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Relationship among diabetes, obesity and cardiovascular disease phenotypes: a UK Biobank cohort study

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Abstract

Objective

Obesity and diabetes frequently co-exist, yet their individual contributions to cardiovascular risk remain debated. We explored cardiovascular disease biomarkers, events and mortality in UK Biobank stratified by body mass index (BMI) and diabetes.

Research design and Methods

451,355 participants were stratified by ethnicity-specific BMI categories (normal, overweight, obese) and diabetes status. We examined cardiovascular biomarkers including: carotid intima-media thickness (CIMT); arterial stiffness; left ventricular ejection fraction (LVEF) and cardiac contractility index (CCI). Poisson regression models estimated adjusted incidence rate ratios (IRR) for myocardial infarction, ischemic stroke and cardiovascular death, with normal weight non-diabetes as comparator.

Results

5% of participants had diabetes (10% normal weight, 34% overweight and 55% obese; versus 34%, 43% and 23%, respectively, in non-diabetes). In the non-diabetes group, overweight/obesity was associated with higher CIMT, arterial stiffness and CCI, and lower LVEF ($p<0.005$); these relationships were diminished in the diabetes group. Within BMI classes, diabetes was associated with adverse cardiovascular biomarker phenotype ($p<0.005$), particularly in the normal weight group. After 5,323,190 person-years follow-up, incident myocardial infarction, ischemic stroke and cardiovascular mortality rose across increasing BMI categories without diabetes ($p<0.005$); this was comparable in the diabetes groups (p-interaction>0.05). Normal weight diabetes had comparable adjusted cardiovascular mortality to obese non-diabetes (IRR 1.22 [95% confidence interval: 0.96-1.56]; $p=0.1$).

Interpretation

Obesity and diabetes are additively associated with adverse cardiovascular biomarkers and mortality risk. Whilst adiposity metrics are more strongly correlated with cardiovascular biomarkers than diabetes-oriented metrics, both correlate weakly,

suggesting other factors underpin the high cardiovascular risk of normal-weight diabetes.

Article highlights

- Diabetes and obesity frequently coexist, but their individual and combined impact on cardiovascular disease remains poorly explored.
- We asked what are the distinct and additive contributions of diabetes and obesity to cardiovascular imaging phenotypes, events and mortality?
- We found that both diabetes and increasing BMI were independently associated with baseline adverse cardiovascular phenotype and incident major cardiovascular events; when combined, their risks were additive.
- As diabetes and obesity independently contribute to cardiovascular risk, it is possible that separate therapeutic strategies may be needed to address distinct pathogenic mechanisms.

Introduction

Diabetes mellitus and obesity are both associated with increased cardiovascular morbidity and mortality. (1) Obesity is a complex condition of increased subcutaneous and visceral adiposity, often associated with adipose dysfunction and insulin resistance, which increases the risk of diabetes and cardiovascular disease. (2) Most people with diabetes are overweight or obese, except for the minority with autoimmune or genetic forms of diabetes, and for each unit increase in body mass index (BMI), the likelihood of diabetes increases exponentially. Moreover, diabetes and obesity are associated with increased vascular stiffness and accelerated atherosclerosis, processes which lead to premature cardiovascular disease and death. (3)

Large population studies attempting to discern the independent cardiovascular risk conferred by diabetes suggest that 'adjusting' for BMI does not substantially diminish the association between diabetes and cardiovascular mortality. (4) However, the relation between BMI and cardiovascular disease is potentially complex, with BMI above or below the normal range being associated with higher risk of cardiovascular (and all-cause) mortality. (5,6) Such data may reflect residual confounding factors and suggest cautious interpretation of epidemiological data in isolation. Cardiovascular imaging studies, whilst much smaller, offer an alternative approach to characterise overt and subclinical cardiovascular disease. These support the notion that diabetes in the context of 'normal' BMI is still associated with important cardiovascular abnormalities.(7,8)

The literature defining the complex relationship between diabetes, BMI and cardiovascular disease lacks data leveraging multimodality cardiovascular imaging and hard outcomes within a single cohort powered to study people with normal BMI and diabetes. To address this, we used the UK Biobank (UKB) cohort study. We hypothesised that diabetes with normal BMI is associated with a cardiovascular phenotype and event rate comparable to obesity without diabetes.

Research design and methods

Study population

UKB is a prospective observational cohort study of 502,462 participants aged 37-73 years, recruited from 22 assessment centres across the United Kingdom (UK) between 2006-10. It is an open access resource developed using UK Government and biomedical research charity funding which linked wide-ranging phenotypic and health care record data. The UK Biobank resource is open to all bona fide researchers. Full details of its design and conduct are available online (https://www.ukbiobank.ac.uk). UKB received ethical approval from the NHS Research Ethics Service (11/NW/0382); we conducted this analysis under application number 59585. All participants provided written informed consent and the research was conducted in line with the Declaration of Helsinki. The study was reported according to the STROBE statement.

Definitions of diabetes, body mass index and study covariates

Baseline sociodemographic characteristics, comorbidities and medication were recorded by participants completing a touchscreen and nurse-led interview at study recruitment, as previously described. (9) Data from face-to-face nurse-led interview was used to ascertain baseline comorbidities and medication. Diabetes was classified

as any of “diabetes” (UK Biobank field ID ‘1220’); “type 1 diabetes mellitus” (‘1222’); “type 2 diabetes mellitus” (‘1223’); “diabetic eye disease” (‘1276’); “diabetic neuropathy/ulcers” (‘1468’) and “diabetic nephropathy” (‘1607’). Duration of diabetes was defined as the time between self-reported diagnosis and study recruitment. Triglyceride to HDL-cholesterol ratio was used as a proxy of insulin resistance, as previously described.(10)

BMI was assessed using standing height and weight data collected by UKB at study recruitment. BMI category was adjusted for ethnicity in accordance with World Health Organisation (WHO) ethnicity-specific threshold recommendations: normal: BMI≥18.5kg/m^2 to <25 kg/m^2 or ≥18.5kg/m^2 to <23 kg/m^2 if South Asian ethnicity; overweight: ≥25kg/m^2 to <30 kg/m^2 or ≥23kg/m^2 to <27.5 kg/m^2 if South Asian ethnicity; obese: ≥30kg/m^2 or ≥27.5kg/m^2 if South Asian ethnicity. (11) Participants with below normal BMI were excluded from this analysis (n=2316) due to an insufficient sample size to study people with diabetes; we did not apply an upper BMI limit for inclusion in the analysis. Definitions of other comorbidities at recruitment has previously been described. (12) We excluded participants with missing data relating to BMI (n=10,135), loss to follow-up or withdrawal consent (n=1,298), or confounding factors: smoking status (n=2,949); ethnicity (n=2,777); socioeconomic status (n=624) and systolic blood pressure (n=34,439, SBP).

Assessment of cardiometabolic phenotype

From 2014, all surviving participants were invited by email and then post, to take part in multimodality imaging assessment. This included cardiac magnetic

resonance imaging (cMRI), carotid artery ultrasound, photoplethysmography derived arterial stiffness index (PASI) and abdominal MRI. Anthropometric measurements of body composition and measurements of serum lipids and biochemistry were collected at baseline. Responding participants were screened for eligibility for inclusion based on safety and tolerability criteria. All participants with metal implants in their body were excluded for safety and image quality concerns. (13) Further details regarding cardiometabolic phenotyping are found in the Supplement Material and full details of all protocols have been published. (14–19)

Definition of primary and secondary outcome measures

Our primary endpoint was cardiovascular mortality and our secondary endpoints were non-fatal myocardial infarction (MI), non-fatal stroke and al-cause mortality; all other analyses were exploratory. UKB mortality outcomes are obtained from the official UK national death registry from National Health Service (NHS) Digital for participants in England and Wales, and from the NHS central register for participants in Scotland. We censored outcomes on 23rd March 2021. Cardiovascular mortality was defined according to the International Classification of Diseases, Tenth Revision (ICD-10) as previously described.(20) In brief, this included all cardiovascular ICD-10 codes from I00-I99 excluding codes relating to infection mortality. Incident non-fatal MI or non-fatal ischemic stroke were defined using a UKB algorithm. (21,22) We only included events ascertained from hospital admission data (excluding self-reported outcomes) and where non-fatal MI or non-fatal ischemic stroke was the primary diagnosis.

Statistical analysis

All analyses were performed using Stata/MP. All statistical tests were 2-sided and statistical significance defined as $p<0.05$. However, in tables presenting multiple exploratory statistical tests this threshold was reduced to $p<0.005$. Missing data were not imputed. Continuous data are presented as median with 25^{th}-75^{th} centile. Categorical data are presented as number (%). Normality of distribution was checked using skewness and kurtosis tests; all continuous variables were found to be non-normally distributed. Differences between BMI categories within the diabetes or the non-diabetes group were assessed using Kruskal-Wallis H tests or Chi^2 test for continuous and categorical variables, respectively. Differences between the diabetes and non-diabetes groups within each BMI category were assessed using the Mann-Whitney U tests. Where appropriate, some analyses were repeated after stratification by sex. We used correlation matrices of Poisson model's coefficients to assess correlations between covariates; no correlation coefficients higher than 0·3 or lower than –0·3 were observed.

Unadjusted and adjusted incident rate ratios (IRR) and their 95% confidence intervals (CI) were estimated for all-cause mortality, cardiovascular mortality, non-fatal MI, and ischemic stroke using Poisson regression models; exposure time was modelled, but time-varying covariates were not used. A dummy variable was used to compare outcomes of diabetes-BMI groups with reference to the normal BMI non-diabetes group. Where indicated, models were adjusted for covariates indicated in the accompanying table or figure legend; this included interaction terms between diabetes and BMI categories to identify differential associations between BMI category and outcome in people without or with diabetes. Crude mortality rates were calculated per 1000 participant-years of follow-up for all-cause mortality, cardiovascular mortality,

non-fatal MI, and ischemic stroke by BMI category for the total population and then stratified by diabetes status. Kaplan-Meier (KM) curves were used to illustrate unadjusted event rates among participants grouped by diabetes status and BMI category. Where specified, we separately modelled BMI as a continuous variable using restricted cubic splines with four knots for all clinical outcomes, as this provided the best fit as assessed by minimising Akaike and Bayesian criteria (models including categorical, linear, or cubic splines with three, four, and five knots and first-degree and second-degree fractional polynomials were compared). Models were constructed independently for participants with and without diabetes. The reference knot was set at the median BMI of the whole cohort and spline curves were truncated at the 1st and 99th centile.

A sensitivity analysis was performed to define cardiovascular events in people with diabetes after exclusion of those diagnosed before the age of 40 who were also receiving insulin treatment at the time of recruitment to UK Biobank. A further sensitivity analysis stratified people with and without diabetes based upon central obesity, defined using waist-hip ratio (WHR) ≥0.85 if female and ≥0.90 if male, in lieu of obesity defined with BMI.(23)

Results

We included 451,355 participants of whom 22,451 (4.9%) had diabetes at recruitment. Among participants with diabetes 2,290 (10.1%) were normal weight, 7,732 (34.4%) overweight and 12,429 (55.3%) obese. In participants without diabetes, 143,557 (33.5%) were normal weight, 185,758 (43.3%) overweight and 99,589 (23.2%) obese. Participants with diabetes were older, more often male, less physically

active, less often of non-white ethnicity and more socio-economically deprived (**Table 1**). There was greater prevalence of all studied cardiometabolic comorbidities at baseline among participants with diabetes, and the prevalence of cardiometabolic comorbidities (except for peripheral vascular disease) increased with BMI, irrespective of diabetes status (**Table 1**). Antihypertensive, statin, aspirin and diuretic use was higher among participants with diabetes at enrolment and usage increased with increasing BMI category regardless of diabetes status. Most participants with diabetes were taking metformin and approximately a fifth were receiving insulin (**Table S1**). Diabetes medication use rose with increasing BMI.

All-cause mortality, cardiovascular mortality and morbidity

During 5,323,190 person-years of follow-up (median 12.0 years), 29,931 participants died (6.6%) of whom 5,831 (1.3%) died from cardiovascular causes. A total of 7,179 (1.6%) participants had non-fatal MI and 3,469 (0.8%) had non-fatal ischemic stroke during follow-up. Kaplan-Meier curves illustrating cardiovascular and all-cause mortality during follow-up are shown in **Figure S1**. Broadly, these demonstrate modestly rising mortality across BMI categories with much greater mortality in groups with diabetes. Indeed, absolute unadjusted rates of all-cause mortality, cardiovascular mortality, non-fatal MI and non-fatal ischemic stroke climbed modestly with increasing BMI category, with much greater mortality in participants with diabetes (**Table S2**). Unadjusted and adjusted IRRs for all-cause and cardiovascular mortality are shown in **Table 2**. Among participants without diabetes, the risk of cardiovascular death was comparable among overweight (adjusted IRR 1.00, CI 0.93-1.08) and increased in obese participants (adjusted IRR 1.27, CI: 1.17-1.37) compared to those with normal BMI. People with diabetes and normal BMI experienced a

nominally larger risk of cardiovascular death (adjusted IRR 1.55, CI: 1.21-1.98), with further increases in the overweight diabetes (adjusted IRR 1.71, CI: 1.47-1.98) and obese diabetes (adjusted IRR 1.96, CI: 1.71-2.25) groups. There was no significant interaction between BMI category and diabetes in the association with cardiovascular mortality; this implies that rising BMI has a similar association with cardiovascular mortality irrespective of diabetes status. When directly comparing obese participants without diabetes to those with normal BMI diabetes, their risk of cardiovascular death was not statistically different, in spite of being nominally lower (adjusted IRR 0.82, CI: 0.64-1.04, p=0.1; **Table S3**). Similar patterns were observed in risk of non-fatal MI or non-fatal ischemic stroke (**Table 2 and Table S3**).

A sensitivity analysis excluding people with diabetes diagnosed before the age of 40 who were also receiving insulin treatment at the time of recruitment yielded similar findings (**Table S4**); this suggests our findings are unlikely to be driven by the inclusion of people with type 1 diabetes. Another sensitivity analysis replacing BMI categories with central adiposity defined using WHO sex-specific WHR thresholds also yielded similar findings (**Table S5**, **Figure S2**). This showed that central adiposity is associated with cardiovascular death, non-fatal MI and non-fatal stroke in people without diabetes; however, the magnitude of this risk was larger for people with diabetes and no central adiposity. The addition of central adiposity to diabetes did not substantially increase the adjusted risk of cardiovascular events beyond diabetes alone; indeed these was a significant interaction between diabetes and central obesity suggesting differential association between centra obesity and cardiovascular outcomes in participants without and with diabetes. When modelled as a continuous

variable, rising BMI had a steeper relationship with cardiovascular mortality in people without diabetes, although with overlapping 95% confidence intervals (**Figure S3**).

Phenotypic measures of metabolic disease

Participants with diabetes had elevated BMI, waist to hip ratio (WHR), body fat percentage and reduced whole body impedance compared to those without diabetes within any given BMI category (**Table 3**). Increasing BMI category was associated with significantly higher serum triglycerides, low-density lipoprotein cholesterol (LDL) and lower high-density lipoprotein cholesterol (HDL) irrespective of diabetes status. Total cholesterol, LDL, HDL and triglycerides were lower in participants with diabetes compared to those without within any given BMI category (**Table 3**). Participants with diabetes had higher serum creatinine, serum cystatin C, urinary microalbumin and serum alanine aminotransferase compared to those without diabetes, which rose with increasing BMI category. Higher BMI categories were also associated with increased serum c-reactive protein (CRP) and HbA1c regardless of diabetes status (**Table 3**). Total abdominal adipose tissue index (TAATI) and abdominal fat ratio (AFR) increased in higher BMI groups, but did not differ according to diabetes status (**Table 3**). Given the sexual dimorphism in body composition, we also performed stratified analyses which show similar patterns in relation to diabetes and BMI category in both sexes (**Table S6**). Collectively, these data illustrate important differences in metabolic parameters associated with increasing BMI, irrespective of diabetes status; however, many of these are also abnormal in people with diabetes and 'normal' BMI versus those without diabetes.

Phenotypic measures of cardiovascular disease

Resting heart rate, SBP and diastolic blood pressure (DBP) increased across rising BMI categories. Participants with diabetes also had higher resting heart rate and SBP but lower DBP than participants without diabetes within each BMI category (**Table 4**). Participants with diabetes had higher carotid intima-media thickness (CIMT) and PASI than those without diabetes within each BMI category; both measures increased with rising BMI in the non-diabetes group, but only PASI (not CIMT) increased with BMI in the diabetes group (**Table 4**). Among those who were overweight or obese, left ventricular ejection fraction (LVEF) was lower in participants with diabetes compared to those without. Furthermore, LVEF declined with rising BMI category, irrespective of diabetes status (**Table 4**). Among those without diabetes, rising BMI was associated with lower left ventricular stroke volume (LVSV), left ventricular end diastolic volume (LVEDV) and cardiac index; however, cardiac contractility index (CCI) increased with rising BMI. In participants with diabetes, rising BMI was only significantly associated with lower LVSV, and not with CCI. Within obese participants, diabetes was associated with elevated CCI. Direct comparison of cardiovascular imaging phenotypes between obese people without diabetes and normal BMI diabetes revealed statistically greater CIMT and lower PASI, but similar LVEF and CCI in the normal BMI diabetes group (**Table S7**) A sensitivity analysis excluding people with diabetes diagnosed before the age of 40 who were also receiving insulin treatment at the time of recruitment did not substantially alter the conclusions drawn from cardiovascular imaging phenotypes (**Table S8**). Given the potential sexual dimorphism in these measures, we also performed stratified analyses which show similar patterns in relation to diabetes and BMI category in both sexes (**Table S9**).

Collectively, these data illustrate an adverse cardiovascular phenotype associated with rising BMI in people without diabetes, although this relationship is less clear in people with diabetes who exhibit marked abnormalities even in the 'normal' BMI group. A sensitivity analysis replacing BMI categories with central adiposity defined using WHO sex-specific WHR thresholds also yielded similar findings, with adverse associations between central adiposity and all cardiovascular imaging phenotypes in people without diabetes (**Table S10**). In people with diabetes, there was also an adverse association with central adiposity for CIMT, LVEF and PASI, but not CCI (**Table S10**). Next, we explored the association between metabolic parameters and cardiovascular imaging phenotypes. Pairwise correlation analysis demonstrated that duration of diabetes weakly correlated with CIMT and LVEF, but not PASI or CCI (**Figure S4**); no correlations were noted with HbA1c in the diabetes group, but in people without diabetes, HbA1c correlated with PASI, CIMT, LVEF and CCI. The strongest correlates of cardiovascular parameters were markers of adiposity; this was apparent in the diabetes and non-diabetes groups, although these remained modest with Pearson's correlation coefficients of no more than 0.25. Importantly, all four cardiovascular imaging phenotypes were associated with our primary endpoint of cardiovascular mortality, and this association was comparable in people with and without diabetes (**Table S11**)

Conclusions

We present a detailed analysis of cardiovascular phenotypes and outcomes in relation to metabolic parameters in a large cohort stratified by baseline diabetes status and BMI category. Cardiovascular mortality and non-fatal events were more common as BMI rose, but in the presence of diabetes event rates were much greater. Indeed,

people with diabetes and normal BMI experienced nominally higher adjusted event rates than obese people without diabetes. However, the adverse association of obesity with cardiovascular mortality and events was comparable in people with and without diabetes, indicating that combine additively rather than synergistically. In contrast, whilst our sensitivity analysis revealed central obesity was associated with increased adjusted risk of cardiovascular death in people without diabetes, this was not apparent in people with diabetes. These data emphasise the complex interplay between diabetes and obesity in the modulation of cardiovascular disease.

Imaging data corroborated progressive cardiovascular abnormalities with rising BMI in people without diabetes. Notably, the cardiovascular imaging phenotype of diabetes with normal BMI was broadly comparable to obesity without diabetes, with only modest progression of these cardiovascular abnormalities with rising BMI in the diabetes group. Furthermore, the duration of diabetes and HbA1c correlated poorly with cardiovascular phenotype in people with diabetes, with metrics of adiposity demonstrating the strongest (albeit modest) correlation. This raises the possibility that the ideal target range for metrics of adiposity may be lower than currently proposed in people with diabetes. Our data also reveal scope to improve adherence to existing targets around modifiable cardiovascular risk factors (such as smoking cessation) in people with diabetes and/or elevated BMI.

Epidemiological insights

To the best of our knowledge, our study is the largest investigating interactions between diabetes and obesity in terms of cardiovascular phenotype and long-term outcomes. However, other epidemiological studies provide important context. In over

10 million participants, Di Angelantonio *et al* showed being overweight *or* obese was associated with higher all-cause and cardiovascular mortality versus normal weight. (6) However, they did not directly compare cardiovascular mortality stratified by diabetes status. In a prospective cohort of 10,568 people with type 2 diabetes, Costanzo *et al* showed overweight and obese people were more likely to be hospitalized for myocardial infarction or stroke, although cardiovascular mortality was not reported. (24,25) In a meta-analysis of 16 cohort studies including 445,125 people with type 2 diabetes, Kwon *et al* report a U-shaped relationship between BMI and all-cause or cardiovascular mortality; (26) no data were included from people without diabetes. Notably, their analysis found a nadir of cardiovascular mortality at a BMI of 29-31Kg/m^2, highlighting an 'obesity paradox'. This contrasts with our analysis and that of Costanzo *et al*, possibly reflecting cohort differences in important confounding factors, such as comorbidity and smoking status.

Cardiovascular imaging insights

We found participants with diabetes had more advanced atherosclerosis and greater arterial stiffness than participants without diabetes within all BMI categories. Moreover, participants with normal BMI and diabetes had a nominally higher CIMT than any other diabetes-BMI category, emphasising their substantial burden of arterial disease. Participants with diabetes also exhibited supraphysiological cardiac contractility without differences in cardiac output. This, combined with associated increased arterial stiffness, suggests chronically elevated left ventricular afterload – a risk factor for incident heart failure and atrial fibrillation, amongst others. (27) Indeed, serial cardiac MRI studies in people with uncomplicated type 2 diabetes have revealed important reductions in LVEF over a 6-year period. (28) Whilst we found statistically

lower LVEF in people with diabetes, these were smaller than the margin of error with any cardiac imaging modality. Given we observed much larger differences in CCI, this may be a better biomarker of early diabetic heart disease; this warrants assessment in future studies.

Clinical implications

We showed that people with diabetes and normal BMI had significantly elevated WHR and a numerically greater abdominal fat ratio and TAATI compared to people of normal BMI without diabetes. These measures suggest unfavourable body composition, and greater visceral versus subcutaneous adipose deposition. Chowdary *et al* recently described that people with diabetes have greater visceral adiposity than those without diabetes, even when of normal weight. (8) Visceral adiposity is independently associated with higher 10-year cardiovascular disease risk, (29) which is supported by our sensitivity analyses of central obesity defined by WHR (**Table S5**). However, this sensitivity analysis did not find additive effects of this measure of central obesity with diabetes, highlighting complex interactions between diabetes and obesity. Notably, indices of adiposity were the strongest (albeit modest) correlates of abnormal cardiovascular phenotypes in people with and without diabetes in our analysis. Hence, better assessment of visceral adiposity in routine practice may allow clinicians to define high risk groups and our data raise the question of whether lower BMI targets, or possibly alternate adiposity metrics, should guide use of existing and novel therapies.

Increased risk of cardiovascular disease and death among people with diabetes and normal BMI is also likely to relate to suboptimal control of 'traditional'

cardiovascular risk factors. In our study, whilst this group had relatively good glycemic control, they had: low physical activity; higher than ideal systolic blood pressure; suboptimal LDL cholesterol; and approximately 1 in 7 currently smoked. These data emphasise the potential benefits of more effective application of existing cardiovascular risk modification guidelines. Nevertheless, all groups in our analysis had suboptimal cardiovascular risk factor profiles, emphasising the challenges of preventative medicine. Interestingly, systemic inflammation (defined with serum CRP) was similar in people with and without diabetes of normal BMI, conflicting with some literature. However, systemic inflammation increased with BMI irrespective of diabetes status as expected. (30) The modest correlation of included cardiovascular risk factors with cardiovascular imaging phenotypes in people with diabetes, suggests we better routine clinical biomarkers of cardiovascular disease in people with diabetes.

Strengths and limitations

Our study has strengths including: detailed cardiometabolic phenotyping with multi-modality assessment; high quality long-term outcome data; and statistical power to study diabetes with normal BMI. However, we must also acknowledge limitations. First, phenotypic measures of cardiometabolic disease were not assessed in every participant due to the design of UKB, which only performed more complex assessments in a subset. This introduces survivor bias in participants who underwent detailed imaging assessment, which commenced in 2014. (13) We also lacked the statistical power to conduct analyses restricted to people with more pronounced obesity. Second, we did not stratify by type of diabetes since only 404 participants had self-reported type 1 diabetes. However, a sensitivity analysis excluding 1,756 participants with diabetes diagnosed before the age of 40 who also received insulin at

the time of recruitment reached similar conclusions, suggesting our findings are unlikely to be substantially driven by the inclusion of people with type 1 diabetes. Third, our work is observational, so causality cannot be inferred. Fourth, participants were recruited before the use of modern diabetes therapeutics (e.g. sodium-glucose cotransporter 2 inhibitors), which improve cardiovascular outcomes. (31) Therefore, our observed event rates in people with diabetes may be higher than contemporary rates. Fifth, UKB is not representative of the UK population regarding socioeconomic deprivation (SED), some non-communicable diseases and ethnic minorities.(32) Whilst this means event rates should be cautiously extrapolated to the UK population, UKB remains a robust resource to define exposure-disease relationships. (32) Sixth, our adjusted analyses do not account for dietary factors, which may mediate some of the adverse cardiovascular outcomes associated with diabetes and obesity, and are an essential target in disease prevention. Finally, we present many statistical analyses beyond our primary and secondary outcome measures, and whilst these data provides valuable context, these exploratory analyses must be interpreted cautiously.

In conclusion, both obesity and diabetes are independently and additively associated with more advanced cardiovascular disease and more frequent major adverse cardiovascular events. Whilst adiposity metrics are more strongly correlated with cardiovascular biomarkers than diabetes-oriented metrics, both correlate weakly, suggesting other factors underpin the high cardiovascular risk of normal-weight diabetes. Whilst there is clear scope for better use of existing screening and preventative approaches in people with diabetes, our data suggest that more refined risk assessment aligned with targeted preventative interventions are needed to improve outcomes.

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References

1. Piché ME, Tchernof A, Després JP. Obesity Phenotypes, Diabetes, and Cardiovascular Diseases. Circ Res 2020; 126: 1477–1500.
2. Adams KF, Schatzkin A, Harris TB, Kipnis V, Mouw T, Ballard-Barbash R, et al. Overweight, obesity, and mortality in a large prospective cohort of persons 50 to 71 years old. N Engl J Med 2006; 355: 763–778.
3. Wildman RP, Mackey RH, Bostom A, Thompson T, Sutton-Tyrrell K. Measures of obesity are associated with vascular stiffness in young and older adults. Hypertension 2003; 42: 468–473.
4. Raghavan S, Vassy JL, Ho YL, Song RJ, Gagnon DR, Cho K, et al. Diabetes Mellitus-Related All-Cause and Cardiovascular Mortality in a National Cohort of Adults. J Am Heart Assoc 2019; 8: e011295.
5. Chen Y, Copeland WK, Vedanthan R, Grant E, Lee JE, Gu D, et al. Association between body mass index and cardiovascular disease mortality in east Asians and south Asians: pooled analysis of prospective data from the Asia Cohort Consortium. BMJ; 347: f5446.
6. di Angelantonio E, Bhupathiraju S, Wormser D, Gao P, Kaptoge S, et al. Body-mass index and all-cause mortality: individual-participant-data meta-analysis of 239 prospective studies in four continents. Lancet 2016; 388: 776–786.
7. Levelt E, Pavlides M, Banerjee R, Mahmod M, Kelly C, Sellwood J, et al. Ectopic and Visceral Fat Deposition in Lean and Obese Patients With Type 2 Diabetes. J Am Coll Cardiol 2016; 68: 53–63.
8. Chowdhary A, Thirunavukarasu S, Jex N, Coles L, Bowers C, Sengupta A, et al. Coronary microvascular function and visceral adiposity in patients with

normal body weight and type 2 diabetes. Obesity (Silver Spring) 2022; 30: 1079–1090.

9. Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS Med 2015; 12: e1001779.
10. McLaughlin T, Abbasi F, Cheal K, Chu J, Lamendola C, Reaven G. Use of metabolic markers to identify overweight individuals who are insulin resistant. Ann Intern Med 2003; 139: 802–809.
11. WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet 2004; 363: 157–163.
12. Drozd M, Pujades-Rodriguez M, Lillie PJ, Straw S, Morgan AW, Kearney MT, et al. Non-communicable disease, sociodemographic factors, and risk of death from infection: a UK Biobank observational cohort study. Lancet Infect Dis 2021; 21: 1184–1191.
13. Littlejohns TJ, Holliday J, Gibson LM, Garratt S, Oesingmann N, Alfaro-Almagro F, et al. The UK Biobank imaging enhancement of 100,000 participants: rationale, data collection, management and future directions. Nat Communs 2020; 11:2624
14. Raisi-Estabragh Z, Harvey NC, Neubauer S, Petersen SE. Cardiovascular magnetic resonance imaging in the UK Biobank: a major international health research resource. Eur Heart J Cardiovasc Imaging 2021; 22: 251–258.
15. Coffey S, Lewandowski AJ, Garratt S, Meijer R, Lynum S, Bedi R, et al. Protocol and quality assurance for carotid imaging in 100,000 participants of

UK Biobank: development and assessment. Eur J Prev Cardiol 2017; 24:1799–1806.

16. Zekavat SM, Aragam K, Emdin C, Khera AV, Klarin D, Zhao H, et al. Genetic Association of Finger Photoplethysmography-Derived Arterial Stiffness Index With Blood Pressure and Coronary Artery Disease. Arterioscler Thromb Vasc Biol 2019; 39: 1253–1261.
17. Liu Y, Basty N, Whitcher B, Bell JD, Sorokin EP, van Bruggen N, et al. Genetic architecture of 11 organ traits derived from abdominal MRI using deep learning. Elife. 2021; 10: e65554
18. Tong TY, Key TJ, Sobiecki JG, Bradbury KE. Anthropometric and physiologic characteristics in white and British Indian vegetarians and nonvegetarians in the UK Biobank. Am J Clin Nutr 2018; 107: 909–920.
19. Elliott P, Peakman TC, UK Biobank. The UK Biobank sample handling and storage protocol for the collection, processing and archiving of human blood and urine. Int J Epidemiol 2008; 37: 234–244.
20. Drozd M, Pujades-Rodriguez M, Sun F, Franks KN, Lillie PJ, Witte KK, et al. Causes of Death in People With Cardiovascular Disease: A UK Biobank Cohort Study. J Am Heart Assoc 2021; 10: e023188.
21. Schnier Schnier C, Bush K, Nolan J, Sudlow C. Definitions of Acute Myocardial Infarction and Main Myocardial Infarction Pathological Types UK Biobank Phase 1 Outcomes Adjudication On behalf of UK Biobank Outcome Adjudication Group. Available at http://biobank.ctsu.ox.ac.uk/crystal/crystal/ docs/alg_outcome_mi.pdf. Accessed April 17, 2023.

22. Millett ERC, Peters SAE, Woodward M. Sex differences in risk factors for myocardial infarction: cohort study of UK Biobank participants. BMJ 2018; 363: k4247.
23. Geneva: World Health Organization; 2008. World Health Organization (WHO). Waist Circumference and Waist-Hip Ratio. Report of WHO Expert Consultation..
24. Brown O, Costanzo P, Clark AL, Condorelli G, Cleland JGF, Sathyapalan T, et al. Relationship between a single measurement at baseline of body mass index, glycated hemoglobin, and the risk of mortality and cardiovascular morbidity in type 2 diabetes mellitus. Cardiovasc Endocrinol Metab 2020; 9: 177–182.
25. Costanzo P, Cleland JGF, Pellicori P, Clark AL, Hepburn D, Kilpatrick ES, et al. The obesity paradox in type 2 diabetes mellitus: Relationship of body mass index to prognosis a cohort study. Ann Intern Med 2015; 162: 610–618.
26. Kwon Y, Kim HJ, Park S, Park YG, Cho KH. Body Mass Index-Related Mortality in Patients with Type 2 Diabetes and Heterogeneity in Obesity Paradox Studies: A Dose-Response Meta-Analysis. PLoS One 2017; 12: e0168247.
27. Fuchs FD, Whelton PK. High Blood Pressure and Cardiovascular Disease. Hypertension 2020; 75: 285–292.
28. Chowdhary A, Jex N, Thirunavukarasu S, MacCannell A, Haywood N, Almutairi A, et al. Prospective Longitudinal Characterization of the Relationship between Diabetes and Cardiac Structural and Functional Changes. Cardiol Res Pract 2022; 2022: 6401180.

29. Kouli GM, Panagiotakos DB, Kyrou I, Georgousopoulou EN, Chrysohoou C, Tsigos C, et al. Visceral adiposity index and 10-year cardiovascular disease incidence: The ATTICA study. Nutr Metab Cardiovasc Dis 2017; 27: 881–889.
30. Ellulu MS, Patimah I, Khaza'ai H, Rahmat A, Abed Y. Obesity and inflammation: the linking mechanism and the complications. Arch Med Sci 2017; 13: 851–863.
31. McGuire DK, Shih WJ, Cosentino F, Charbonnel B, Cherney DZI, Dagogo-Jack S, et al. Association of SGLT2 Inhibitors With Cardiovascular and Kidney Outcomes in Patients With Type 2 Diabetes: A Meta-analysis. JAMA Cardiol 2021; 6: 148–158.
32. Fry A, Littlejohns TJ, Sudlow C, Doherty N, Adamska L, Sprosen T, et al. Comparison of Sociodemographic and Health-Related Characteristics of UK Biobank Participants With Those of the General Population. Am J Epidemiol 2017; 186: 1026–1034.

	Missing	No Diabetes			Diabetes		
		Normal (N=143 557)	Overweight (N=185 758)	Obese (N=99 589)	Normal (N=2290)	Overweight (N=7732)	Obese (N=12 429)
				Demographic characteristics			
Age, *years*	0	56 (49-62)*†	58 (50-63)*†	58 (50-63)*†	61 (55-66)*†	62 (57-66)*†	61 (51-65)*†
Male sex, *n (%)*	0	49 099 (34.2)*†	96 862 (52.1)*†	45 938 (46.1)*†	1326 (57.9)*†	5366 (69.4)*†	7317 (58.9)†
Ethnicity, *n (%)*	0						
White	-	138 120 (96.2)*†	176 483 (95.1)*†	92 500 (92.9)*†	2006 (87.6)*†	6569 (85.0)*†	10 958 (88.2)*†
Mixed	-	964 (0.7)*†	1011 (0.5)*†	606 (0.6)*†	<50 (0.7)*†	56 (0.7)*†	81 (0.7)*†
Asian	-	1147 (0.8)*†	3448 (1.9)*†	2895 (2.9)*†	98 (4.3)*†	600 (7.8)*†	775 (6.2)*†
Black	-	1320 (0.9)*†	2804 (1.5)*†	2566 (2.6)*†	88 (3.8)*†	301 (3.9)*†	422 (3.4)*†
Chinese	-	857 (0.6)*†	400 (0.2)*†	69 (0.1)*†	<50 (1.2)*†	<50 (0.5)*†	<50 (0.1)*†
Other	-	1149 (0.8)*†	1613 (0.9)*†	953 (1.0)*†	55 (2.4)*†	170 (2.2)*†	179 (1.4)*†
Townsend Deprivation Index, *n (%)*	0						
Q1	-	31 140 (21.7)*†	39 054 (21.0)*†	16 960 (17.0)*†	398 (17.4)*†	1254 (16.2)*†	1648 (13.3)*†
Q2	-	29 964 (20.9)*†	38 622 (20.8)*†	18 241 (18.3)*†	423 (18.5)*†	1368 (17.7)*†	1864 (15.0)*†
Q3	-	28 771 (20.0)*†	38 063 (20.5)*†	19 275 (19.4)*†	428 (18.7)*†	1488 (19.2)*†	2125 (17.1)*†
Q4	-	28 053 (19.5)*†	36 481 (19.6)*†	21 012 (21.1)*†	468 (20.4)*†	1590 (20.6)*†	2632 (21.2)*†
Q5	-	25 629 (17.9)*†	33 538 (18.1)*†	24 101 (24.2)*†	573 (25.0)*†	2032 (26.3)*†	4160 (33.5)*†
Smoking, *n (%)*	0						
Never	-	84 895 (59.1)*†	100 138 (53.9)*†	52 108 (52.3)*†	1187 (51.8)*†	3476 (45.0)*†	5541 (44.6)*†
Former	-	42 604 (29.7)*†	66 762 (35.9)*†	37 896 (38.1)*†	780 (34.1)*†	3388 (43.8)*†	5656 (45.5)*†
Current	-	16 058 (11.2)*†	18 858 (10.2)*†	9585 (9.6)*†	323 (14.1)*†	868 (11.2)*†	1232 (9.9)*†
Summed MET activity per week, *minutes*	86 677	2009 (975-3813)*†	1813 (847-3625)*†	1428 (594-3110)*†	1769 (822-3550)*†	1536 (677-3200)*†	1184 (450-2754)*†
				Cardiometabolic diseases			
Hypertension, *n (%)*	0	20 184 (14.1)*†	46 104 (24.8)*†	38 399 (38.6)*†	1023 (44.7)*†	4588 (59.3)*†	8947 (72.0)*†
Atrial fibrillation/flutter, *n* (%)	0	678 (0.5)*†	1317 (0.7)*	869 (0.9)*†	<50 (1.0)†	71 (0.9)	172 (1.4)†
Peripheral vascular disease *n* (%)	0	524 (0.4)†	643 (0.4)†	396 (0.4)†	<50 (1.0)†	93 (1.2)†	116 (0.9)†
Stroke or transient ischaemic attack, *n* (%)	0	1562 (1.1)*†	2831 (1.5)*†	2140 (2.2)*†	73 (3.2)*†	340 (4.4)*†	585 (4.7)*†
Heart failure, *n* (%)	0	98 (0.1)*†	180 (0.1)*†	164 (0.2)*†	<50 (0.3)†	<50 (0.3)†	56 (0.5)†
Ischaemic heart disease, *n (%)*	0	2961 (2.1)*†	7644 (4.1)*†	5965 (6.0)*†	243 (10.6)*†	1208 (15.6)*†	2196 (17.7)*†
Chronic cardiac syndrome, *n (%)*	0	3065 (2.1)*†	7824 (4.2)*†	6108 (6.1)*†	252 (11.0)*†	1224 (15.8)*†	2234 (18.0)*†
Aortic aneurysmal disease, *n (%)*	0	74 (0.1)*	142 (0.1)*†	106 (0.1)*†	<50 (0)	<50 (0.3)†	<50 (0.2)†
				Non-cardiometabolic diseases			
Chronic liver disease, *n (%)*	0	223 (0.2)	345 (0.2)†	204 (0.2)†	<50 (0.3)	<50 (0.3)†	53 (0.4)†
Chronic respiratory disease, *n (%)*	0	16 708 (11.6)*	22 857 (12.3)*	15 436 (15.5)*†	298 (13.0)*	989 (12.8)*	2206 (17.8)*†
Chronic renal disease, *n (%)*	0	288 (0.2)†	405 (0.2)†	237 (0.4)†	<50 (1.1)†	61 (0.8)†	116 (0.9)†
Neurological disease, *n (%)*	0	1829 (1.3)*	2303 (1.2)*	1381 (1.4)*	<50 (1.6)	89 (1.2)	154 (1.2)
Psychiatric disease, *n (%)*	0	7356 (5.1)*†	10 255 (5.5)*	7816 (7.9)*†	150 (6.6)*†	449 (5.8)*	1097 (8.8)*†
Rheumatological disease, *n (%)*	0	2810 (2.0)*†	3935 (2.1)*	2621 (2.6)*†	71 (0.3)*†	192 (2.5)*	391 (3.2)*†

Table 1. Population demographic characteristics and comorbidities at study recruitment. Participants stratified by diabetes status and then by ethnicity adjusted BMI category. Normal: BMI ≥18.5kg/m^2 to <25 kg/m^2 *or* ≥18.5kg/m^2 to <23 kg/m^2 if south Asian ethnicity; Overweight: ≥25kg/m^2 to <30 kg/m^2 *or* ≥23kg/m^2 to <27.5 kg/m^2 if south Asian ethnicity; Obese: ≥30kg/m^2 *or* ≥27.5kg/m^2 if south Asian ethnicity. Continuous data presented as median with 25th and 75th centile. Categorical data presented as n (%). * represents Kruskal-Wallis p value or chi^2 test <0.005 between BMI categories for continuous variables and categorical variables respectively within diabetes or non-diabetes groups. † represents p value <0.005 between each BMI category in diabetes participants and their respective BMI category in non-diabetes participants from Mann Whitney U test and chi^2 test for categorical variables. Abbreviations: metabolic equivalent (MET), body mass index (BMI). Where fewer than 50 participants are within any group, UK Biobank requires that the specific number of participants is not listed to reduce the risk of de-anonymisation.

	Unadjusted	Model 1	Model 2	Model 3
	IRR (95% CI)	Adjusted IRR* (95% CI)	Adjusted IRR (95% CI)	Adjusted IRR* (95% CI)
Cardiovascular mortality				
Normal + non-diabetes	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Overweight + non-diabetes	1.38 (1.28-1.48, p<0.001)	1.10 (1.02-1.18, p=0.012)	1.01 (0.94-1.09, p=0.735)	1.00 (0.93-1.08, p=0.887)
Obese + non-diabetes	1.96 (1.82-2.12, p<0.001)	1.67 (1.53-1.79, p<0.001)	1.35 (1.25-1.46, p<0.001)	1.27 (1.17-1.37, p<0.001)
Normal + diabetes	4.38 (3.47-5.23, p<0.001)	2.39 (1.90-3.02, p<0.001)	1.88 (1.49-2.37, p<0.001)	1.55 (1.21-1.98, p<0.001)
Overweight + diabetes	5.71 (5.06-6.44, p<0.001)	2.82 (2.49-3.19, p<0.001)	2.00 (1.76-2.27, p<0.001)	1.71 (1.47-1.98, p<0.001)
Obese + diabetes	7.05 (6.40-7.75, p<0.001)	4.05 (3.68-4.47, p<0.001)	2.57 (2.32-2.84, p<0.001)	1.96 (1.71-2.25, p<0.001)
All-cause mortality				
Normal + non-diabetes	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Overweight + non-diabetes	1.15 (1.11-1.18, p<0.001)*	0.97 (0.95-1.00, p=0.075)	0.95 (0.92-0.97, p<0.001)*	0.94 (0.92-0.97, p<0.001)
Obese + non-diabetes	1.38 (1.34-1.43, p<0.001)*	1.22 (1.18-1.26, p<0.001)	1.12 (1.09-1.16, p<0.001)	1.10 (1.06-1.13, p<0.001)
Normal + diabetes	3.16 (2.84-3.50, p<0.001)	1.97 (1.77-2.19, p<0.001)	1.79 (1.61-1.99, p<0.001)	1.57 (1.40-1.76, p<0.001)
Overweight + diabetes	3.01 (2.83-3.20, p<0.001)*	1.74 (1.63-1.85, p<0.001)	1.49 (1.40-1.59, p<0.001)*	1.36 (1.26-1.46, p<0.001)
Obese + diabetes	3.52 (3.36-3.69, p<0.001)*	2.28 (2.17-2.39, p<0.001)	1.86 (1.77-1.95, p<0.001)	1.61 (1.50-1.72, p<0.001)
Non-fatal myocardial infarction				
Normal + non-diabetes	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Overweight + non-diabetes	1.59 (1.49-1.69, p<0.001)	1.27 (1.20-1.36, p<0.001)	1.22 (1.14-1.30, p<0.001)	1.22 (1.15-1.30, p<0.001)
Obese + non-diabetes	1.86 (1.73-1.99, p<0.001)	1.60 (1.49-1.71, p<0.001)	1.41 (1.31-1.51, p<0.001)	1.41 (1.32-1.52, p<0.001)
Normal + diabetes	2.65 (2.04-3.44, p<0.001)	1.59 (1.22-2.07, p<0.001)	1.38 (1.06-1.80, p=0.017)	1.21 (0.92-1.59, p=0.179)
Overweight + diabetes	3.87 (3.41-4.39, p<0.001)	2.07 (1.82-2.35, p<0.001)	1.67 (1.47-1.91, p<0.001)	1.41 (1.32-1.52, p<0.001)
Obese + diabetes	4.54 (4.11-5.01, p<0.001)	2.85 (2.58-3.16, p<0.001)	2.15 (1.93-2.39, p<0.001)	1.93 (1.67-2.23, p<0.001)
Non-fatal ischemic stroke				
Normal + non-diabetes	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Overweight + non-diabetes	1.37 (1.25-1.50, p<0.001)*	1.15 (1.05-1.26, p=0.002)	1.09 (0.99-1.19, p=0.069)	1.09 (1.00-1.19, p=0.064)
Obese + non-diabetes	1.63 (1.48-1.79, p<0.001)*	1.45 (1.83-2.61, p<0.001)	1.26 (1.14-1.39, p<0.001)	1.24 (1.12-1.37, p<0.001)
Normal + diabetes	3.96 (2.94-5.33, p<0.001)	2.45 (1.82-3.30, p<0.001)	2.06 (1.53-2.78, p<0.001)	1.83 (1.33-2.52, p<0.001)
Overweight + diabetes	3.80 (3.19-4.52, p<0.001)*	2.19 (1.32-1.60, p<0.001)	1.72 (1.44-2.06, p<0.001)	1.60 (1.29-1.99, p<0.001)
Obese + diabetes	4.26 (3.70-4.89, p<0.001)*	2.80 (2.43-3.23, p<0.001)	2.05 (1.77-2.37, p<0.001)	1.80 (1.48-2.21, p<0.001)

