Exploring the Underlying Mechanisms Linking Adiposity and Cardiovascular Disease: A Prospective Cohort Study of 404,332 UK Biobank Participants

Ziyi Zhou, MPH[a], Solange Parra-Soto, MSc[b,c], Jirapitcha Boonpor, MSc[b,e], Fanny Petermann-Rocha, PhD[b,d], Paul Welsh, PhD[b], Patrick B. Mark, PhD[b], Naveed Sattar, PhD[b,1], Jill P. Pell, MD[a,1], Carlos Celis-Morales, PhD[a,b,f,1], and Frederick K. Ho, PhD[a*]

From the [a] School of Health and Wellbeing, University of Glasgow, Glasgow, UK, [b] School of Cardiovascular and Metabolic Health, University of Glasgow, Glasgow, UK, [c] Department of Nutrition and Public Health, Universidad del Bío-Bío, Chillan, Chile, [d] Centro de Investigación Biomédica, