Metabolically healthy obese and incident cardiovascular disease events among 3.5 million men and women

Short running title: Metabolically healthy obese and incident cardiovascular disease

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Abstract

Background: Previous studies have been unclear about the cardiovascular risks for metabolically healthy obese individuals.
Objectives: We aimed to examine the associations of metabolically healthy obese with 4 different presentations of incident cardiovascular disease in a contemporary population.
Methods: We used linked electronic health records (1995 to 2015) in The Health Improvement Network (THIN) to assemble a cohort of 3.5 million individuals, 18 years or older and initially free from cardiovascular disease. We created body size phenotypes defined by BMI categories (underweight, normal weight, overweight and obesity) and three metabolic abnormalities (diabetes, hypertension, and hyperlipidemia). The primary endpoints were the first record of one of 4 cardiovascular presentations [coronary heart disease (CHD), cerebrovascular disease, heart failure, and peripheral vascular disease (PVD)].
Results: During a mean follow-up period of 5.4 years, obese individuals with 0 metabolic abnormalities had a higher risk of CHD (multivariable-adjusted hazard ratio (HR) 1.49, 95% CI 1.45, 1.54), cerebrovascular disease (1.07, 95% CI 1.04, 1.11) and heart failure (1.96, 95% CI 1.86, 2.06) compared to normal weight individuals with 0 metabolic abnormalities. Risk of CHD, cerebrovascular disease and heart failure in normal weight, overweight and obese individuals increased with increasing number of metabolic abnormalities.
Conclusion: Metabolically healthy obese individuals had a higher risk of coronary heart disease, cerebrovascular disease and heart failure than normal weight metabolically healthy individuals. Even individuals who are normal weight can have metabolic abnormalities, and have similar risks for cardiovascular disease events.

Key words: Cardiovascular diseases, Metabolically healthy obese, Phenotype

Condensed abstract

Whether individuals who are metabolically healthy obese (MHO) are associated with excess risk of cardiovascular disease remains a subject of debate. The present study of 3.5 million adults examines and compares associations between body size phenotypes with or without metabolic abnormalities and incident cardiovascular disease. Our results suggest that individuals who are MHO are at higher risk of coronary heart disease, cerebrovascular disease and heart failure than normal weight metabolically healthy individuals. Clinicians additionally need to be aware that individuals with a normal BMI can have metabolic abnormalities, and therefore be at high risk for cardiovascular disease events.

Abbreviations

MHO= metabolically healthy obese
PVD= peripheral vascular disease
THIN= The Health Improvement Network
BMI= body mass index
CVD= cardiovascular disease
HR= hazard ratio
CI= 95% confidence interval
CHD= coronary heart disease

Introduction

Obesity, an established risk factor for cardiovascular diseases (1), has been increasing globally over the past four decades (2). Metabolic abnormalities such as hypertension, dyslipidemia, and dysglycemia are known to mediate its effects, (3) however the clustering of obesity-related metabolic abnormalities varies widely among obese individuals. A subset of obese individuals without obesity-related metabolic abnormalities are often referred to as being "metabolically healthy obese" (MHO) (4-8).

Three meta-analyses (9-11), have demonstrated that compared with metabolically healthy normal-weight individuals, obese individuals are at increased risk for cardiovascular disease events. Whether MHO is associated with excess risk of cardiovascular disease remains a subject of debate, because of important limitations to the evidence base. The main limitation is the inconsistent definition of metabolic health across studies. Previous studies have also not compared the association of MHO and a wide range of cardiovascular disease events such as cerebrovascular disease, heart failure, and peripheral vascular disease (PVD). Additionally, potential confounders have been inconsistently controlled for across studies, and there are a limited number of studies that have examined other metabolically defined body size phenotypes.

We sought to address these limitations in a large contemporary cohort, based on linked electronic health records, which combine routine information about diagnoses, risk factors, and medication use with future cardiovascular disease events. Our objective was to examine associations between body size phenotypes (underweight, normal weight, overweight and obese) with or without metabolic abnormalities (diabetes, hypertension, hyperlipidemia) and incident coronary heart disease (angina, ischemic heart disease, myocardial infarction), cerebrovascular disease (transient ischemic attack, ischemic stroke, haemorrhagic stroke), heart failure, and peripheral vascular disease. We tested the hypothesis that compared with metabolically healthy

(i.e. no metabolic abnormalities) normal weight individuals, MHO individuals are at increased risk for cardiovascular disease events.

Methods

Study design and setting

We undertook a cohort study with prospectively collected data from The Health Improvement Network database (THIN), which contains computerized primary care records from primary care physicians who use the Vision IT system and have agreed at the practice level to participate [covering 6.2% of the United Kingdom (UK) population]. THIN captures diagnoses, prescriptions, and tests from primary care, and referrals to specialists, hospital admissions, and diagnoses made in secondary care, which are typically reported back to the primary care physician. They record lifestyle (e.g. smoking status) and anthropometric measurements (e.g. height, weight); these measurements could be recorded at patient registration, opportunistically during care, or as deemed clinically relevant by the primary care physicians. THIN data is representative of the UK population (12), and comparisons to external statistics and other independent studies have shown that both the clinical diagnostic and prescribing information is well recorded and accurate (12,13). Data collection began in January 1995, and we used all data to September, 2015. For this study, approval was obtained via THIN's independent Scientific Review Committee in August 2016 (SRC reference number: 16THIN078).

Participants

We included all persons in THIN aged 18 years older with BMI data. Patients were only eligible to take part once their general practices had implemented the VISION IT system. Study entry began 12 months after registration to minimize the chance that cardiovascular disease events recorded after registration reflected pre-existing or historical disease. We assigned the

first BMI record from the registration date or the first one recorded after the VISION IT system was initiated. Individuals with any record of cardiovascular disease events before study entry were excluded.

Exposure

BMI was defined as body weight (kilograms) divided by height (meters) squared, and expressed in kg/m^2 at study entry. We defined individuals as having diabetes and hypertension by coded diagnoses (READ codes) recorded in THIN at study entry (Online Table 1). We defined individuals as having hyperlipidemia on the basis of whether individuals had specific prescription records of lipid-lowering agents. Individuals who developed diabetes, hypertension or hyperlipidemia during follow-up were analyzed according to their baseline status of no diabetes, hypertension or hyperlipidemia.

Body size phenotypes were defined using WHO criteria as follows: underweight (BMI < 18.5 kg/m^2), normal-weight (18 kg/m^2 >BMI<25 kg/m^2), overweight (25 $kg/m^2 \geq$ BMI < 30 kg/m^2) and obese (BMI $\geq$ 30 kg/m^2). The three metabolic abnormalities were summed to create a metabolic abnormalities score (0, 1, 2 and 3). Persons were categorized into 14 body size phenotypes: underweight with 0 metabolic abnormalities, underweight with 1 or more metabolic abnormalities, normal weight with 0 metabolic abnormalities, normal weight with 1 metabolic abnormality, normal weight with 2 metabolic abnormalities, normal weight with 3 metabolic abnormalities, overweight with 0 metabolic abnormalities, overweight with 1 metabolic abnormality, overweight with 2 metabolic abnormalities, overweight with 3 metabolic abnormalities, obese with 0 metabolic abnormalities, obese with 1 metabolic abnormality, obese with 2 metabolic abnormalities, and obese with 3 metabolic abnormalities.

Outcomes

The endpoints were the first record of one of the following 4 presentations of cardiovascular disease: coronary heart disease (angina, ischemic heart disease, myocardial infarction), cerebrovascular disease (transient ischemic attack, ischemic stroke, hemorrhagic stroke), heart failure, and peripheral vascular disease. Any events occurring after the first cardiovascular disease presentation were ignored. Endpoint definitions are described in Online Table 2.

Covariates

Participant's age, sex, self-reported smoking status, and social deprivation were included in models. Data recorded at study entry was used to classify participants as never smokers, ex-smokers, or current smokers. Social deprivation was included as quintiles of the index of multiple deprivation (14), a score calculated for each participant's neighborhood on the basis of social indices such as income, education, and employment.

Statistical analysis

Of the 4,091,344 million individuals aged 18 years or older in THIN without a history of CVD, we excluded persons with missing data on sex (128,458/4.09 million [3.1%]), BMI (161,699/4.09 million [4.0%]), smoking (53,262 /4.09 million [1.3%]) and social deprivation (252,148 /4.09 million [6.2%]). After these exclusions, there remained a final sample of 3,495,777 participants (85.4% of the eligible sample). Those excluded due to missing information were less likely to be male (41.4% vs. 43.1%; $p < 0.001$), younger (41.1 years vs. 44.7 years; $p < 0.001$), have a lower BMI (25.9 kg/m^2 vs. 26.4 kg/m^2; $p < 0.001$), more likely to belong to the most deprived quintile (14.5% vs. 14.0%; $p < 0.001$) and more likely to be current smokers (25.1% vs. 24.6%; $p < 0.001$).

Follow-up was censored at the occurrence of first cardiovascular disease endpoint, death,

de-registration from the practice, or the last data collection for the practice, whichever occurred first. We used Cox proportional hazard models to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for associations between each body size phenotype with or without metabolic abnormalities and cardiovascular disease event. We adjusted for age at BMI record, sex, self-reported smoking and social deprivation. We assessed the proportional hazards assumption by visually checking the Kaplan-Meier curves and tested it using Schoenfeld residuals. In sub-group analyses, we stratified associations by sex and age (<65 y, ≥ 65 y). The cut-off at 65 years was chosen as this is commonly used to designate an individual as an older person (15). In sensitivity analyses we defined metabolic status by diagnostic or prescription codes as well as laboratory or physical measurements; adjusted analyses for hormone replacement therapy (HRT) and oral contraceptives, respectively; and excluded patients with type 1 diabetes. Residual confounding by cigarette smoking has been suggested as a possible explanation for inconsistent associations between obesity and PVD (16). Excess risk for cardiovascular disease events associated with low BMI can also be associated with smoking-related diseases (such as chronic obstructive pulmonary disease (COPD) and lung cancer). Therefore, in sensitivity analyses we examined body size phenotypes with or without metabolic abnormalities and cardiovascular disease events only among individuals who reported never smoking cigarettes.

Results

Among 3,495,777 individuals, 2.7% were classified as underweight with no metabolic abnormalities, 37.7% were classified as normal weight with no metabolic abnormalities, 25.7% were classified as overweight with no metabolic abnormalities, and 14.8% were classified as obese with no metabolic abnormalities (Online Table 3). The prevalence of 3 metabolic

abnormalities was rare regardless of the weight category, with underweight individuals having the lowest (0%) (Online Table 3). Metabolically healthy obese individuals were more likely to be younger, male, current smokers and socioeconomically deprived compared with metabolically unhealthy obese individuals (**Table 1**).

There were 154,051 (4.4%) deaths and 1,182,658 (30.8%) patients transferred out of their general practice. Over a mean 5.4 year follow-up, there were 165,302 initial cardiovascular disease presentations: 61,546(37.2%) developed CHD, 54,705 (33.1%) developed cerebrovascular disease, 25,254 (15.3%) developed heart failure and 23,797 (14.4%) developed PVD. Incidence rates of cardiovascular disease events by body size phenotype and metabolic status are shown in Online Tables 5-7. Among initially metabolically healthy overweight individuals, approximately 1.9% of developed diabetes, 9.4% developed hyperlipidemia, and 7.2% developed hypertension. Among initially MHO individuals, approximately 5.6% developed diabetes, 11.5% developed hyperlipidemia, and 10.5% developed hypertension.

The **Central Illustration** depicts the associations between the 14 body size phenotypes with or without metabolic abnormalities and cardiovascular disease events (CHD, cerebrovascular disease, heart failure, and PVD) with the normal weight 0 metabolic abnormalities group as the reference.

Coronary heart disease

Individuals who were overweight with 0 metabolic abnormalities (HR 1.30, 95% CI 1.27, 1.34) and obese with 0 metabolic abnormalities (HR 1.49, 95% CI 1.45, 1.54), had an increased risk of coronary heart disease, compared to normal weight individuals with no metabolic abnormalities after adjustment for potential confounders (central illustration). Risk of coronary heart disease in the normal weight, overweight and obese groups increased with increased

number of metabolic abnormalities (**Central Illustration**).

Cerebrovascular disease

Individuals who were underweight (HR 1.31, 95% CI 1.23, 1.40) and obese with 0 metabolic abnormalities (HR 1.07, 95% CI 1.04, 1.11) had an increased risk of cerebrovascular disease, compared to normal weight individuals with no metabolic abnormalities after adjustment for potential confounders (central illustration). Risk of cerebrovascular disease in the normal weight, overweight and obese groups increased with the increasing number of metabolic abnormalities (**Central Illustration**).

Heart failure

Individuals who were underweight (HR 1.36, 95% CI 1.23, 1.51), overweight with 0 metabolic abnormalities (HR 1.11, 95% CI 1.06, 1.16) and obese with 0 metabolic abnormalities (HR 1.96, 95% CI 1.86, 2.06) had an increased risk of heart failure, compared to normal weight individuals with no metabolic abnormalities after adjustment for potential confounders (central illustration). Risk of heart failure in the normal weight, overweight and obese groups increased with increased number of metabolic abnormalities (**Central Illustration**).

Peripheral vascular disease

Individuals who were underweight had an increased risk of PVD (HR 1.49, 95% CI 1.36, 1.63), compared to normal weight individuals with no metabolic abnormalities after adjustment for potential confounders (central illustration). Individuals who were overweight with 0 metabolic abnormalities (adjusted HR 0.92, 95% CI 0.88, 0.96) and obese with 0 metabolic abnormalities (adjusted HR 0.91, 95% CI 0.86, 0.96) had a decreased risk of PVD compared to normal weight individuals with no metabolic abnormalities (central illustration). Risk of PVD

increased with the number of metabolic abnormalities in the normal weight, overweight and obese groups (central illustration).

Sub-group analyses

We undertook several sub-group analyses (Online Tables 8-15). There was some evidence that the risk of cerebrovascular disease in overweight and obese individuals without metabolic abnormalities, heart failure in overweight individuals without metabolic abnormalities, differed significantly by sex. Females had stronger positive associations with cerebrovascular disease and heart failure compared to males. There was some evidence that the risk of CHD, cerebrovascular disease, heart failure and PVD in overweight and obese individuals without metabolic abnormalities differed significantly by age. Individuals < 65 years had significantly stronger positive associations with CHD, cerebrovascular disease, heart failure and PVD than individuals ≥ 65 years. Among overweight and obese individuals without metabolic abnormalities, age-stratified analyses revealed significant positive associations with PVD.

Sensitivity analyses

When metabolic status was derived from diagnostic codes or prescription records as well as laboratory/physical measurements, the magnitude of associations between the body size phenotypes and metabolic status with CHD, cerebrovascular disease, heart failure and PVD were generally larger (Online Tables 9, 11, 13, & 15). For metabolically healthy overweight or obese groups, the negative association with PVD became non-significant (Online Table 15). Further adjustment for HRT or oral contraceptives did not significantly change the estimates (Online Tables 9 & 11). Exclusion of participants with type 1 diabetes did not significantly alter the results (Online Tables 9, 11, 13, & 15). In analyses restricted to individuals who reported they never smoked cigarettes, individuals who were obese with no metabolic abnormalities, had a

significantly stronger positive association with PVD (Online Table 15). For individuals who were underweight with no metabolic abnormalities, we repeated analyses only in those who reported they never smoked cigarettes. This did not significantly alter the results, with the exception that the positive association with cerebrovascular disease became non-significant (Online Table 15).

Discussion

In this study of approximately 3.5 million individuals accruing 165,302 cardiovascular disease events during 5.4 years average follow-up, we showed that individuals who are obese and classified as metabolically healthy (either no metabolic abnormalities, 1 or 2) are still at an increased risk for CHD, cerebrovascular disease and heart failure compared with individuals who are normal weight with no metabolic risk factors. These associations were not dependent on participants' sex. Approximately, one in ten who were normal weight had metabolic abnormalities and had increased risks for CHD, cerebrovascular disease, heart failure and PVD compared to normal weight individuals without metabolic abnormalities.

Although three meta-analyses (9-11) have assessed the risks of cardiovascular disease for the MHO phenotype, these each had limitations. The meta-analysis of Kramer et al (10) demonstrated that MHO individuals had increased risk for cardiovascular disease events compared with metabolically healthy normal-weight individuals. However, their findings were controversial. The meta-analysis roughly merged cardiovascular disease events and all-cause mortality together to calculate the pooled risk estimates for MHO individuals. Another limitation of the meta-analysis was the fact that it did not adequately adjust for important baseline factors, including age, and sex. Similarly, in the meta-analysis of Fan et al (11), they did not differentiate cardiovascular disease events and all-cause death events separately, but merged them together to

calculate the pooled risk estimate. Whereas, in our study we examined MHO with the incidence of specific cardiovascular disease events (i.e. CHD, cerebrovascular disease, heart failure and PVD) based on validated electronic health records (17-19). We were also able to adjust for important baseline factors including age, sex, smoking status and socio-economic deprivation. Recently, Zheng et al (9) meta-analysis attempted to examine the association between MHO and cardiovascular disease events in only studies using the strictest definition for metabolic health (absence of all metabolic abnormalities). They found an insignificant association between MHO and cardiovascular disease events, however only 2 studies provided data and, as such, the statistical power was limited to detect significant associations. In our study, we had unprecedented statistical power to examine obese individuals classified by the number of metabolic abnormalities, potentially reflecting several definitions of the 'metabolically healthy' phenotype in relation to a range of cardiovascular disease events.

Being metabolically unhealthy, regardless of BMI, generally conferred increased risk for cardiovascular disease events and normal weight status did not necessarily indicate metabolic health. Some individuals with normal weight have previously been reported to have elevated metabolic abnormalities (20,21). In the United States, the Preventive Services Task Force currently recommends that clinicians in primary care settings use overweight and obesity as the main criteria to screen adults for abnormal blood glucose as part of cardiovascular risk assessment (22). This could result in the failure to identify metabolic abnormalities in many patients. Early detection and management of normal weight individuals with metabolic abnormalities may therefore be beneficial in the prevention of cardiovascular disease events. We found that underweight individuals had an increased risk of cerebrovascular disease, heart failure, and PVD. The impact of underweight on cardiovascular disease events has been

understudied, with most previous research not evaluating underweight individuals separately from normal weight individuals. (3,23) Excess risk for cardiovascular disease events associated with low BMI may be related to smoking-related diseases such as chronic obstructive pulmonary disease (COPD) and lung cancer. To minimize this possibility, in sensitivity analyses we only examined the association between underweight with no metabolic abnormalities and cardiovascular disease events restricted to individuals who never reported smoking cigarettes. The results were unchanged from the main results with the exception that underweight individuals with no metabolic abnormalities now had a non-significant risk for cerebrovascular disease.

Our finding that obesity was associated with a lower risk of PVD was surprising, considering that it may influence the atherosclerotic process (24). Previous studies on the association between obesity and PVD have been inconsistent (16). In the Israeli Ischemic Heart Disease Project (25), those with new-onset intermittent claudication had a higher BMI than those who remained symptom free. Other large population-based studies however have failed to demonstrate that obesity increases risk for PVD (26-28), with some studies even reporting a reduction in risk for PVD (29-31). In the Framingham Study Cohort, relative weight was found to be inversely associated with intermittent claudication (30). One potential explanation for this is residual confounding by cigarette smoking (cigarette smoking is strongly associated with both PVD and lower BMI) (16). In sensitivity analyses, restricted to individuals who were obese with no metabolic abnormalities and reported never smoking cigarettes, risk for PVD was increased, compared to normal weight individuals with no metabolic abnormalities.

To the best of our knowledge, this is the largest prospective study of the association between body size phenotypes with or without metabolic abnormalities (including MHO) and a

range of incident cardiovascular disease events, with unprecedented precision and power. Dividing our participants into four BMI groups according to the classification provided by World Health Organization, gave us the possibility of a more granular analysis of the CVD risk in the different body size phenotypes.

Several limitations of our study however require careful consideration. BMI has many advantages as a surrogate of body fat, such as simplicity and reproducibility (32) however we are unable to distinguish differences between high percentage of body fat and preserved or increased lean mass, particularly in participants with a BMI <30 kg/m^2. Even though patients registered in THIN are representative of the general UK adult population (12), persons with a BMI measurement might not necessarily be representative of the general population. BMI data if not recorded at registration, tends to be opportunistically recorded (i.e. recorded when the patient is attending for other reasons or when the matter is of direct clinical importance). We limited this possibility by only using the first BMI recorded from the registration date (because they would have probably been recorded for administrative and not health reasons). Our findings are drawn from baseline measurements of BMI and metabolic abnormalities. Considering the difficulty in losing weight, it is more likely that individuals transition to higher weight (i.e. normal weight/overweight to obese) categories than transition to lower weight categories (i.e. obese to overweight/normal weight) (10). Thus, the potential misclassification effect of changes in weight over time was probably conservative. In our study, a small proportion of individuals who were initially metabolically healthy overweight or obese did progress to metabolically unhealthy overweight or obesity. Therefore, due to changes in metabolic abnormalities, a degree of misclassification, did occur. We did not have access to appropriate data on diet or physical activity, and therefore could not examine for example, whether physical activity could modify

the association between MHO and incident cardiovascular disease. Patients were defined as having diabetes or hypertension utilizing diagnostic codes and hyperlipidemia was defined utilizing prescription codes. Given that a proportion of individuals with metabolic abnormalities may be undiagnosed in the UK (33,34) we used available measures of HbA1c, blood pressure and serum lipids to minimize misclassification error. Additionally, given that improvement of glycemic, blood pressure, or lipid control obtained through treatment can prevent cardiovascular disease events in the long term, we may therefore expect that optimally treated/controlled patients would have a reduced risk of developing a cardiovascular disease events compared to those who are uncontrolled, and therefore our HR estimates would be conservative. The proportion of participants who transferred out of their practice was high (30.8%). However, the difference between the proportion of participants who were obese with no metabolic abnormalities transferring out of their practice and those who remained in their practice was small (13.0% vs. 16.0%), and therefore less likely to bias the HRs substantially.

Taking into consideration the genetic heterogeneity related to obesity (35), it is not implausible to assume that a distinct, benign phenotype in terms of CVD risk may be present. Of the body size phenotypes, MHO has been the most commonly examined phenotype (36), and it has been suggested that the concept of metabolically healthy obesity might be important in the stratification of individuals in the clinical treatment of obesity (36). Some researchers have called for a shift in the public health focus away from markers of adiposity such as BMI (37) and suggest that health providers prescribing weight loss interventions may be misusing time and resources (38). Our study robustly challenges the assertion that MHO is a benign condition and adds to the evidence base that MHO is a high-risk state for future cardiovascular disease events.

Conclusions

Individuals who are obese with no metabolic abnormalities are at higher risk of coronary heart disease, cerebrovascular disease and heart failure than normal weight metabolically healthy persons. Clinicians need to be aware that individuals who would otherwise be considered non-obese, based on a normal BMI, can have metabolic abnormalities, and therefore also be at high risk for cardiovascular disease events.

Perspectives

Competency in patient care and medical knowledge: Metabolically healthy obesity is a unique body size phenotype that apparently protects people from the metabolic complications of obesity including cardiovascular disease. However, whether these individuals are truly at less risk of cardiovascular disease has remained controversial. Our study of 3.5 million electronic primary care records suggest individuals who are obese and classified as metabolically healthy (either no metabolic abnormalities, 1 or 2) are still at an increased risk for coronary heart disease, cerebrovascular disease and heart failure compared with individuals who are normal weight with no metabolic risk factors. Individuals who are normal weight can also have metabolic abnormalities, and be at high risk for cardiovascular disease events.

Translational Outlook: Large and long-term cohort trials are still required to determine the effect of weight loss on risk of developing cardiovascular disease events among metabolically healthy obese individuals.

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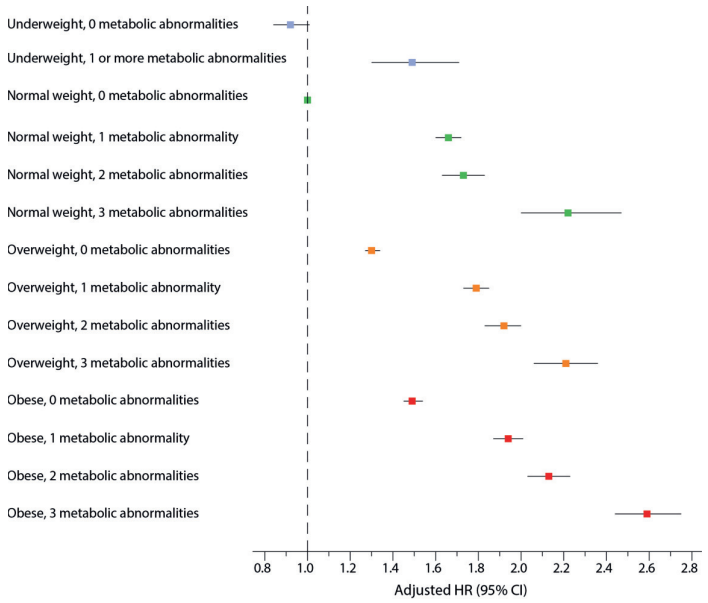
Figure Legend

Central Illustration: Association of body size phenotypes and metabolic status with cardiovascular disease events in 3.5 million UK adults. Analyses adjusted for age, sex, smoking status and social deprivation. The reference category is normal weight, 0 metabolic abnormalities.

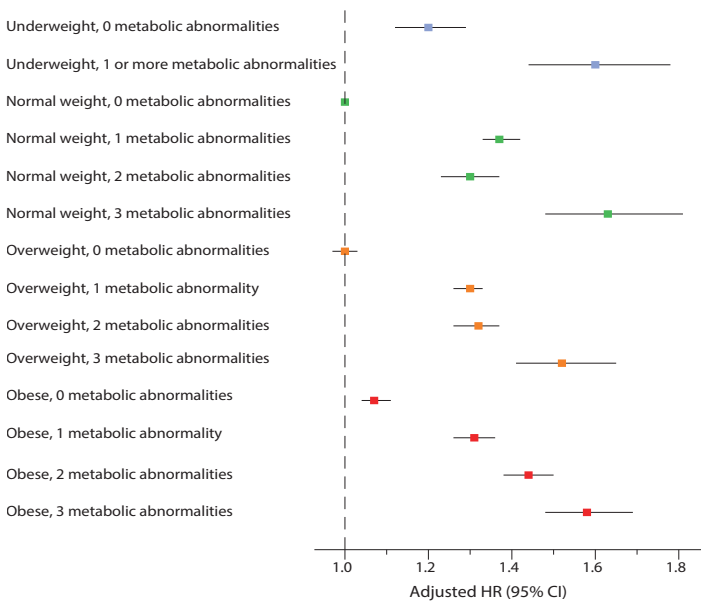
Table 1 Baseline characteristics of the study population, by body size phenotypes and metabolic health status

	Underweight	**Normal weight**	**Overweight**	**Metabolically healthy and obese***	**Metabolically unhealthy and obese†**
Mean age (SD), (years)	38.0 (20.3)	41.3 (17.6)	47.7 (16.6)	42.6 (13.8)	58.6 (12.6)
Sex					
Male	24,753 (26.3)	547,600 (37.0)	603,492 (52.1)	301,974 (58.4)	114,196 (46.6)
Female	69,276 (73.7)	932,626 (63.0)	555,324 (47.9)	215,470 (41.6)	131,066 (53.4)
Smoking status					
Never smoker	51,614 (54.9)	842,573 (56.9)	637,442 (55.0)	284,510 (55.0)	133,878 (54.6)
Ex- smoker	10,075 (10.7)	235,766 (15.9)	257,903 (22.3)	109,051 (21.1)	73,015 (29.8)
Current smoker	32,340 (34.4)	401,887 (27.2)	263,471 (22.7)	123,883 (23.9)	38,369 (15.6)
Social deprivation quintile					
1 (least deprived)	16,736 (17.8)	352,906 (23.8)	295,984 (25.5)	110,089 (21.3)	54,712 (22.3)
2	16,119 (17.1)	303,729 (20.5)	256,192 (22.1)	104,285 (20.2)	52,844 (21.6)
3	20,083 (21.4)	318,076 (21.5)	248,836 (21.5)	114,512 (22.1)	53,628 (21.9)
4	22,583 (24.0)	293,845 (19.9)	212,177 (18.3)	108,679 (21.0)	49,278 (20.1)
5 (most deprived)	18,508 (19.7)	211,670 (14.3)	145,627 (12.6)	79,879 (15.4)	34,800 (14.2)
Mean BMI (SD), kg/m2	17.4 (1.0)	22.3 (1.7)	27.2 (1.4)	34.4 (4.5)	34.9 (4.8)

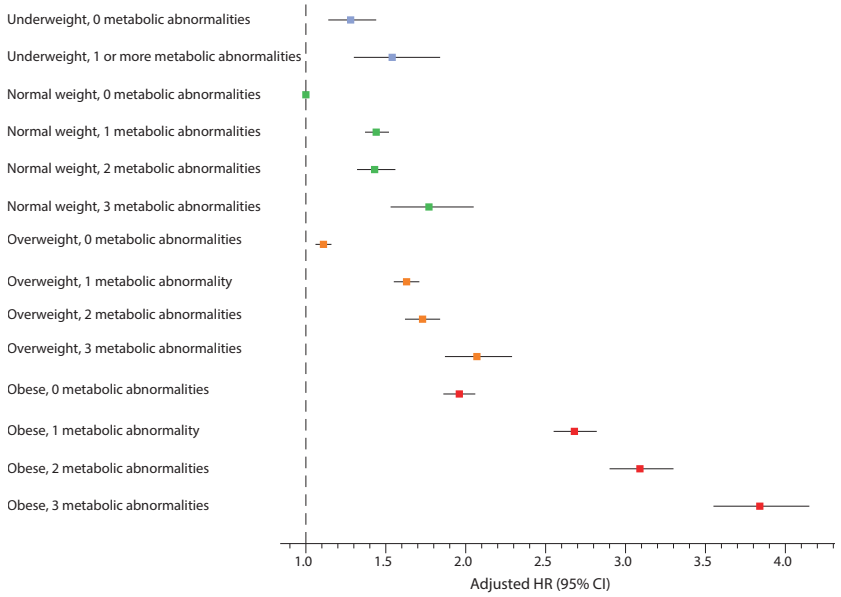
BMI= body mass index
*Obese with 0 metabolic abnormalities
†Obese with 1 or more metabolic abnormalities



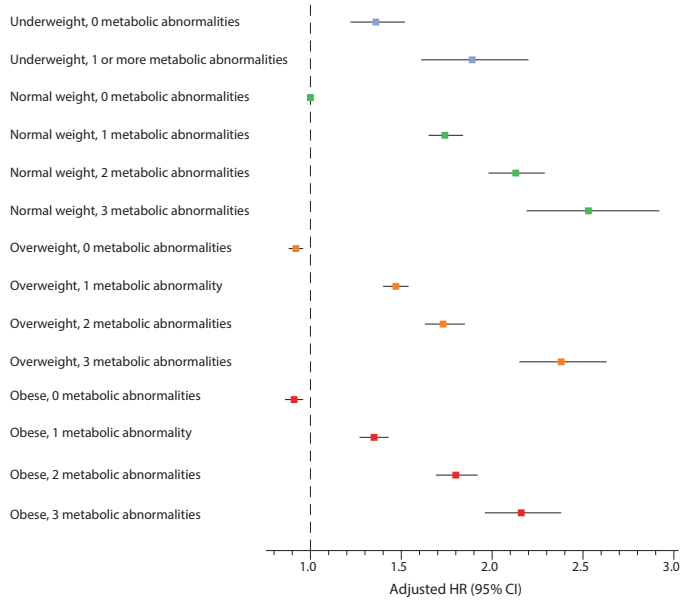
C oronary heart disease



Cerebrovascular disease



Heart failure



Peripheral vascular disease

Central Illustration : Association of body size phenotypes and metabolic status with cardiovascular disease events in 3.5 million UK adults.
Analyses adjusted for age, sex, smoking status and social deprivation. The reference category is normal weight, 0 metabolic abnormalities.

Table S1 Overview of codes used to define metabolic abnormalities

Metabolic abnormality	READ code	Description
Diabetes	C10..00	Diabetes mellitus
	C100.00	Diabetes mellitus with no mention of complication
	C100000	Diabetes mellitus, juvenile type, no mention of complication
	C100011	Insulin dependent diabetes mellitus
	C100100	Diabetes mellitus, adult onset, no mention of complication
	C100111	Maturity onset diabetes
	C100112	Non-insulin dependent diabetes mellitus
	C100z00	Diabetes mellitus NOS with no mention of complication
	C101.00	Diabetes mellitus with ketoacidosis
	C101000	Diabetes mellitus, juvenile type, with ketoacidosis
	C101100	Diabetes mellitus, adult onset, with ketoacidosis
	C101y00	Other specified diabetes mellitus with ketoacidosis
	C101z00	Diabetes mellitus NOS with ketoacidosis
	C102.00	Diabetes mellitus with hyperosmolar coma
	C102000	Diabetes mellitus, juvenile type, with hyperosmolar coma
	C102100	Diabetes mellitus, adult onset, with hyperosmolar coma
	C102z00	Diabetes mellitus NOS with hyperosmolar coma
	C103.00	Diabetes mellitus with ketoacidotic coma
	C103000	Diabetes mellitus, juvenile type, with ketoacidotic coma
	C103100	Diabetes mellitus, adult onset, with ketoacidotic coma
	C103y00	Other specified diabetes mellitus with coma
	C103z00	Diabetes mellitus NOS with ketoacidotic coma
	C104.00	Diabetes mellitus with renal manifestation
	C104.11	Diabetic nephropathy
	C104000	Diabetes mellitus, juvenile type, with renal manifestation
	C104100	Diabetes mellitus, adult onset, with renal manifestation
	C104y00	Other specified diabetes mellitus with renal complications
	C104z00	Diabetes mellitus with nephropathy NOS
	C105.00	Diabetes mellitus with ophthalmic manifestation
	C105000	Diabetes mellitus, juvenile type, + ophthalmic manifestation
	C105100	Diabetes mellitus, adult onset, + ophthalmic manifestation
	C105y00	Other specified diabetes mellitus with ophthalmic complicatn
	C105z00	Diabetes mellitus NOS with ophthalmic manifestation
	C106.00	Diabetes mellitus with neurological manifestation
	C106.11	Diabetic amyotrophy
	C106.12	Diabetes mellitus with neuropathy
	C106.13	Diabetes mellitus with polyneuropathy
	C106000	Diabetes mellitus, juvenile, + neurological manifestation
	C106100	Diabetes mellitus, adult onset, + neurological manifestation
	C106y00	Other specified diabetes mellitus with neurological comps

C106z00	Diabetes mellitus NOS with neurological manifestation
C108.00	Insulin dependent diabetes mellitus
C108.11	IDDM-Insulin dependent diabetes mellitus
C108.12	Type 1 diabetes mellitus
C108.13	Type I diabetes mellitus
C108000	Insulin-dependent diabetes mellitus with renal complications
C108011	Type I diabetes mellitus with renal complications
C108012	Type 1 diabetes mellitus with renal complications
C108100	Insulin-dependent diabetes mellitus with ophthalmic comps
C108111	Type I diabetes mellitus with ophthalmic complications
C108112	Type 1 diabetes mellitus with ophthalmic complications
C108200	Insulin-dependent diabetes mellitus with neurological comps
C108211	Type I diabetes mellitus with neurological complications
C108212	Type 1 diabetes mellitus with neurological complications
C108300	Insulin dependent diabetes mellitus with multiple complicatn
C108311	Type I diabetes mellitus with multiple complications
C108312	Type 1 diabetes mellitus with multiple complications
C108400	Unstable insulin dependent diabetes mellitus
C108411	Unstable type I diabetes mellitus
C108412	Unstable type 1 diabetes mellitus
C108500	Insulin dependent diabetes mellitus with ulcer
C108511	Type I diabetes mellitus with ulcer
C108512	Type 1 diabetes mellitus with ulcer
C108700	Insulin dependent diabetes mellitus with retinopathy
C108711	Type I diabetes mellitus with retinopathy
C108712	Type 1 diabetes mellitus with retinopathy
C108800	Insulin dependent diabetes mellitus - poor control
C108811	Type I diabetes mellitus - poor control
C108812	Type 1 diabetes mellitus - poor control
C108900	Insulin dependent diabetes maturity onset
C108911	Type I diabetes mellitus maturity onset
C108912	Type 1 diabetes mellitus maturity onset
C108A00	Insulin-dependent diabetes without complication
C108A11	Type I diabetes mellitus without complication
C108A12	Type 1 diabetes mellitus without complication
C108B00	Insulin dependent diabetes mellitus with mononeuropathy
C108B11	Type I diabetes mellitus with mononeuropathy
C108B12	Type 1 diabetes mellitus with mononeuropathy
C108C00	Insulin dependent diabetes mellitus with polyneuropathy
C108C11	Type I diabetes mellitus with polyneuropathy
C108C12	Type 1 diabetes mellitus with polyneuropathy
C108D00	Insulin dependent diabetes mellitus with nephropathy
C108D11	Type I diabetes mellitus with nephropathy
C108D12	Type 1 diabetes mellitus with nephropathy
C108E00	Insulin dependent diabetes mellitus with hypoglycaemic coma
C108E11	Type I diabetes mellitus with hypoglycaemic coma

C108E12	Type 1 diabetes mellitus with hypoglycaemic coma
C108F00	Insulin dependent diabetes mellitus with diabetic cataract
C108F11	Type I diabetes mellitus with diabetic cataract
C108F12	Type 1 diabetes mellitus with diabetic cataract
C108G00	Insulin dependent diab mell with peripheral angiopathy
C108G11	Type I diabetes mellitus with peripheral angiopathy
C108G12	Type 1 diabetes mellitus with peripheral angiopathy
C108H00	Insulin dependent diabetes mellitus with arthropathy
C108H11	Type I diabetes mellitus with arthropathy
C108H12	Type 1 diabetes mellitus with arthropathy
C108J00	Insulin dependent diab mell with neuropathic arthropathy
C108J11	Type I diabetes mellitus with neuropathic arthropathy
C108J12	Type 1 diabetes mellitus with neuropathic arthropathy
C108y00	Other specified diabetes mellitus with multiple comps
C108z00	Unspecified diabetes mellitus with multiple complications
C109.00	Non-insulin dependent diabetes mellitus
C109.11	NIDDM - Non-insulin dependent diabetes mellitus
C109.12	Type 2 diabetes mellitus
C109.13	Type II diabetes mellitus
C109000	Non-insulin-dependent diabetes mellitus with renal comps
C109011	Type II diabetes mellitus with renal complications
C109012	Type 2 diabetes mellitus with renal complications
C109100	Non-insulin-dependent diabetes mellitus with ophthalm comps
C109111	Type II diabetes mellitus with ophthalmic complications
C109112	Type 2 diabetes mellitus with ophthalmic complications
C109200	Non-insulin-dependent diabetes mellitus with neuro comps
C109211	Type II diabetes mellitus with neurological complications
C109212	Type 2 diabetes mellitus with neurological complications
C109300	Non-insulin-dependent diabetes mellitus with multiple comps
C109311	Type II diabetes mellitus with multiple complications
C109312	Type 2 diabetes mellitus with multiple complications
C109400	Non-insulin dependent diabetes mellitus with ulcer
C109411	Type II diabetes mellitus with ulcer
C109412	Type 2 diabetes mellitus with ulcer
C109600	Non-insulin-dependent diabetes mellitus with retinopathy
C109611	Type II diabetes mellitus with retinopathy
C109612	Type 2 diabetes mellitus with retinopathy
C109700	Non-insulin dependent diabetes mellitus - poor control
C109711	Type II diabetes mellitus - poor control
C109712	Type 2 diabetes mellitus - poor control
C109800	Reaven's syndrome
C109900	Non-insulin-dependent diabetes mellitus without complication
C109911	Type II diabetes mellitus without complication
C109912	Type 2 diabetes mellitus without complication
C109A00	Non-insulin dependent diabetes mellitus with mononeuropathy
C109A11	Type II diabetes mellitus with mononeuropathy

C109A12	Type 2 diabetes mellitus with mononeuropathy
C109B00	Non-insulin dependent diabetes mellitus with polyneuropathy
C109B11	Type II diabetes mellitus with polyneuropathy
C109B12	Type 2 diabetes mellitus with polyneuropathy
C109C00	Non-insulin dependent diabetes mellitus with nephropathy
C109C11	Type II diabetes mellitus with nephropathy
C109C12	Type 2 diabetes mellitus with nephropathy
C109D00	Non-insulin dependent diabetes mellitus with hypoglyca coma
C109D11	Type II diabetes mellitus with hypoglycaemic coma
C109D12	Type 2 diabetes mellitus with hypoglycaemic coma
C109E00	Non-insulin depend diabetes mellitus with diabetic cataract
C109E11	Type II diabetes mellitus with diabetic cataract
C109E12	Type 2 diabetes mellitus with diabetic cataract
C109G00	Non-insulin dependent diabetes mellitus with arthropathy
C109G11	Type II diabetes mellitus with arthropathy
C109G12	Type 2 diabetes mellitus with arthropathy
C109H00	Non-insulin dependent d m with neuropathic arthropathy
C109H11	Type II diabetes mellitus with neuropathic arthropathy
C109H12	Type 2 diabetes mellitus with neuropathic arthropathy
C109J00	Insulin treated Type 2 diabetes mellitus
C109J11	Insulin treated non-insulin dependent diabetes mellitus
C109J12	Insulin treated Type II diabetes mellitus
C109K00	Hyperosmolar non-ketotic state in type 2 diabetes mellitus
C10A.00	Malnutrition-related diabetes mellitus
C10A000	Malnutrition-related diabetes mellitus with coma
C10A100	Malnutrition-related diabetes mellitus with ketoacidosis
C10A200	Malnutrition-related diabetes mellitus with renal complicatn
C10A300	Malnutrit-related diabetes mellitus wth ophthalmic complicat
C10A400	Malnutrition-related diabetes mellitus wth neuro complicatns
C10A600	Malnutrition-related diabetes mellitus with multiple comps
C10A700	Malnutrition-related diabetes mellitus without complications
C10AW00	Malnutrit-related diabetes mellitus with unspec complics
C10AX00	Malnutrit-relat diabetes mellitus with other spec comps
C10B.00	Diabetes mellitus induced by steroids
C10B000	Steroid induced diabetes mellitus without complication
C10C.00	Diabetes mellitus autosomal dominant
C10C.11	Maturity onset diabetes in youth
C10C.12	Maturity onset diabetes in youth type 1
C10D.00	Diabetes mellitus autosomal dominant type 2
C10D.11	Maturity onset diabetes in youth type 2
C10E.00	Type 1 diabetes mellitus
C10E.11	Type I diabetes mellitus
C10E.12	Insulin dependent diabetes mellitus
C10E000	Type 1 diabetes mellitus with renal complications
C10E011	Type I diabetes mellitus with renal complications
C10E012	Insulin-dependent diabetes mellitus with renal complications

C10E100	Type 1 diabetes mellitus with ophthalmic complications
C10E111	Type I diabetes mellitus with ophthalmic complications
C10E112	Insulin-dependent diabetes mellitus with ophthalmic comps
C10E200	Type 1 diabetes mellitus with neurological complications
C10E211	Type I diabetes mellitus with neurological complications
C10E212	Insulin-dependent diabetes mellitus with neurological comps
C10E300	Type 1 diabetes mellitus with multiple complications
C10E311	Type I diabetes mellitus with multiple complications
C10E312	Insulin dependent diabetes mellitus with multiple complicat
C10E400	Unstable type 1 diabetes mellitus
C10E411	Unstable type I diabetes mellitus
C10E412	Unstable insulin dependent diabetes mellitus
C10E500	Type 1 diabetes mellitus with ulcer
C10E511	Type I diabetes mellitus with ulcer
C10E512	Insulin dependent diabetes mellitus with ulcer
C10E700	Type 1 diabetes mellitus with retinopathy
C10E711	Type I diabetes mellitus with retinopathy
C10E712	Insulin dependent diabetes mellitus with retinopathy
C10E800	Type 1 diabetes mellitus - poor control
C10E811	Type I diabetes mellitus - poor control
C10E812	Insulin dependent diabetes mellitus - poor control
C10E900	Type 1 diabetes mellitus maturity onset
C10E911	Type I diabetes mellitus maturity onset
C10E912	Insulin dependent diabetes maturity onset
C10EA00	Type 1 diabetes mellitus without complication
C10EA11	Type I diabetes mellitus without complication
C10EA12	Insulin-dependent diabetes without complication
C10EB00	Type 1 diabetes mellitus with mononeuropathy
C10EB11	Type I diabetes mellitus with mononeuropathy
C10EB12	Insulin dependent diabetes mellitus with mononeuropathy
C10EC00	Type 1 diabetes mellitus with polyneuropathy
C10EC11	Type I diabetes mellitus with polyneuropathy
C10EC12	Insulin dependent diabetes mellitus with polyneuropathy
C10ED00	Type 1 diabetes mellitus with nephropathy
C10ED11	Type I diabetes mellitus with nephropathy
C10ED12	Insulin dependent diabetes mellitus with nephropathy
C10EE00	Type 1 diabetes mellitus with hypoglycaemic coma
C10EE11	Type I diabetes mellitus with hypoglycaemic coma
C10EE12	Insulin dependent diabetes mellitus with hypoglycaemic coma
C10EF00	Type 1 diabetes mellitus with diabetic cataract
C10EF11	Type I diabetes mellitus with diabetic cataract
C10EF12	Insulin dependent diabetes mellitus with diabetic cataract
C10EH00	Type 1 diabetes mellitus with arthropathy
C10EH11	Type I diabetes mellitus with arthropathy
C10EH12	Insulin dependent diabetes mellitus with arthropathy
C10EJ00	Type 1 diabetes mellitus with neuropathic arthropathy

C10EJ11	Type I diabetes mellitus with neuropathic arthropathy
C10EJ12	Insulin dependent diab mell with neuropathic arthropathy
C10EK00	Type 1 diabetes mellitus with persistent proteinuria
C10EK11	Type I diabetes mellitus with persistent proteinuria
C10EL00	Type 1 diabetes mellitus with persistent microalbuminuria
C10EL11	Type I diabetes mellitus with persistent microalbuminuria
C10EM00	Type 1 diabetes mellitus with ketoacidosis
C10EM11	Type I diabetes mellitus with ketoacidosis
C10EN00	Type 1 diabetes mellitus with ketoacidotic coma
C10EN11	Type I diabetes mellitus with ketoacidotic coma
C10EP00	Type 1 diabetes mellitus with exudative maculopathy
C10EP11	Type I diabetes mellitus with exudative maculopathy
C10EQ00	Type 1 diabetes mellitus with gastroparesis
C10EQ11	Type I diabetes mellitus with gastroparesis
C10ER00	Latent autoimmune diabetes mellitus in adult
C10F.00	Type 2 diabetes mellitus
C10F.11	Type II diabetes mellitus
C10F000	Type 2 diabetes mellitus with renal complications
C10F011	Type II diabetes mellitus with renal complications
C10F100	Type 2 diabetes mellitus with ophthalmic complications
C10F111	Type II diabetes mellitus with ophthalmic complications
C10F200	Type 2 diabetes mellitus with neurological complications
C10F211	Type II diabetes mellitus with neurological complications
C10F300	Type 2 diabetes mellitus with multiple complications
C10F311	Type II diabetes mellitus with multiple complications
C10F400	Type 2 diabetes mellitus with ulcer
C10F411	Type II diabetes mellitus with ulcer
C10F600	Type 2 diabetes mellitus with retinopathy
C10F611	Type II diabetes mellitus with retinopathy
C10F700	Type 2 diabetes mellitus - poor control
C10F711	Type II diabetes mellitus - poor control
C10F800	Reaven's syndrome
C10F811	Metabolic syndrome X
C10F900	Type 2 diabetes mellitus without complication
C10F911	Type II diabetes mellitus without complication
C10FA00	Type 2 diabetes mellitus with mononeuropathy
C10FA11	Type II diabetes mellitus with mononeuropathy
C10FB00	Type 2 diabetes mellitus with polyneuropathy
C10FB11	Type II diabetes mellitus with polyneuropathy
C10FC00	Type 2 diabetes mellitus with nephropathy
C10FC11	Type II diabetes mellitus with nephropathy
C10FD00	Type 2 diabetes mellitus with hypoglycaemic coma
C10FD11	Type II diabetes mellitus with hypoglycaemic coma
C10FE00	Type 2 diabetes mellitus with diabetic cataract
C10FE11	Type II diabetes mellitus with diabetic cataract
C10FG00	Type 2 diabetes mellitus with arthropathy

	C10FG11	Type II diabetes mellitus with arthropathy
	C10FH00	Type 2 diabetes mellitus with neuropathic arthropathy
	C10FH11	Type II diabetes mellitus with neuropathic arthropathy
	C10FJ00	Insulin treated Type 2 diabetes mellitus
	C10FJ11	Insulin treated Type II diabetes mellitus
	C10FK00	Hyperosmolar non-ketotic state in type 2 diabetes mellitus
	C10FK11	Hyperosmolar non-ketotic state in type II diabetes mellitus
	C10FL00	Type 2 diabetes mellitus with persistent proteinuria
	C10FL11	Type II diabetes mellitus with persistent proteinuria
	C10FM00	Type 2 diabetes mellitus with persistent microalbuminuria
	C10FM11	Type II diabetes mellitus with persistent microalbuminuria
	C10FN00	Type 2 diabetes melli
Hypertension	G2...00	Hypertensive disease
	G2...11	BP - hypertensive disease
	G20..00	Essential hypertension
	G20..11	High blood pressure
	G20..12	Primary hypertension
	G200.00	Malignant essential hypertension
	G201.00	Benign essential hypertension
	G202.00	Systolic hypertension
	G203.00	Diastolic hypertension
	G20z.00	Essential hypertension NOS
	G20z.11	Hypertension NOS
	G24..00	Secondary hypertension
	G240.00	Secondary malignant hypertension
	G240000	Secondary malignant renovascular hypertension
	G240z00	Secondary malignant hypertension NOS
	G241.00	Secondary benign hypertension
	G241000	Secondary benign renovascular hypertension
	G241z00	Secondary benign hypertension NOS
	G244.00	Hypertension secondary to endocrine disorders
	G24z.00	Secondary hypertension NOS
	G24z000	Secondary renovascular hypertension NOS
	G24z100	Hypertension secondary to drug
	G24zz00	Secondary hypertension NOS
	G25..00	Stage 1 hypertension (NICE - Nat Ins for Hth Clin Excl 2011)
	G25..11	Stage 1 hypertension
	G250.00	Stage 1 hyperten (NICE 2011) without evidence end organ damage
	G251.00	Stage 1 hyperten (NICE 2011) with evidence end organ damage
	G26..00	Severe hypertension (Nat Inst for Health Clinical Ex 2011)
	G26..11	Severe hypertension
	G27..00	Hypertension resistant to drug therapy
	G28..00	Stage 2 hypertension (NICE - Nat Ins for Hth Clin Excl 2011)
	Gyu2000	[X]Other secondary hypertension
	Gyu2100	[X]Hypertension secondary to other renal disorders

Hyperlipidaemia	81048998	Atorvastatin 20mg chewable tablets sugar free
	81051998	Atorvastatin 10mg chewable tablets sugar free
	83099998	Simvastatin 40mg/5ml oral suspension sugar free
	82655998	Nicotinic acid & laropiprant 1g+20mg tablets
	83030998	Simvastatin 80mg tablets
	81050998	Atorvastatin 10mg chewable tablets sugar free
	84268998	Colesevelam 625mg tablets
	84267998	Colesevelam 625mg tablets
	83594998	Nicotinic acid 1g / laropiprant 20mg modified-release tablets
	79254979	Simvastatin 20mg/5ml oral suspension sugar free
	83188998	Bezafibrate 200mg tablets
	83187998	Bezafibrate 400mg modified-release tablets
	81049998	Atorvastatin 20mg chewable tablets sugar free
	82141978	Eicosapentaenoic acid 460mg / Docosahexaenoic acid 380mg capsules
	87853998	Nicotinic acid 1g modified-release tablets
	87852998	Nicotinic acid 500mg modified release tablets
	89154996	Cerivastatin 300microgram tablets
	86791998	Simvastatin 80mg / Ezetimibe 10mg tablets
	87854998	Nicotinic acid 750mg modified-release tablets
	89153996	Cerivastatin sodium 300mcg tablets
	88298997	Fenofibrate micronised 267mg capsules
	88534998	Rosuvastatin 10mg tablets
	86794998	Simvastatin 80mg / Ezetimibe 10mg tablets
	86510979	Ispaghula husk 3.5g sugar free granules
	87025998	Bezafibrate 400mg modified-release tablets
	87418998	Simvastatin 10mg tablets
	87918998	Simvastatin 10mg tablets
	89401998	Bezafibrate 400mg modified-release tablets
	87917998	Simvastatin 20mg tablets
	89089998	Bezafibrate 400mg modified release tablets
	87373998	Simvastatin 10mg tablets
	87760998	Colestipol 5g granules sachets sugar free
	86798998	Simvastatin 20mg / Ezetimibe 10mg tablets
	88297996	Fenofibrate micronised 267mg capsules
	87848998	Nicotinic acid pack
	86796998	Simvastatin 40mg / Ezetimibe 10mg tablets
	87849998	Nicotinic acid 375mg + 500mg + 750mg modified-release tablet
	87850998	Nicotinic acid 1g modified release tablets
	87851998	Nicotinic acid 750mg modified release tablets
	86797998	Simvastatin 20mg / Ezetimibe 10mg tablets
	87916998	Simvastatin 40mg tablets
	89306996	Atorvastatin 40mg tablets
	89311998	Atorvastatin 10mg tablets
	89617998	Ispaghula husk 3.5g sugar free granules

89154997	Cerivastatin 200microgram tablets
86795998	Simvastatin 40mg / Ezetimibe 10mg tablets
89311997	Atorvastatin 20mg tablets
89306998	Atorvastatin 10mg tablets
89311996	Atorvastatin 40mg tablets
88298996	Fenofibrate micronised 200mg capsules
86788998	Simvastatin 40mg / Ezetimibe 10mg tablets
86789998	Simvastatin 20mg / Ezetimibe 10mg tablets
89153998	Cerivastatin sodium 100mcg tablets
86787998	Simvastatin 80mg / Ezetimibe 10mg tablets
89154998	Cerivastatin 100microgram tablets
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86467998	Rosuvastatin 5mg tablets
89285979	Nicotinic acid 500mg modified release tablets
89800998	Eicosapentaenoic acid 460mg / Docosahexaenoic acid 380mg capsules
89284979	Nicotinic acid 750mg modified release tablets
88298998	Fenofibrate micronised 67mg capsules
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87855998	Nicotinic acid 500mg modified-release tablets
89283979	Nicotinic acid 1g modified release tablets
89153997	Cerivastatin sodium 200mcg tablets
86468998	Rosuvastatin 5mg tablets
92447998	Cerivastatin sodium 400mcg tablets
90973998	Rosuvastatin 20mg tablets
93619998	Simvastatin 10mg tablets
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93620996	Simvastatin 40mg tablets
92448997	Cerivastatin 800microgram tablets
92410998	Rosuvastatin 40mg tablets
93620997	Simvastatin 20mg tablets
93620998	Simvastatin 10mg tablets
93871990	Simvastatin 40mg tablets
92409998	Rosuvastatin 10mg tablets
93243996	Pravastatin 40mg tablets
91194998	Fluvastatin 80mg modified-release tablets
93010990	Colestyramine 4g oral powder sachets sugar free
92549990	Fenofibrate micronised 200mg capsules
93244998	Pravastatin 10mg tablets
93244997	Pravastatin 20mg tablets
93244996	Pravastatin 40mg tablets
92539998	Rosuvastatin 40mg tablets
90310998	Atorvastatin 80mg tablets
93243997	Pravastatin 20mg tablets
92448998	Cerivastatin 400microgram tablets