Table 2 – **Unadjusted and adjusted incidence rate ratios (IRR) for cardiovascular outcomes by diabetes and ethnicity adjusted BMI category**. Data presented as incidence rate ratios (IRR) with 95% confidence intervals (CI) obtained from Poisson regression analysis. * represents p value <0.05 for interaction between diabetes status and BMI category. Model 1 = Unadjusted model + adjustment for sex, age, ethnicity, smoking status, and deprivation score. Model 2 = Model 1 + adjustment for chronic cardiac condition, hypertension, cancer, chronic respiratory condition, chronic liver disease, chronic renal disease, neurological disease. Model 3 = Model 2 + adjustment for calcium channel blocker, beta blocker, angiotensin receptor blocker, thiazide diuretic, loop diuretic, mineralocorticoid receptor antagonist, statin, ACE inhibitor, aspirin, clopidogrel, warfarin, insulin, and metformin. Abbreviations: body mass index (BMI); confidence interval (CI); incident rate ratio (IRR).

	Missing	No Diabetes			Diabetes		
		Normal (N=143 557)	Overweight (N=185 758)	Obese (N=99 589)	Normal (N=2290)	Overweight (N=7732)	Obese (N=12 429)
				Diabetes metrics			
Diabetes duration, *years*	159	-	-	-	8 (3-19)*	6 (2-11)*	5 (2-10)*
Age of diabetes diagnosis, *years*	159	-	-	-	52 (37-59)*	55 (46-60)*	53 (46-59)*
				Body composition			
BMI	0	23.1 (21.8-24.1)*†	27.1 (26.0-28.4)*†	32.6 (31.1-35.1)*†	23.4 (22.3-24.3)*†	27.7 (26.4-28.8)*†	34.0 (31.7-37.5)*†
Waist circumference, cm	63	78 (72-84)*†	91 (85-97)*†	104 (97-110)*†	84 (77-89)*†	96 (90-101)*†	110 (103-118)*†
Hip circumference, cm	56	96 (93-99)*†	103 (100-106)*†	112 (108-118)*†	96 (92-99)*†	102 (99-105)*†	113 (108-120)*†
Waist to hip ratio	88	0.81 (0.76-0.87)*†	0.89 (0.82-0.94)*†	0.92 (0.85-0.98)*†	0.88 (0.82-0.93)*†	0.94 (0.89-0.98)*†	0.97 (0.91-1.03)*†
Body fat percentage	219	28 (22-33)*†	31 (25-38)*†	40 (31-45)*†	24 (20-30)*†	28 (25-35)*†	37 (32-44)*†
Whole body fat mass, *kg*	557	17.2 (14.1-20.4)*†	23.9 (20.4-27.5)*†	34.8 (29.9-40.6)*†	16.2 (13.2-19.5)*†	23.3 (20.1-26.7)*†	36.0 (30.5-43.4)*†
Whole body impedance, *ohms*	37	656 (597-710)*†	585 (532-648)*†	539 (488-597)*†	617 (565-675)*†	559 (517-612)*†	507 (464-561)*†
				Lipids			
Serum Apolipoprotein A, *g/L*	65 270	1.6 (1.4-1.8)*†	1.5 (1.3-1.7)*†	1.4 (1.3-1.6)*†	1.5 (1.3-1.7)*†	1.4 (1.2-1.6)*†	1.3 (1.2-1.5)*†
Serum Apolipoprotein B, *g/L*	29 354	1.0 (0.8-1.1)*†	1.0 (0.9-1.2)*†	1.1 (0.9-1.2)*†	0.8 (0.7-0.9)*†	0.8 (0.7-1.0)*†	0.8 (0.7-1.0)*†
Serum total cholesterol, *mmol/L*	27 198	5.7 (5.0-6.4)*†	5.8 (5.0-6.5)*†	5.7 (4.9-6.5)*†	4.4 (3.8-5.1)*†	4.3 (3.8-5.1)*†	4.3 (3.8-5.0)*†
Serum HDL cholesterol, *mmol/L*	63 179	1.6 (1.3-1.9)*†	1.4 (1.2-1.6)*†	1.3 (1.1-1.5)*†	1.4 (1.1-1.7)*†	1.2 (1.0-1.4)*†	1.1 (0.9-1.3)*†
Serum LDL cholesterol, *mmol/L*	28 008	3.4 (2.9-4.1)*†	3.6 (3.1-4.2)*†	3.6 (3.0-4.2)*†	2.5 (2.1-3.0)*†	2.5 (2.1-3.1)*†	2.6 (2.2-3.1)*†
Serum lipoprotein A, *nmol/L*	112 118	20.6 (9.5-60.3)*	21.4 (9.7-61.6)*	21.5 (9.5-64.3)*†	19.8 (8.8-60.1)*	21.4 (9.0-67.2)*	18.7 (8.3-62.2)*†
Serum triglycerides, *mmol/L*	27 550	1.2 (0.9-1.6)*	1.6 (1.1-2.2)*†	1.9 (1.3-2.6)*†	1.2 (0.8-1.7)*	1.7 (1.2-2.5)*†	2.0 (1.5-2.8)*†
Triglyceride / HDL cholesterol ratio	63 488	0.72 (0.49-1.11)*†	1.13 (0.73-1.79)*†	1.47 (0.96-2.24)*†	0.87 (0.54-1.41)*†	1.47 (0.92-2.29)*†	1.83 (1.21-2.76)*†
				Biochemistry			
Creatinine, *µmol/L*	27 425	67 (59-76)*†	73 (63-83)*†	72 (63-82)*†	70 (60-81)*†	73 (64-85)*†	72 (62-84)*†
Serum cystatin C, *mg/L*	27 240	0.84 (0.77-0.92)*†	0.89 (0.81-0.98)*†	0.94 (0.86-1.04)*†	0.87 (0.78-0.99)*†	0.92 (0.83-1.04)*†	0.97 (0.87-1.11)*†
Urinary microalbumin, *mg/L*	314 521	10.7 (8.2-16.8)*†	10.9 (8.2-17.6)*†	12.1 (8.7-21.1)*†	14.4 (9.2-29.7)*†	14.9 (9.8-32.2)*†	17.6 (10.3-42.2)*†
Alanine aminotransferase, *U/L*	27 210	17 (14-22)*†	21 (16-28)*†	24 (18-33)*†	21 (16-27)*†	24 (18-32)*†	26 (19-37)*†
C-reactive protein, *mg/L*	28 117	0.8 (0.4-1.5)*†	1.3 (0.7-2.5)*	2.5 (1.4-4.7)*†	0.9 (0.4-1.9)*†	1.3 (0.7-2.6)*	2.5 (1.2-4.9)*†
				Diabetes related biomarkers			
Glucose, *mmol/L*	63 478	4.9 (4.5-5.2)*†	4.9 (4.6-5.3)*†	5.0 (4.7-5.4)*†	6.4 (5.2-9.5)*†	6.4 (5.3-8.6)*†	6.6 (5.4-9.0)*†
HbA1c, *mmol/mol*	29 788	34 (32-37)*†	35 (33-37)*†	36 (34-39)*†	50 (43-59)*†	50 (43-58)*†	51 (44-60)*†
HbA1c, %	29 788	5.3 (5.1-5.5)*†	5.4 (5.2-5.5)*†	5.4 (5.3-5.7)*†	6.7 (6.1-7.5)*†	6.7 (6.1-7.5)*†	6.8 (6.2-7.6)*†
IGF-1, *nmol/L*	29 518	21.7 (18.1-25.2)*†	21.7 (18.1-25.2)*†	20.1 (16.3-23.8)*†	21.0 (17.1-25.2)*†	20.9 (16.7-24.8)*†	18.5 (14.4-22.8)*†
				Abdominal MRI			
Abdominal fat ratio, *fraction*	442 119	0.44 (0.36-0.51)*	0.51 (0.44-0.58)*	0.60 (0.53-0.66)*	0.46 (0.45-0.57)*	0.50 (0.45-0.57)*	0.61 (0.56-0.67)*
Total abdominal adipose tissue index, *L/m²*	441 948	2.5 (1.9-3.2)*	3.8 (3.1-4.6)*	5.7 (4.7-6.8)*†	2.6 (1.8-3.5)*	3.8 (3.2-4.7)*	6.1 (5.2-7.0)*†

