	0.0025	-0.008	0.007
rs56223081	11	65961498	G	T	0.946	0.056	0.0056	0.034	0.0159
rs7952436	11	67024534	C	T	0.917	0.083	0.0045	0.012	0.0143
rs584961	11	75277628	A	G	0.115	0.042	0.0039	0.035	0.0108
rs2450138	11	77924870	T	C	0.163	0.023	0.0033	-0.011	0.0083
rs10894192	11	130266117	A	T	0.569	0.021	0.0025	0.003	0.007
rs215226	12	591300	G	A	0.402	0.021	0.0025	-0.007	0.0063
rs7139060	12	28693144	A	G	0.670	0.032	0.0026	0.047	0.0066
rs12228854	12	48396920	T	G	0.222	0.028	0.0030	-0.009	0.0077
rs762625671	12	51116036	G	GTTTATTTTATTTTAT	0.315	0.030	0.0026	0.000	0.0067
rs869073048	12	54443741	A	AAAC	0.292	0.019	0.0027	-0.017	0.0071
rs703842	12	58162739	A	G	0.671	0.023	0.0026	-0.009	0.0066
rs6581627	12	65719229	G	C	0.478	0.018	0.0025	-0.006	0.0062
rs8756	12	66359752	C	A	0.484	0.028	0.0025	-0.006	0.0062
rs11177668	12	69828528	G	T	0.259	0.020	0.0028	0.004	0.0077
rs9705466	12	77654536	A	G	0.751	0.021	0.0029	-0.002	0.0073
rs17018712	12	91496137	C	T	0.138	0.026	0.0036	-0.013	0.0095

rs11107120	12	93985482	C	T	0.222	0.023	0.0030	0.010	0.0075
rs10777561	12	94331007	G	A	0.594	0.019	0.0025	-0.007	0.0067
rs7980305	12	108098039	C	T	0.395	0.020	0.0025	0.016	0.0066
rs2062506	12	123084836	G	A	0.736	0.024	0.0028	0.016	0.0071
rs1716407	12	124515218	G	A	0.409	0.019	0.0025	0.020	0.0064
rs7995591	13	91991743	A	G	0.223	0.026	0.0030	0.012	0.0075
rs76140469	13	114749713	T	A	0.903	0.031	0.0042	-0.011	0.0108
rs4901541	14	55235282	T	C	0.562	0.019	0.0025	0.005	0.007
rs10138637	14	59310233	G	C	0.823	0.029	0.0032	-0.003	0.0079
rs28711886	14	61072658	G	A	0.320	0.019	0.0027	0.004	0.0067
14:74988127	14	74988127	C	CCACAT	0.637	0.029	0.0026	0.001	0.0067
rs11466414	14	76447850	G	A	0.930	0.040	0.0048	-0.005	0.0132
rs76497846	14	92531888	G	A	0.635	0.024	0.0026	-0.008	0.0064
rs4775762	15	48744005	C	T	0.775	0.031	0.0029	-0.025	0.0083
rs73408568	15	51379196	C	T	0.783	0.021	0.0030	0.021	0.0075
rs35874463	15	67457698	G	A	0.058	0.079	0.0053	0.067	0.0142
rs7177657	15	70041693	T	C	0.896	0.042	0.0040	-0.002	0.0106
rs8039718	15	70356150	T	C	0.179	0.023	0.0032	0.016	0.0084
rs4337252	15	74226765	C	G	0.495	0.034	0.0025	-0.015	0.0062
15:75786472	15	75786472	C	CATAT	0.510	0.018	0.0025	-0.003	0.0063
rs17466257	15	77376183	C	A	0.604	0.024	0.0025	-0.006	0.0065
rs768397327	15	84575367	C	CCACACACCA	0.514	0.066	0.0025	-0.007	0.0062
rs1879529	15	89414295	G	T	0.735	0.056	0.0028	-0.012	0.0082
rs72755233	15	100692953	G	A	0.887	0.087	0.0039	-0.004	0.0127
rs62621400	15	101718239	C	G	0.943	0.056	0.0053	0.022	0.0138
rs75516813	16	2179719	G	A	0.928	0.043	0.0048	-0.025	0.0126
rs59945160	16	4356206	G	C	0.231	0.022	0.0030	0.009	0.0078
rs12103006	16	24726237	G	A	0.571	0.019	0.0025	0.001	0.0063
16:28823630	16	28823630	A	AT	0.415	0.025	0.0025	0.006	0.0065
rs3814283	16	50268817	G	T	0.261	0.021	0.0028	0.003	0.0074
16:68305708	16	68305708	T	TTTTC	0.099	0.029	0.0042	0.017	0.0102
rs62046625	16	81578706	A	G	0.116	0.030	0.0038	0.006	0.0106
rs75309741	16	84893698	CCTTCCTCT	C	0.789	0.022	0.0030	0.002	0.0083
rs4843585	16	87320279	C	A	0.758	0.021	0.0029	-0.004	0.0075
rs7191697	16	89678165	G	A	0.900	0.041	0.0041	0.018	0.0115
rs4790812	17	1618135	G	A	0.711	0.023	0.0027	-0.001	0.0071
rs2605134	17	18130144	C	T	0.394	0.020	0.0025	-0.010	0.0064
rs542939	17	27889986	C	T	0.656	0.022	0.0026	0.019	0.0073
rs7223535	17	29211667	G	A	0.730	0.028	0.0028	0.044	0.007
rs67856160	17	42286541	TA	T	0.227	0.023	0.0030	-0.001	0.0076
rs552290972	17	43947883	T	G	0.786	0.033	0.0030	0.048	0.008
rs35701113	17	45882237	G	T	0.816	0.031	0.0032	0.004	0.0083