94407990	Simvastatin 20mg tablets
93838990	Bezafibrate 200mg tablets
92471998	Simvastatin 80mg tablets
93851992	Colestipol 5g granules sachets sugar free
90309998	Atorvastatin 80mg tablets
92460998	Fenofibrate micronised 160mg tablets
91316998	Colestyramine sugar free powder
93243998	Pravastatin 10mg tablets
92292998	Ezetimibe 10mg tablets
92154990	Simvastatin 20mg/5ml oral suspension sugar free
93541998	Colestyramine 4g oral powder sachets
93542998	Colestyramine 4g oral powder sachets sugar free
92804997	Fluvastatin 40mg capsules
94189997	Fenofibrate micronised 200mg capsules
92293998	Ezetimibe 10mg tablets
90649998	Fenofibrate 200mg capsules
92805998	Fluvastatin 20mg capsules
92804998	Fluvastatin 20mg capsules
92805997	Fluvastatin 40mg capsules
93619996	Simvastatin 40mg tablets
92220998	Simvastatin 80mg tablets
90653998	Colestyramine 4g oral powder sachets sugar free
94188997	Fenofibrate micronised 200mg capsules
94112992	Cholestyramine 325 mg cap
94188998	Fenofibrate 100mg capsule
94189998	Fenofibrate 100mg capsules
92804996	Fluvastatin 80mg modified-release tablets
93619997	Simvastatin 20mg tablets
95480990	Simvastatin 10mg tablets
95479990	Simvastatin 20mg tablets
95952997	Bezafibrate 400mg modified-release tablets
95550990	Simvastatin 20mg tablets
95551990	Simvastatin 10mg tablets
94925998	Eicosapentaenoic acid 170mg / Docosahexaenoic acid 115mg capsules
95478990	Simvastatin 40mg tablets
95471990	Simvastatin 40mg tablets
95475990	Simvastatin 20mg tablets
94799998	Fenofibrate micronised 160mg tablets
96295997	Gemfibrozil 600mg tablets
95474990	Simvastatin 40mg tablets
95472990	Simvastatin 20mg tablets
95451990	Simvastatin 10mg tablets
95549990	Simvastatin 40mg tablets
96295998	Gemfibrozil 300mg capsules
94927990	Simvastatin 80mg tablets

94827992	Colestyramine 4g oral powder sachets
95501990	Simvastatin 40mg tablets
94782990	Pravastatin 20mg tablets
95185990	Simvastatin 80mg tablets
95494990	Simvastatin 20mg tablets
94605998	Colestipol 5g granules sachets sugar free
95495990	Simvastatin 10mg tablets
94851990	Pravastatin 10mg tablets
95500990	Simvastatin 80mg tablets
94830990	Pravastatin 20mg tablets
95502990	Simvastatin 20mg tablets
97078998	Fish oil concentrate 1g capsules
96685990	Bezafibrate 400mg modified-release tablets
96685989	Bezafibrate 200mg tablets
97377979	Cerivastatin sodium 300mcg tablets
94831990	Pravastatin 10mg tablets
97078997	Fish oil concentrate oral liquid
94661998	Colestipol 5g granules sachets sugar free
95482990	Simvastatin 20mg tablets
95483990	Simvastatin 10mg tablets
95486990	Simvastatin 40mg tablets
95508990	Simvastatin 10mg tablets
95487990	Simvastatin 20mg tablets
95952998	Bezafibrate 200mg tablets
97078996	Fish oil concentrate oral emulsion
94850990	Pravastatin 20mg tablets
94849990	Pravastatin 40mg tablets
94662998	Colestipol 5g granules sachets sugar free
95493990	Simvastatin 40mg tablets
95847990	Colestyramine 4g oral powder sachets sugar free
95098992	Hexopal 200 mg tab
97455979	Pravastatin 10mg tablets
95481990	Simvastatin 40mg tablets
94661997	Colestipol 5g granules sachets sugar free
97430979	Fluvastatin 20mg capsules
95805998	Bezafibrate 400mg modified release tablets
95405990	Simvastatin 40mg tablets
94789990	Pravastatin 10mg tablets
95401998	Probucol 250mg tablet
97247997	Gemfibrozil 600mg tablets
97247998	Gemfibrozil 300mg capsules
96134990	Colestyramine 4g oral powder sachets
95278990	Simvastatin 20mg tablets
95277990	Simvastatin 40mg tablets
95372990	Simvasta

Table S2 Overview of codes used to define each cardiovascular disease endpoints

Endpoint	THIN READ Codes	Description
Coronary heart disease	G3...00	Ischaemic heart disease
	G3...11	Arteriosclerotic heart disease
	G3...12	Atherosclerotic heart disease
	G3...13	IHD - Ischaemic heart disease
	G30..00	Acute myocardial infarction
	G30..11	Attack - heart
	G30..12	Coronary thrombosis
	G30..13	Cardiac rupture following myocardial infarction (MI)
	G30..14	Heart attack
	G30..15	MI - acute myocardial infarction
	G30..16	Thrombosis - coronary
	G30..17	Silent myocardial infarction
	G300.00	Acute anterolateral infarction
	G301.00	Other specified anterior myocardial infarction
	G301000	Acute anteroapical infarction
	G301100	Acute anteroseptal infarction
	G301z00	Anterior myocardial infarction NOS
	G302.00	Acute inferolateral infarction
	G303.00	Acute inferoposterior infarction
	G304.00	Posterior myocardial infarction NOS
	G305.00	Lateral myocardial infarction NOS
	G306.00	True posterior myocardial infarction
	G307.00	Acute subendocardial infarction
	G307000	Acute non-Q wave infarction
	G307100	Acute non-ST segment elevation myocardial infarction
	G308.00	Inferior myocardial infarction NOS
	G309.00	Acute Q-wave infarct
	G30A.00	Mural thrombosis
	G30B.00	Acute posterolateral myocardial infarction
	G30X.00	Acute transmural myocardial infarction of unspecif site
	G30X000	Acute ST segment elevation myocardial infarction
	G30y.00	Other acute myocardial infarction
	G30y000	Acute atrial infarction
	G30y100	Acute papillary muscle infarction
	G30y200	Acute septal infarction
	G30yz00	Other acute myocardial infarction NOS
	G30z.00	Acute myocardial infarction NOS
	G31..00	Other acute and subacute ischaemic heart disease
	G310.00	Postmyocardial infarction syndrome

G310.11	Dressler's syndrome
G311.00	Preinfarction syndrome
G311.11	Crescendo angina
G311.12	Impending infarction
G311.13	Unstable angina
G311.14	Angina at rest
G311000	Myocardial infarction aborted
G311011	MI - myocardial infarction aborted
G311100	Unstable angina
G311200	Angina at rest
G311300	Refractory angina
G311400	Worsening angina
G311500	Acute coronary syndrome
G311z00	Preinfarction syndrome NOS
G312.00	Coronary thrombosis not resulting in myocardial infarction
G31y.00	Other acute and subacute ischaemic heart disease
G31y000	Acute coronary insufficiency
G31y100	Microinfarction of heart
G31y200	Subendocardial ischaemia
G31y300	Transient myocardial ischaemia
G31yz00	Other acute and subacute ischaemic heart disease NOS
G32..00	Old myocardial infarction
G32..11	Healed myocardial infarction
G32..12	Personal history of myocardial infarction
G33..00	Angina pectoris
G330.00	Angina decubitus
G330000	Nocturnal angina
G330z00	Angina decubitus NOS
G331.00	Prinzmetal's angina
G331.11	Variant angina pectoris
G332.00	Coronary artery spasm
G33z.00	Angina pectoris NOS
G33z000	Status anginosus
G33z100	Stenocardia
G33z200	Syncope anginosa
G33z300	Angina on effort
G33z400	Ischaemic chest pain
G33z500	Post infarct angina
G33z600	New onset angina
G33z700	Stable angina
G33zz00	Angina pectoris NOS
G34..00	Other chronic ischaemic heart disease
G340.00	Coronary atherosclerosis
G340.11	Triple vessel disease of the heart
G340.12	Coronary artery disease
G340000	Single coronary vessel disease

G340100	Double coronary vessel disease
G341.00	Aneurysm of heart
G341.11	Cardiac aneurysm
G341000	Ventricular cardiac aneurysm
G341100	Other cardiac wall aneurysm
G341111	Mural cardiac aneurysm
G341200	Aneurysm of coronary vessels
G341300	Acquired atrioventricular fistula of heart
G341z00	Aneurysm of heart NOS
G342.00	Atherosclerotic cardiovascular disease
G343.00	Ischaemic cardiomyopathy
G344.00	Silent myocardial ischaemia
G34y.00	Other specified chronic ischaemic heart disease
G34y000	Chronic coronary insufficiency
G34y100	Chronic myocardial ischaemia
G34yz00	Other specified chronic ischaemic heart disease NOS
G34z.00	Other chronic ischaemic heart disease NOS
G34z000	Asymptomatic coronary heart disease
G35..00	Subsequent myocardial infarction
G350.00	Subsequent myocardial infarction of anterior wall
G351.00	Subsequent myocardial infarction of inferior wall
G353.00	Subsequent myocardial infarction of other sites
G35X.00	Subsequent myocardial infarction of unspecified site
G36..00	Certain current complication follow acute myocardial infarct
G360.00	Haemopericardium/current comp folow acut myocard infarct
G361.00	Atrial septal defect/curr comp folow acut myocardal infarct
G362.00	Ventric septal defect/curr comp fol acut myocardal infarctn
G363.00	Ruptur cardiac wall w'out haemopericard/cur comp fol ac MI
G364.00	Ruptur chordae tendinae/curr comp fol acute myocard infarct
G365.00	Rupture papillary muscle/curr comp fol acute myocard infarct
G366.00	Thrombosis atrium,auric append&vent/curr comp foll acute MI
G37..00	Cardiac syndrome X
G38..00	Postoperative myocardial infarction
G380.00	Postoperative transmural myocardial infarction anterior wall
G381.00	Postoperative transmural myocardial infarction inferior wall
G382.00	Postoperative transmural myocardial infarction other sites
G383.00	Postoperative transmural myocardial infarction unspec site
G384.00	Postoperative subendocardial myocardial infarction
G38z.00	Postoperative myocardial infarction, unspecified
G39..00	Coronary microvascular disease
G3y..00	Other specified ischaemic heart disease
G3z..00	Ischaemic heart disease NOS
Gyu3.00	[X]Ischaemic heart diseases
Gyu3000	[X]Other forms of angina pectoris
Gyu3100	[X]Other current complications following acute myocard infarct
Gyu3200	[X]Other forms of acute ischaemic heart disease

	Gyu3300	[X]Other forms of chronic ischaemic heart disease
	Gyu3400	[X]Acute transmural myocardial infarction of unspecif site
	Gyu3500	[X]Subsequent myocardial infarction of other sites
	Gyu3600	[X]Subsequent myocardial infarction of unspecified site
Cerebrovascular disease		
	G6...00	Cerebrovascular disease
	G60..00	Subarachnoid haemorrhage
	G600.00	Ruptured berry aneurysm
	G601.00	Subarachnoid haemorrhage from carotid siphon and bifurcation
	G602.00	Subarachnoid haemorrhage from middle cerebral artery
	G603.00	Subarachnoid haemorrhage from anterior communicating artery
	G604.00	Subarachnoid haemorrhage from posterior communicating artery
	G605.00	Subarachnoid haemorrhage from basilar artery
	G606.00	Subarachnoid haemorrhage from vertebral artery
	G60X.00	Subarachnoid haemorrh from intracranial artery, unspecif
	G60z.00	Subarachnoid haemorrhage NOS
	G61..00	Intracerebral haemorrhage
	G61..11	CVA - cerebrovascular accid due to intracerebral haemorrhage
	G61..12	Stroke due to intracerebral haemorrhage
	G610.00	Cortical haemorrhage
	G611.00	Internal capsule haemorrhage
	G612.00	Basal nucleus haemorrhage
	G613.00	Cerebellar haemorrhage
	G614.00	Pontine haemorrhage
	G615.00	Bulbar haemorrhage
	G616.00	External capsule haemorrhage
	G617.00	Intracerebral haemorrhage, intraventricular
	G618.00	Intracerebral haemorrhage, multiple localized
	G619.00	Lobar cerebral haemorrhage
	G61X.00	Intracerebral haemorrhage in hemisphere, unspecified
	G61X000	Left sided intracerebral haemorrhage, unspecified
	G61X100	Right sided intracerebral haemorrhage, unspecified
	G61z.00	Intracerebral haemorrhage NOS
	G62..00	Other and unspecified intracranial haemorrhage
	G620.00	Extradural haemorrhage - nontraumatic
	G621.00	Subdural haemorrhage - nontraumatic
	G622.00	Subdural haematoma - nontraumatic
	G623.00	Subdural haemorrhage NOS
	G62z.00	Intracranial haemorrhage NOS
	G63..00	Precerebral arterial occlusion
	G63..11	Infarction - precerebral
	G63..12	Stenosis of precerebral arteries
	G630.00	Basilar artery occlusion
	G631.00	Carotid artery occlusion