Table 3 – Metabolic phenotypes of study participants. Participants stratified by diabetes status and then by ethnicity adjusted BMI category. Normal: BMI ≥18.5kg/m^2 to <25 kg/m^2 *or* ≥18.5kg/m^2 to <23 kg/m^2 if south Asian ethnicity; Overweight: ≥25kg/m^2 to <30 kg/m^2 *or* ≥23kg/m^2 to <27.5 kg/m^2 if south Asian ethnicity; Obese: ≥30kg/m^2 *or* ≥27.5kg/m^2 if south Asian ethnicity. Continuous data presented as median with 25th and 75th centile. Categorical data presented as n (%). * represents Kruskal-Wallis p value <0.005 between BMI categories for continuous variables within diabetes or non-diabetes groups. † represents p value <0.005 between each BMI category in diabetes participants and their respective BMI category in non-diabetes participants from Mann-Whitney U-tests for continuous variables and chi^2 test for categorical variables. Abbreviations: glycated hemoglobin (HbA1c); high density lipoprotein (HDL); insulin-like growth factor 1 (IGF-1); low density lipoprotein (LDL), (LVEF), left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), left ventricular end-systolic volume indexed to body surface area (LVESVi), left ventricular stroke volume (LVSV), systolic blood pressure (SBP).

Table 4 – **Phenotypic measurements of cardiovascular disease**. Participants are stratified by diabetes status and then by ethnicity adjusted BMI category. Normal: BMI ≥18.5kg/m^2 to <25 kg/m^2 *or* ≥18.5kg/m^2 to <23 kg/m^2 if south Asian ethnicity; Overweight: ≥25kg/m^2 to <30 kg/m^2 *or* ≥23kg/m^2 to <27.5 kg/m^2 if south Asian ethnicity; Obese: ≥30kg/m^2 *or* ≥27.5kg/m^2 if south Asian ethnicity. Continuous data presented as median with 25th and 75th centile. Categorical data presented as n (%). * represents Kruskal-Wallis p value or chi^2 test <0.005 between BMI categories for continuous variables and categorical variables respectively within diabetes or non-diabetes groups. † represents p value <0.005 between each BMI category in diabetes participants and their respective BMI category in non-diabetes participants from Mann Whitney U tests for continuous variables and chi^2 test for categorical variables. Abbreviations: body mass index (BMI) body surface area (BSA), intima media thickness (IMT), left ventricular ejection fraction

		No Diabetes			Diabetes		
	Missing	**Normal (N=143 557)**	**Overweight (N=185 758)**	**Obese (N=99 589)**	**Normal (N=2290)**	**Overweight (N=7732)**	**Obese (N=12 429)**
				Vital signs			
Systolic blood pressure, *mmHg*	0	132 (120-147)*†	139 (127-153)*†	142 (131-155)*	139 (126-153)*†	143 (131-155)*†	143 (132-155)*
Diastolic blood pressure, *mmHg*	0	78 (71-85)*†	82 (76-90)*†	86 (79-93)*†	77 (70-83)†	80 (74-87)†	83 (76-89)†
Resting heart rate, *bpm*	0	67 (60-74)*†	68 (61-75)*†	71 (64-79)*†	71 (63-80)*†	72 (64-81)*†	75 (66-85)*†
				Carotid intima-media thickness			
Mean carotid IMT, *μm*	409 913	650 (583-736)*†	677 (602-770)*†	685 (611-779)*†	725 (642-791)†	720 (629-810)†	703 (639-794)†
				Cardiac MRI			
LVEF, *%*	415 383	57 (53-60)*	56 (52-60)*†	56 (52-60)*†	57 (54-60)*	54 (49-58)*†	55 (50-58)*†
LVEDV, *ml*	415 383	126 (109-149)*	138 (117-162)*†	142 (122-166)*†	121 (102-142)*	131 (109-159)*†	133 (114-160)*†
LVESV, *ml*	415 383	55 (46-67)*	60 (49-74)*	62 (51-76)*	53 (42-63)*	60 (48-74)*	60 (49-76)*
LVSV, *ml*	415 383	71 (61-83)*	76 (65-89)*†	79 (67-92)*†	70 (57-80)	69 (57-84)†	72 (60-85)†
LVEDV / BSA, *ml/m^2*	415 390	74 (65-83)*†	73 (64-82)*†	71 (62-80)*†	70 (59-77)*†	69 (60-79)*†	65 (56-75)*†
LVESV / BSA, *ml/m^2*	415 390	32 (27-37)*†	32 (27-38)*	31 (26-36)*†	28 (25-35)*†	31 (26-37)*	30 (24-36)*†
LVSV / BSA, *ml/m^2*	415 390	41 (36-47)*†	41 (35-46)*†	39 (34-45)*†	39 (33-44)*†	37 (31-42)*†	35 (30-41)*†
Cardiac output, L/min^{-1}	415 383	4.3 (3.7-5.0)*	4.7 (4.0-5.4)*	4.9 (4.2-5.7)*	4.5 (3.8-5.1)*	4.5 (3.9-5.3)*	4.9 (4.1-5.7)*
Cardiac index, L/min^{-1}/m^2	415 390	2.5 (2.2-2.8)*	2.5 (2.2-2.8)*	2.4 (2.1-2.8)*†	2.5 (2.1-2.9)	2.4 (2.1-2.7)†	2.4 (2.1-2.7)
Cardiac contractility index (SBP/LVESVi)	415 390	4.1 (3.4-4.9)*†	4.3 (3.6-5.2)*†	4.5 (3.8-5.5)*†	4.7 (4.0-5.5)*†	4.5 (3.7-5.5)*†	4.8 (3.9-5.8)*†
				Photoplethysmography derived arterial stiffness			
Pulse wave arterial stiffness index	289 326	8.1 (6.4-10.5)*†	9.2 (7.0-11.4)*†	9.6 (7.5-11.4)*†	9.2 (6.9-11.4)*†	9.9 (7.7-11.9)*†	9.7 (7.9-11.5)*†