rs521833	17	46892436	G	A	0.640	0.021	0.0026	-0.001	0.0064
17:47423912	17	47423912	TCAAA	T	0.631	0.035	0.0026	-0.014	0.0065
rs1401795	17	54839652	A	G	0.500	0.022	0.0025	0.000	0.0068
rs7214743	17	59498052	A	G	0.330	0.022	0.0026	0.011	0.0066
rs2006122	17	61987405	T	A	0.271	0.022	0.0028	0.009	0.007
rs55931203	17	65854602	T	C	0.188	0.031	0.0032	0.001	0.0082
rs7238093	18	20728158	T	A	0.787	0.041	0.0030	-0.015	0.0077
rs12456780	18	46947541	A	T	0.671	0.023	0.0026	0.009	0.0065
rs34592412	18	77222828	C	CG	0.687	0.018	0.0027	-0.008	0.007
rs7249081	19	2157167	C	T	0.477	0.018	0.0025	0.015	0.0062
rs35533339	19	3438636	T	C	0.320	0.021	0.0026	0.011	0.0068
rs10853981	19	4965064	G	A	0.668	0.023	0.0026	0.024	0.0066
rs12609574	19	7178517	T	G	0.311	0.019	0.0027	0.002	0.0068
rs62105756	19	9973933	G	A	0.768	0.024	0.0029	-0.001	0.0073
rs34831515	19	17275777	C	T	0.767	0.021	0.0029	-0.001	0.0074
rs4531856	19	18388383	C	T	0.367	0.024	0.0026	0.008	0.0066
rs8103992	19	19665643	A	C	0.199	0.030	0.0031	0.022	0.0077
rs62102718	19	33891013	A	T	0.715	0.031	0.0027	-0.019	0.0072
rs8105450	19	41886859	T	C	0.392	0.021	0.0025	0.007	0.0067
rs58842569	20	4099558	G	T	0.346	0.024	0.0026	0.007	0.0071
rs1321432	20	6614691	A	C	0.371	0.032	0.0026	0.006	0.0066
rs6087571	20	32912091	G	A	0.138	0.036	0.0036	-0.002	0.0096
rs224331	20	34022387	C	A	0.342	0.036	0.0026	0.006	0.0065
rs77371365	20	39941782	C	G	0.156	0.023	0.0034	0.029	0.0088
rs61734651	20	61451332	T	C	0.072	0.060	0.0050	-0.014	0.0147
rs2834457	21	35712214	A	T	0.620	0.022	0.0025	0.006	0.0065
rs11450220	22	38607534	T	TG	0.448	0.032	0.0025	-0.036	0.0063
rs5845503	22	41891630	C	CT	0.209	0.026	0.0031	0.000	0.0079
rs6007043	22	45838646	C	T	0.200	0.027	0.0031	0.011	0.0079
rs4253755	22	46615376	A	G	0.129	0.027	0.0037	-0.007	0.0096

* Effect alleles: body fat measure trait increasing alleles
** Estimates of associations of SNPs with body fat mass and distribution from previous GWAS for BMI and WHRadjBMI, and from UK Biobank GWAS conducted for other body fat measure traits
*** EAF: Effect allele frequency
**** Estimates of associations of SNPs with breast cancer from BCAC summary statistics

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