G631.11	Stenosis, carotid artery
G631.12	Thrombosis, carotid artery
G632.00	Vertebral artery occlusion
G633.00	Multiple and bilateral precerebral arterial occlusion
G634.00	Carotid artery stenosis
G63y.00	Other precerebral artery occlusion
G63y000	Cerebral infarct due to thrombosis of precerebral arteries
G63y100	Cerebral infarction due to embolism of precerebral arteries
G63z.00	Precerebral artery occlusion NOS
G64..00	Cerebral arterial occlusion
G64..11	CVA - cerebral artery occlusion
G64..12	Infarction - cerebral
G64..13	Stroke due to cerebral arterial occlusion
G640.00	Cerebral thrombosis
G640000	Cerebral infarction due to thrombosis of cerebral arteries
G641.00	Cerebral embolism
G641.11	Cerebral embolus
G641000	Cerebral infarction due to embolism of cerebral arteries
G64z.00	Cerebral infarction NOS
G64z.11	Brainstem infarction NOS
G64z.12	Cerebellar infarction
G64z000	Brainstem infarction
G64z100	Wallenberg syndrome
G64z111	Lateral medullary syndrome
G64z200	Left sided cerebral infarction
G64z300	Right sided cerebral infarction
G64z400	Infarction of basal ganglia
G65..00	Transient cerebral ischaemia
G65..11	Drop attack
G65..12	Transient ischaemic attack
G65..13	Vertebro-basilar insufficiency
G650.00	Basilar artery syndrome
G650.11	Insufficiency - basilar artery
G651.00	Vertebral artery syndrome
G651000	Vertebro-basilar artery syndrome
G652.00	Subclavian steal syndrome
G653.00	Carotid artery syndrome hemispheric
G654.00	Multiple and bilateral precerebral artery syndromes
G655.00	Transient global amnesia
G656.00	Vertebrobasilar insufficiency
G657.00	Carotid territory transient ischaemic attack
G65y.00	Other transient cerebral ischaemia
G65z.00	Transient cerebral ischaemia NOS
G65z000	Impending cerebral ischaemia
G65z100	Intermittent cerebral ischaemia
G65zz00	Transient cerebral ischaemia NOS

G66..00	Stroke and cerebrovascular accident unspecified
G66..11	CVA unspecified
G66..12	Stroke unspecified
G66..13	CVA - Cerebrovascular accident unspecified
G660.00	Middle cerebral artery syndrome
G661.00	Anterior cerebral artery syndrome
G662.00	Posterior cerebral artery syndrome
G663.00	Brain stem stroke syndrome
G664.00	Cerebellar stroke syndrome
G665.00	Pure motor lacunar syndrome
G666.00	Pure sensory lacunar syndrome
G667.00	Left sided CVA
G668.00	Right sided CVA
G669.00	Cerebral palsy, not congenital or infantile, acute
G67..00	Other cerebrovascular disease
G670.00	Cerebral atherosclerosis
G670.11	Precerebral atherosclerosis
G671.00	Generalised ischaemic cerebrovascular disease NOS
G671000	Acute cerebrovascular insufficiency NOS
G671100	Chronic cerebral ischaemia
G671z00	Generalised ischaemic cerebrovascular disease NOS
G672.00	Hypertensive encephalopathy
G672.11	Hypertensive crisis
G673.00	Cerebral aneurysm, nonruptured
G673000	Dissection of cerebral arteries, nonruptured
G673100	Carotico-cavernous sinus fistula
G673200	Carotid artery dissection
G673300	Vertebral artery dissection
G674.00	Cerebral arteritis
G674000	Cerebral amyloid angiopathy
G675.00	Moyamoya disease
G676.00	Nonpyogenic venous sinus thrombosis
G676000	Cereb infarct due cerebral venous thrombosis, nonpyogenic
G677.00	Occlusion/stenosis cerebral arts not result cerebral infarct
G677000	Occlusion and stenosis of middle cerebral artery
G677100	Occlusion and stenosis of anterior cerebral artery
G677200	Occlusion and stenosis of posterior cerebral artery
G677300	Occlusion and stenosis of cerebellar arteries
G677400	Occlusion+stenosis of multiple and bilat cerebral arteries
G678.00	Cereb autosom dominant arteriop subcort infarcts leukoenceph
G679.00	Small vessel cerebrovascular disease
G67A.00	Cerebral vein thrombosis
G67B.00	Reversible cerebral vasoconstriction syndrome
G67B.11	Call-Fleming syndrome
G67y.00	Other cerebrovascular disease OS
G67z.00	Other cerebrovascular disease NOS

	G68..00	Late effects of cerebrovascular disease
	G680.00	Sequelae of subarachnoid haemorrhage
	G681.00	Sequelae of intracerebral haemorrhage
	G682.00	Sequelae of other nontraumatic intracranial haemorrhage
	G683.00	Sequelae of cerebral infarction
	G68W.00	Sequelae/other + unspecified cerebrovascular diseases
	G68X.00	Sequelae of stroke,not specfd as h'morrhage or infarction
	G6y..00	Other specified cerebrovascular disease
	G6z..00	Cerebrovascular disease NOS
	Gyu6.00	[X]Cerebrovascular diseases
	Gyu6000	[X]Subarachnoid haemorrhage from other intracranial arteries
	Gyu6100	[X]Other subarachnoid haemorrhage
	Gyu6200	[X]Other intracerebral haemorrhage
	Gyu6300	[X]Cerebrl infarctn due/unspcf occlusn or sten/cerebrl artrs
	Gyu6400	[X]Other cerebral infarction
	Gyu6500	[X]Occlusion and stenosis of other precerebral arteries
	Gyu6600	[X]Occlusion and stenosis of other cerebral arteries
	Gyu6700	[X]Other specified cerebrovascular diseases
	Gyu6C00	[X]Sequelae of stroke;not specfd as h'morrhage or infarction
	Gyu6D00	[X]Sequelae/other unspecified cerebrovascular diseases
	Gyu6E00	[X]Subarachnoid haemorrh from intracranial artery, unspecif
	Gyu6F00	[X]Intracerebral haemorrhage in hemisphere, unspecified
	Gyu6G00	[X]Cereb infarct due unsp occlus/stenos precerebr arteries
	G6W..00	Cereb infarct due unsp occlus/stenos precerebr arteries
	G6X..00	Cerebrl infarctn due/unspcf occlusn or sten/cerebrl artrs
Heart Failure		
	1O1..00	Heart failure confirmed
	2JZ..00	On optimal heart failure therapy
	662f.00	New York Heart Association classification - class I
	662g.00	New York Heart Association classification - class II
	662h.00	New York Heart Association classification - class III
	662i.00	New York Heart Association classification - class IV
	8B29.00	Cardiac failure therapy
	G58..00	Heart failure
	G58..11	Cardiac failure
	G580.00	Congestive heart failure
	G580.11	Congestive cardiac failure
	G580.14	Biventricular failure
	G580000	Acute congestive heart failure
	G580100	Chronic congestive heart failure
	G580200	Decompensated cardiac failure
	G580300	Compensated cardiac failure
	G580400	Congestive heart failure due to valvular disease
	G581.00	Left ventricular failure
	G581.11	Asthma - cardiac
	G581.13	Impaired left ventricular function

	G581000	Acute left ventricular failure
	G582.00	Acute heart failure
	G583.00	Heart failure with normal ejection fraction
	G583.11	HFNEF - heart failure with normal ejection fraction
	G583.12	Heart failure with preserved ejection fraction
	G58z.00	Heart failure NOS
	G58z.12	Cardiac failure NOS
	G5y4z00	Post cardiac operation heart failure NOS
	661M500	Heart failure self-management plan agreed
	661N500	Heart failure self-management plan review
	662p.00	Heart failure 6 month review
	662T.00	Congestive heart failure monitoring
	662W.00	Heart failure annual review
	679W100	education about deteriorating heart failure
	8H2S.00	Admit heart failure emergency
	8HBE.00	Heart failure follow-up
	8HTL000	Referral to rapid access heart failure clinic
	G232.00	Hypertensive heart&renal dis wth (congestive) heart failure
	G234.00	Hyperten heart&renal dis+both(congestv)heart and renal fail
	G581.12	Pulmonary oedema - acute
	G58z.11	Weak heart
	SP11111	Heart failure as a complication of care
	SP11200	Cardiorespiratory failure as a complication of care
	G554000	Congestive cardiomyopathy
Peripheral vascular disease		
	C108G00	Insulin dependent diab mell with peripheral angiopathy
	C108G11	Type I diabetes mellitus with peripheral angiopathy
	C108G12	Type 1 diabetes mellitus with peripheral angiopathy
	C109F11	Type II diabetes mellitus with peripheral angiopathy
	C109F12	Type 2 diabetes mellitus with peripheral angiopathy
	C10EG00	Type 1 diabetes mellitus with peripheral angiopathy
	C10EG11	Type I diabetes mellitus with peripheral angiopathy
	C10EG12	Insulin dependent diab mell with peripheral angiopathy
	C10FF00	Type 2 diabetes mellitus with peripheral angiopathy
	C10FF11	Type II diabetes mellitus with peripheral angiopathy
	G711.00	Thoracic aortic aneurysm which has ruptured
	G711.11	Ruptured thoracic aortic aneurysm
	G712.00	Thoracic aortic aneurysm without mention of rupture
	G713.00	Abdominal aortic aneurysm which has ruptured
	G713.11	Ruptured abdominal aortic aneurysm
	G713000	Ruptured suprarenal aortic aneurysm
	G714.00	Abdominal aortic aneurysm without mention of rupture
	G714.11	AAA - Abdominal aortic aneurysm without mention of rupture
	G714000	Juxtarenal aortic aneurysm
	G714200	Infrarenal abdominal aortic aneurysm

G714300	Aneurysm of suprarenal aorta
G715.00	Ruptured aortic aneurysm NOS
G715000	Thoracoabdominal aortic aneurysm, ruptured
G716.00	Aortic aneurysm without mention of rupture NOS
G716000	Thoracoabdominal aortic aneurysm, without mention of rupture
G718.00	Leaking abdominal aortic aneurysm
G71z.00	Aortic aneurysm NOS
G72..00	Other aneurysm
G720.00	Aneurysm of artery of arm
G720000	Aneurysm of brachial artery
G720100	Aneurysm of radial artery
G720200	Aneurysm of ulnar artery
G720z00	Aneurysm of arm artery NOS
G721.00	Aneurysm of renal artery
G721000	Acquired renal artery aneurysm
G722.00	Aneurysm of iliac artery
G722000	Aneurysm of common iliac artery
G722100	Aneurysm of external iliac artery
G722200	Aneurysm of internal iliac artery
G722z00	Aneurysm of iliac artery NOS
G723.00	Aneurysm of leg artery
G723000	Aneurysm of femoral artery
G723100	Aneurysm of popliteal artery
G723200	Aneurysm of anterior tibial artery
G723300	Aneurysm of dorsalis pedis artery
G723400	Aneurysm of posterior tibial artery
G723500	Ruptured popliteal artery aneurysm
G723600	Post radiological femoral false aneurysm
G723z00	Aneurysm of leg artery NOS
G73..00	Other peripheral vascular disease
G731.00	Thromboangiitis obliterans
G731000	Buerger's disease
G734.00	Peripheral arterial disease
G73y.00	Other specified peripheral vascular disease
G73y000	Diabetic peripheral angiopathy
G73z.00	Peripheral vascular disease NOS
G73z000	Intermittent claudication
G73zz00	Peripheral vascular disease NOS
G740.13	Leriche's syndrome
G76z100	Femoral artery occlusion
G76z200	Popliteal artery occlusion
Gyu7400	[X]Other specified peripheral vascular diseases
Gyu7A00	[X]Peripheral angiopathy in diseases classified elsewhere
G73..11	Peripheral ischaemic vascular disease
G73..12	Ischaemia of legs
G73..13	Peripheral ischaemia

C107.11	Diabetes mellitus with gangrene
C107.12	Diabetes with gangrene
C107000	Diabetes mellitus, juvenile +peripheral circulatory disorder
C107100	Diabetes mellitus, adult, + peripheral circulatory disorder
C107200	Diabetes mellitus, adult with gangrene
C107300	IDDM with peripheral circulatory disorder
C107400	NIDDM with peripheral circulatory disorder
C107y00	Other specified diabetes mellitus with periph circ comps
C107z00	Diabetes mellitus NOS with peripheral circulatory disorder
C108600	Insulin dependent diabetes mellitus with gangrene
C108611	Type I diabetes mellitus with gangrene
C108612	Type 1 diabetes mellitus with gangrene
C109500	Non-insulin dependent diabetes mellitus with gangrene
C109511	Type II diabetes mellitus with gangrene
C109512	Type 2 diabetes mellitus with gangrene
C10E600	Type 1 diabetes mellitus with gangrene
C10E611	Type I diabetes mellitus with gangrene
C10E612	Insulin dependent diabetes mellitus with gangrene
C10F500	Type 2 diabetes mellitus with gangrene
C10F511	Type II diabetes mellitus with gangrene
G71..00	Aortic aneurysm
G710.00	Dissecting aortic aneurysm
G72y.00	Aneurysm of other artery
G72y000	Aneurysm of common carotid art
G72y100	Aneurysm of external carotid artery
G72y200	Aneurysm of internal carotid artery
G72y300	Aneurysm of neck artery NOS
G72y400	Aneurysm of subclavian artery
G72y500	Aneurysm of splenic artery
G72y600	Aneurysm of axillary artery
G72y700	Aneurysm of coeliac artery
G72y800	Aneurysm of superior mesenteric artery
G72y900	Aneurysm of inferior mesenteric artery
G72yA00	Aneurysm of hepatic artery
G72yB00	Aneurysm of other visceral artery
G72z.00	Aneurysm NOS
G733.00	Ischaemic foot
G73y100	Peripheral angiopathic disease EC NOS
G73z011	Claudication
G73z012	Vascular claudication
G73z100	Spasm of peripheral artery
G74..00	Arterial embolism and thrombosis
G74..11	Arterial embolus and thrombosis
G74..12	Thrombosis - arterial
G74..13	Arterial embolic and thrombotic occlusion
G740.00	Embolism and thrombosis of the abdominal aorta

Table S3 Distribution of body size phenotypes and metabolic status in the Health Improvement Network (N=3,495,777)

Body size phenotype and metabolic status	N	(%)
Underweight, 0 metabolic abnormalities	86,847	2.5
Underweight, 1 metabolic abnormalities	5,758	0.2
Underweight, 2 metabolic abnormalities	1,259	0.0
Underweight, 3 metabolic abnormalities	165	0.0
Normal weight, 0 metabolic abnormalities	1,318,516	37.7
Normal weight, 1 metabolic abnormality	118,684	3.4
Normal weight, 2 metabolic abnormalities	36,808	1.1
Normal weight, 3 metabolic abnormalities	6,218	0.2
Overweight, 0 metabolic abnormalities	899,471	25.7
Overweight, 1 metabolic abnormality	171,412	4.9
Overweight, 2 metabolic abnormalities	71,439	2.0
Overweight, 3 metabolic abnormalities	16,494	0.5
Obese, 0 metabolic abnormalities	517,444	14.8
Obese, 1 metabolic abnormality	148,190	4.24
Obese, 2 metabolic abnormalities	70,278	2.01
Obese, 3 metabolic abnormalities	26,794	0.77

Table S4 Incidence rate of coronary heart disease by body size phenotype and metabolic status

	# patients	# patients with event	# patient years of follow up	Incidence rate/1000 y
Underweight, 0 metabolic abnormalities	86,847	439	382367.07	1.15
Underweight, ≥ 1 metabolic abnormality	7,182	208	30594.24	6.80
Normal weight, 0 metabolic abnormalities	1,318,516	9895	6661783.30	1.49
Normal weight, 1 metabolic abnormality	118,684	4783	684828.15	6.98
Normal weight, 2 metabolic abnormalities	36,808	1631	190514.26	8.56
Normal weight, 3 metabolic abnormalities	6,218	359	31149.97	11.52
Overweight, 0 metabolic abnormalities	899,471	13056	4914040.90	2.66
Overweight, 1 metabolic abnormality	171,412	7960	1047503.00	7.60
Overweight, 2 metabolic abnormalities	71,439	3656	389450.18	9.39
Overweight, 3 metabolic abnormalities	16,494	1018	89959.21	11.32
Obese, 0 metabolic abnormalities	517,444	7526	2847791.80	2.64
Obese, 1 metabolic abnormality	148,190	6127	916305.49	6.69
Obese, 2 metabolic abnormalities	70,278	3324	382390.31	8.69
Obese, 3 metabolic abnormalities	26,794	1564	140615.84	11.12

Table S5 Incidence rate of cerebrovascular disease by body size phenotype and metabolic status

	# patients	# patients with event	# patient years of follow up	Incidence rate/1000 y
Underweight, 0 metabolic abnormalities	86,847	750	381629.72	1.97
Underweight, ≥ 1 metabolic abnormality	7,182	390	30374.81	12.84
Normal weight, 0 metabolic abnormalities	1,318,516	10918	6665697.30	1.64
Normal weight, 1 metabolic abnormality	118,684	5628	687108.94	8.19
Normal weight, 2 metabolic abnormalities	36,808	1706	191754.77	8.90
Normal weight, 3 metabolic abnormalities	6,218	381	31396.80	12.13
Overweight, 0 metabolic abnormalities	899,471	10097	4935219.40	2.05
Overweight, 1 metabolic abnormality	171,412	7179	1058514.00	6.78
Overweight, 2 metabolic abnormalities	71,439	3064	394740.39	7.76
Overweight, 3 metabolic abnormalities	16,494	883	91070.76	9.70
Obese, 0 metabolic abnormalities	517,444	5266	2861789.20	1.84
Obese, 1 metabolic abnormality	148,190	4791	926935.57	5.17
Obese, 2 metabolic abnormalities	70,278	2550	388122.06	6.57
Obese, 3 metabolic abnormalities	26,794	1102	143326.81	7.69

Table S6 Incidence rate of heart failure by body size phenotype and metabolic status

	# patients	# patients with event	# patient years of follow up	Incidence rate/1000 y
Underweight, 0 metabolic abnormalities	86,847	283	383187.38	0.74
Underweight, ≥ 1 metabolic abnormality	7,182	158	30990.91	5.10
Normal weight, 0 metabolic abnormalities	1,318,516	3555	6693309.60	0.53
Normal weight, 1 metabolic abnormality	118,684	2381	699540.86	3.40
Normal weight, 2 metabolic abnormalities	36,808	744	195390.05	3.81
Normal weight, 3 metabolic abnormalities	6,218	169	32063.14	5.27
Overweight, 0 metabolic abnormalities	899,471	3619	4961523.10	0.73
Overweight, 1 metabolic abnormality	171,412	3457	1074562.70	3.22
Overweight, 2 metabolic abnormalities	71,439	1514	400568.30	3.78
Overweight, 3 metabolic abnormalities	16,494	463	92695.20	4.99
Obese, 0 metabolic abnormalities	517,444	2813	2871691.70	0.98
Obese, 1 metabolic abnormality	148,190	3330	2871691.70	3.57
Obese, 2 metabolic abnormalities	70,278	1858	391089.97	4.75
Obese, 3 metabolic abnormalities	26,794	910	144252.07	6.31

Table S7 Incidence rate of peripheral vascular disease by body size phenotype and metabolic status

	# patients	# patients with event	# patient years of follow up	Incidence rate/1000 y
Underweight, 0 metabolic abnormalities	86,847	283	383187.38	0.74
Underweight, ≥ 1 metabolic abnormality	7,182	158	30990.91	5.10
Normal weight, 0 metabolic abnormalities	1,318,516	3555	6693309.60	0.53
Normal weight, 1 metabolic abnormality	118,684	2381	699540.86	3.40
Normal weight, 2 metabolic abnormalities	36,808	744	195390.05	3.81
Normal weight, 3 metabolic abnormalities	6,218	169	32063.14	5.27
Overweight, 0 metabolic abnormalities	899,471	3619	4961523.10	0.73
Overweight, 1 metabolic abnormality	171,412	3457	1074562.70	3.22
Overweight, 2 metabolic abnormalities	71,439	1514	400568.30	3.78
Overweight, 3 metabolic abnormalities	16,494	463	92695.20	4.99
Obese, 0 metabolic abnormalities	517,444	2813	2871691.70	0.98
Obese, 1 metabolic abnormality	148,190	3330	2871691.70	3.57
Obese, 2 metabolic abnormalities	70,278	1858	391089.97	4.75
Obese, 3 metabolic abnormalities	26,794	910	144252.07	6.31

Table S8 Sensitivity analysis results: Association between body size phenotype and metabolic status with coronary heart disease by sex and age

Body size phenotype and metabolic status	**Sex HR (95% CI)***		**Age (years) HR (95% CI)†**	
	Male	Female	<65	≥ 65
Underweight, 0 metabolic abnormalities	0.83(0.71-0.98)	0.99(0.88-1.11)	0.87(0.76-0.87)	0.88(0.78-1.00)
Underweight, 1 or more metabolic abnormalities	1.05(0.78-1.41)	1.59(1.37-1.86)	1.73(1.31-1.73)	1.15(0.98-1.35)
Normal weight, 0 metabolic abnormalities	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Normal weight, 1 metabolic abnormality	1.54(1.47-1.62)	1.73(1.63-1.83)	2.10(1.98-2.10)	1.23(1.17-1.29)
Normal weight, 2 metabolic abnormalities	1.53(1.42-1.65)	1.90(1.75-2.06)	2.30(2.09-2.30)	1.27(1.19-1.36)
Normal weight, 3 metabolic abnormalities	1.89(1.63-2.20)	2.55(2.19-2.97)	3.38(2.83-3.38)	1.56(1.37-1.78)
Overweight, 0 metabolic abnormalities	1.26(1.22-1.31)	1.26(1.20-1.32)	1.40(1.35-1.40)	1.16(1.11-1.21)
Overweight, 1 metabolic abnormality	1.68(1.61-1.75)	1.87(1.78-1.96)	2.21(2.11-2.21)	1.33(1.27-1.39)
Overweight, 2 metabolic abnormalities	1.72(1.63-1.82)	2.17(2.03-2.31)	2.53(2.38-2.53)	1.38(1.30-1.45)
Overweight, 3 metabolic abnormalities	2.00(1.84-2.17)	2.48(2.22-2.77)	3.11(2.81-3.11)	1.55(1.42-1.70)
Obese, 0 metabolic abnormalities	1.46(1.40-1.52)	1.48(1.41-1.55)	1.72(1.66-1.72)	1.15(1.09-1.22)
Obese, 1 metabolic abnormality	1.78(1.71-1.86)	2.04(1.94-2.16)	2.41(2.30-2.41)	1.36(1.29-1.43)
Obese, 2 metabolic abnormalities	1.86(1.76-1.96)	2.40(2.24-2.56)	2.83(2.68-2.83)	1.40(1.31-1.49)
Obese, 3 metabolic abnormalities	2.28(2.11-2.46)	2.90(2.66-3.16)	3.62(3.35-3.62)	1.65(1.52-1.79)

HR= Hazard Ratio; CI= Confidence interval

*Model adjusted for age, smoking status and social deprivation

†Model adjusted for sex, smoking status and social deprivation

Table S9 Sensitivity analysis results: Association between body size phenotype and metabolic status with coronary heart disease using metabolic status derived from prescription records or measurement, different adjustments and exclusion of type 1 diabetes cases

Body size phenotype and metabolic status	Metabolic status derived from prescription records or measurement HR (95% CI)[*]	HRT HR (95% CI) [†§]	Adjusted for oral contraceptives HR (95% CI)[‡ §]	Excluded Type 1 DM cases[*]	Never smoked HR (95% CI) [‖]
Underweight, 0 metabolic abnormalities	0.91(0.78-1.06)	0.99(0.88-1.11)	0.98(0.88-1.10)	0.92(0.84-1.01)	0.92(0.77-1.09)
Underweight, 1 or more metabolic abnormalities	1.82(1.65-2.02)	1.60(1.37-1.86)	1.59(1.36-1.85)	1.46(1.27-1.68)	1.61(1.31-1.96)
Normal weight, 0 metabolic abnormalities	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Normal weight, 1 metabolic abnormality	1.76(1.69-1.83)	1.73(1.63-1.83)	1.72(1.63-1.83)	1.64(1.58-1.70)	1.77(1.67-1.86)
Normal weight, 2 metabolic abnormalities	2.24(2.13-2.36)	1.91(1.76-2.07)	1.90(1.75-2.05)	1.65(1.56-1.75)	1.95(1.79-2.12)
Normal weight, 3 metabolic abnormalities	3.08(2.84-3.33)	2.57(2.21-2.99)	2.54(2.18-2.96)	2.03(1.80-2.27)	2.55(2.20-2.95)
Overweight, 0 metabolic abnormalities	1.32(1.26-1.37)	1.26(1.20-1.31)	1.25(1.20-1.31)	1.30(1.26-1.33)	1.33(1.28-1.39)
Overweight, 1 metabolic abnormality	2.07(1.99-2.16)	1.86(1.78-1.96)	1.86(1.77-1.95)	1.76(1.71-1.82)	1.91(1.83-2.00)
Overweight, 2 metabolic abnormalities	2.46(2.35-2.58)	2.17(2.03-2.32)	2.16(2.02-2.30)	1.87(1.79-1.96)	2.22(2.09-2.36)
Overweight, 3 metabolic abnormalities	3.18(2.99-3.37)	2.49(2.23-2.79)	2.47(2.21-2.76)	2.13(1.98-2.28)	2.60(2.36-2.87)
Obese, 0 metabolic abnormalities	1.59(1.50-1.68)	1.49(1.42-1.56)	1.48(1.41-1.55)	1.50(1.45-1.54)	1.53(1.46-1.60)
Obese, 1 metabolic abnormality	2.24(2.15-2.34)	2.05(1.94-2.16)	2.03(1.93-2.15)	1.92(1.85-1.99)	2.10(1.99-2.21)
Obese, 2 metabolic abnormalities	2.61(2.50-2.73)	2.41(2.25-2.58)	2.38(2.23-2.55)	2.07(1.98-2.17)	2.46(2.31-2.63)
Obese, 3 metabolic abnormalities	3.63(3.43-3.83)	2.92(2.68-3.18)	2.89(2.65-3.14)	2.50(2.36-2.65)	3.08(2.84-3.34)

HR= Hazard Ratio; CI= Confidence interval; HRT= hormone replacement therapy

[*]Model adjusted for age, sex, smoking status and social deprivation

[†]Model adjusted for age, sex, smoking status, social deprivation and HRT

[‡]Model adjusted for age, sex, smoking status, social deprivation and oral contraceptives

[§]Women only

[‖] Model adjusted for age, sex, and social deprivation

Table S10 Sensitivity analysis results: Association between body size phenotype and metabolic status with cerebrovascular disease by sex and age

Body size phenotype and metabolic status	Sex HR (95% CI)*		Age (years) HR (95% CI)†	
	Male	Female	<65	≥ 65
Underweight, 0 metabolic abnormalities	1.15(1.01-1.32)	1.23(1.12-1.34)	1.27(1.13-1.42)	1.11(1.00-1.22)
Underweight, 1 or more metabolic abnormalities	1.99(1.59-2.48)	1.52(1.35-1.72)	2.79(2.23-3.49)	1.33(1.18-1.50)
Normal weight, 0 metabolic abnormalities	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Normal weight, 1 metabolic abnormality	1.32(1.26-1.39)	1.41(1.35-1.47)	1.69(1.59-1.79)	1.19(1.14-1.24)
Normal weight, 2 metabolic abnormalities	1.25(1.15-1.35)	1.34(1.25-1.43)	1.77(1.58-1.98)	1.11(1.04-1.18)
Normal weight, 3 metabolic abnormalities	1.50(1.28-1.75)	1.73(1.52-1.97)	2.76(2.22-3.43)	1.34(1.20-1.50)
Overweight, 0 metabolic abnormalities	0.96(0.92-0.99)	1.03(0.99-1.07)	1.05(1.01-1.09)	0.97(0.93-1.00)
Overweight, 1 metabolic abnormality	1.21(1.16-1.27)	1.36(1.30-1.42)	1.57(1.49-1.65)	1.12(1.08-1.16)
Overweight, 2 metabolic abnormalities	1.19(1.12-1.26)	1.44(1.35-1.53)	1.73(1.60-1.87)	1.11(1.05-1.17)
Overweight, 3 metabolic abnormalities	1.40(1.26-1.55)	1.63(1.47-1.82)	1.99(1.73-2.28)	1.30(1.20-1.42)
Obese, 0 metabolic abnormalities	1.01(0.96-1.07)	1.11(1.07-1.16)	1.20(1.15-1.25)	0.95(0.90-1.00)
Obese, 1 metabolic abnormality	1.20(1.14-1.27)	1.39(1.32-1.45)	1.61(1.53-1.69)	1.09(1.04-1.14)
Obese, 2 metabolic abnormalities	1.33(1.25-1.42)	1.51(1.43-1.61)	1.84(1.72-1.97)	1.18(1.11-1.25)
Obese, 3 metabolic abnormalities	1.38(1.24-1.52)	1.75(1.61-1.90)	2.22(2.02-2.44)	1.23(1.13-1.34)

HR= Hazard Ratio; CI= Confidence interval

*Model adjusted for age, smoking status and social deprivation

†Model adjusted for sex, smoking status and social deprivation

Table S11 Sensitivity analysis results: Association between body size phenotype and metabolic status with cerebrovascular disease using metabolic status derived from prescription records or measurement, different adjustments, exclusion of type 1 diabetes cases and inclusion of only those who never smoked cigarettes

Body size phenotype and metabolic status	Metabolic status derived from prescription records or measurement HR (95% CI)[*]	HRT HR (95% CI)[†§]	Adjusted for oral contraceptives HR (95% CI)[‡ §]	Excluded Type 1 DM cases[*]	Never smoked HR (95% CI)[‖]
Underweight, 0 metabolic abnormalities	1.30(1.17-1.45)	1.23(1.13-1.35)	1.23(1.12-1.34)	1.20(1.11-1.29)	1.12(0.99-1.26)
Underweight, 1 or more metabolic abnormalities	1.74(1.60-1.89)	1.53(1.35-1.72)	1.52(1.35-1.71)	1.56(1.40-1.75)	1.60(1.38-1.86)
Normal weight, 0 metabolic abnormalities	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Normal weight, 1 metabolic abnormality	1.44(1.39-1.50)	1.41(1.35-1.47)	1.41(1.35-1.47)	1.36(1.32-1.41)	1.40(1.33-1.46)
Normal weight, 2 metabolic abnormalities	1.57(1.50-1.64)	1.34(1.25-1.43)	1.34(1.25-1.43)	1.28(1.21-1.35)	1.31(1.22-1.40)
Normal weight, 3 metabolic abnormalities	1.91(1.77-2.06)	1.74(1.52-1.98)	1.73(1.51-1.97)	1.56(1.41-1.74)	1.68(1.46-1.92)
Overweight, 0 metabolic abnormalities	1.03(0.98-1.07)	1.03(0.99-1.07)	1.03(0.99-1.07)	1.00(0.97-1.03)	1.04(1.00-1.08)
Overweight, 1 metabolic abnormality	1.37(1.32-1.43)	1.36(1.30-1.42)	1.36(1.30-1.42)	1.29(1.25-1.33)	1.37(1.31-1.42)
Overweight, 2 metabolic abnormalities	1.51(1.45-1.57)	1.44(1.35-1.53)	1.43(1.35-1.52)	1.30(1.24-1.36)	1.40(1.32-1.49)
Overweight, 3 metabolic abnormalities	1.87(1.76-1.99)	1.64(1.47-1.82)	1.63(1.46-1.81)	1.49(1.37-1.61)	1.65(1.48-1.83)
Obese, 0 metabolic abnormalities	1.16(1.10-1.23)	1.11(1.07-1.16)	1.11(1.06-1.16)	1.07(1.04-1.11)	1.20(1.14-1.25)
Obese, 1 metabolic abnormality	1.38(1.33-1.44)	1.39(1.33-1.46)	1.38(1.32-1.45)	1.30(1.26-1.35)	1.43(1.36-1.50)
Obese, 2 metabolic abnormalities	1.55(1.49-1.62)	1.52(1.43-1.61)	1.51(1.42-1.60)	1.41(1.36-1.48)	1.59(1.49-1.69)
Obese, 3 metabolic abnormalities	2.01(1.91-2.13)	1.76(1.62-1.90)	1.75(1.61-1.89)	1.50(1.41-1.61)	1.72(1.57-1.88)

HR= Hazard Ratio; CI= Confidence interval; HRT= hormone replacement therapy

[*]Model adjusted for age, sex, smoking status and social deprivation

[†]Model adjusted for age, sex, smoking status, social deprivation and HRT

[‡]Model adjusted for age, sex, smoking status, social deprivation and oral contraceptives

[§]Women only

[‖] Model adjusted for age, sex, and social deprivation

Table S12 Sensitivity analysis results: Association between body size phenotype and metabolic status with heart failure by sex and age

Body size phenotype and metabolic status	**Sex HR (95% CI)***		**Age (years) HR (95% CI)†**	
	Male	Female	<65	≥ 65
Underweight, 0 metabolic abnormalities	1.08(0.87-1.34)	1.39(1.20-1.62)	1.41(1.13-1.75)	1.18(1.02-1.35)
Underweight, 1 or more metabolic abnormalities	1.58(1.09-2.28)	1.54(1.26-1.87)	2.54(1.55-4.14)	1.33(1.11-1.60)
Normal weight, 0 metabolic abnormalities	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Normal weight, 1 metabolic abnormality	1.34(1.24-1.45)	1.52(1.41-1.63)	1.72(1.52-1.95)	1.30(1.22-1.38)
Normal weight, 2 metabolic abnormalities	1.26(1.11-1.43)	1.57(1.40-1.75)	2.21(1.84-2.65)	1.23(1.12-1.35)
Normal weight, 3 metabolic abnormalities	1.55(1.21-1.98)	1.95(1.60-2.37)	3.38(2.34-4.88)	1.48(1.26-1.74)
Overweight, 0 metabolic abnormalities	1.02(0.96-1.08)	1.19(1.11-1.28)	1.12(1.04-1.20)	1.12(1.05-1.19)
Overweight, 1 metabolic abnormality	1.52(1.43-1.62)	1.70(1.58-1.83)	1.93(1.74-2.14)	1.47(1.39-1.55)
Overweight, 2 metabolic abnormalities	1.62(1.50-1.76)	1.79(1.63-1.97)	2.39(2.11-2.70)	1.49(1.38-1.60)
Overweight, 3 metabolic abnormalities	1.91(1.67-2.18)	2.21(1.91-2.56)	3.30(2.68-4.07)	1.74(1.56-1.95)
Obese, 0 metabolic abnormalities	1.84(1.72-1.97)	2.05(1.91-2.21)	2.22(2.05-2.41)	1.84(1.72-1.97)
Obese, 1 metabolic abnormality	2.56(2.39-2.75)	2.73(2.55-2.92)	3.51(3.21-3.84)	2.28(2.15-2.43)
Obese, 2 metabolic abnormalities	2.76(2.54-3.00)	3.34(3.06-3.64)	4.33(3.90-4.80)	2.54(2.35-2.74)
Obese, 3 metabolic abnormalities	3.48(3.11-3.90)	4.08(3.66-4.54)	5.99(5.28-6.80)	2.98(2.71-3.28)

HR= Hazard Ratio; CI= Confidence interval

*Model adjusted for age, smoking status and social deprivation

†Model adjusted for sex, smoking status and social deprivation

Table S13 Sensitivity analysis results: Association between body size phenotype and metabolic status with heart failure using metabolic status derived from prescription records or measurement and exclusion of type 1 diabetes cases

Body size phenotype and metabolic status	Metabolic status derived from prescription records or measurement HR (95% CI)*	Excluded Type 1 DM cases*	Never smoked HR (95% CI)†
Underweight, 0 metabolic abnormalities	1.16(0.95-1.41)	1.28(1.13-1.44)	1.33(1.10-1.60)
Underweight, 1 or more metabolic abnormalities	1.75(1.54-1.98)	1.50(1.26-1.79)	1.73(1.37-2.19)
Normal weight, 0 metabolic abnormalities	1.00 (reference)	1.00 (reference)	1.00 (reference)
Normal weight, 1 metabolic abnormality	1.43(1.34-1.53)	1.43(1.35-1.51)	1.54(1.43-1.66)
Normal weight, 2 metabolic abnormalities	1.43(1.33-1.54)	1.39(1.28-1.51)	1.52(1.35-1.70)
Normal weight, 3 metabolic abnormalities	2.09(1.86-2.34)	1.70(1.45-1.98)	1.84(1.48-2.28)
Overweight, 0 metabolic abnormalities	1.12(1.03-1.21)	1.11(1.06-1.16)	1.17(1.09-1.25)
Overweight, 1 metabolic abnormality	1.58(1.48-1.68)	1.61(1.53-1.70)	1.75(1.64-1.87)
Overweight, 2 metabolic abnormalities	1.65(1.54-1.77)	1.69(1.59-1.81)	1.93(1.77-2.10)
Overweight, 3 metabolic abnormalities	2.55(2.34-2.78)	2.00(1.81-2.22)	2.37(2.04-2.74)
Obese, 0 metabolic abnormalities	1.99(1.82-2.18)	1.96(1.87-2.06)	2.11(1.96-2.29)
Obese, 1 metabolic abnormality	2.68(2.51-2.87)	2.66(2.53-2.80)	2.96(2.77-3.16)
Obese, 2 metabolic abnormalities	2.87(2.68-3.07)	3.03(2.84-3.23)	3.60(3.29-3.93)
Obese, 3 metabolic abnormalities	4.46(4.12-4.83)	3.69(3.40-3.99)	4.23(3.79-4.72)

HR= Hazard Ratio; CI= Confidence interval; HRT= hormone replacement therapy

*Model adjusted for age, sex, smoking status and social deprivation

†Model adjusted for age, sex, and social deprivation

Table S14 Sensitivity analysis results: Association between body size phenotype and metabolic status with peripheral vascular disease by sex and age

Body size phenotype and metabolic status	**Sex HR (95% CI)***		**Age (years) HR (95% CI)†**	
	Male	Female	<65	≥ 65
Underweight, 0 metabolic abnormalities	1.28(1.08-1.53)	1.42(1.23-1.64)	1.45(1.23-1.69)	1.22(1.06-1.41)
Underweight, 1 or more metabolic abnormalities	1.60(1.19-2.15)	1.99(1.64-2.41)	2.31(1.71-3.11)	1.57(1.31-1.90)
Normal weight, 0 metabolic abnormalities	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Normal weight, 1 metabolic abnormality	1.66(1.55-1.78)	1.82(1.68-1.98)	2.27(2.09-2.47)	1.37(1.29-1.47)
Normal weight, 2 metabolic abnormalities	1.88(1.70-2.07)	2.44(2.19-2.72)	2.93(2.59-3.31)	1.66(1.52-1.82)
Normal weight, 3 metabolic abnormalities	2.33(1.92-2.83)	2.75(2.21-3.42)	4.27(3.33-5.46)	1.85(1.56-2.19)
Overweight, 0 metabolic abnormalities	0.89(0.85-0.95)	0.94(0.88-1.01)	0.94(0.89-1.00)	0.91(0.86-0.97)
Overweight, 1 metabolic abnormality	1.42(1.34-1.51)	1.50(1.38-1.63)	1.70(1.58-1.83)	1.23(1.15-1.31)
Overweight, 2 metabolic abnormalities	1.66(1.54-1.79)	1.81(1.63-2.01)	2.28(2.08-2.50)	1.34(1.23-1.46)
Overweight, 3 metabolic abnormalities	2.30(2.05-2.57)	2.44(2.07-2.89)	3.46(2.98-4.03)	1.78(1.57-2.01)
Obese, 0 metabolic abnormalities	0.93(0.86-1.00)	0.87(0.79-0.95)	1.02(0.95-1.10)	0.80(0.73-0.88)
Obese, 1 metabolic abnormality	1.30(1.21-1.40)	1.39(1.27-1.52)	1.60(1.48-1.73)	1.10(1.01-1.19)
Obese, 2 metabolic abnormalities	1.64(1.51-1.78)	2.00(1.80-2.23)	2.30(2.09-2.53)	1.35(1.24-1.48)
Obese, 3 metabolic abnormalities	2.07(1.84-2.33)	2.22(1.92-2.58)	3.05(2.68-3.47)	1.49(1.31-1.69)

HR= Hazard Ratio; CI= Confidence interval

*Model adjusted for age, smoking status and social deprivation

†Model adjusted for sex, smoking status and social deprivation

Table S15 Sensitivity analysis results: Association between body size phenotype and metabolic status with peripheral vascular disease using metabolic status derived from prescription records or measurement and different exclusions

Body size phenotype and metabolic status	Metabolic status derived from prescription records or measurement HR (95% CI)*	Excluded Type 1 DM cases HR (95% CI)*	Never smoked HR (95% CI)†
Underweight, 0 metabolic abnormalities	1.46(1.24-1.72)	1.35(1.21-1.51)	1.36(1.04-1.77)
Underweight, 1 or more metabolic abnormalities	2.12(1.89-2.38)	1.83(1.56-2.15)	1.55(1.07-2.25)
Normal weight, 0 metabolic abnormalities	1.00 (reference)	1.00 (reference)	1.00 (reference)
Normal weight, 1 metabolic abnormality	1.62(1.52-1.72)	1.68(1.59-1.77)	1.81(1.63-2.01)
Normal weight, 2 metabolic abnormalities	2.13(1.99-2.27)	2.00(1.86-2.15)	2.42(2.12-2.77)
Normal weight, 3 metabolic abnormalities	3.35(3.00-3.73)	2.23(1.91-2.61)	2.58(1.98-3.35)
Overweight, 0 metabolic abnormalities	0.96(0.90-1.03)	0.92(0.88-0.96)	0.97(0.89-1.06)
Overweight, 1 metabolic abnormality	1.37(1.29-1.45)	1.42(1.35-1.49)	1.75(1.61-1.90)
Overweight, 2 metabolic abnormalities	1.78(1.67-1.89)	1.66(1.55-1.77)	2.12(1.88-2.38)
Overweight, 3 metabolic abnormalities	3.10(2.84-3.39)	2.25(2.03-2.49)	3.04(2.57-3.59)
Obese, 0 metabolic abnormalities	0.93(0.84-1.03)	0.92(0.86-0.97)	1.11(1.00-1.24)
Obese, 1 metabolic abnormality	1.38(1.29-1.48)	1.32(1.25-1.40)	1.66(1.49-1.85)
Obese, 2 metabolic abnormalities	1.66(1.56-1.77)	1.73(1.62-1.85)	2.64(2.36-2.96)
Obese, 3 metabolic abnormalities	2.82(2.58-3.09)	2.05(1.85-2.27)	3.05(2.56-3.64)

HR= Hazard Ratio; CI= Confidence interval

*Model adjusted for age, sex, smoking status and social deprivation

†Model adjusted for age, sex, and social deprivation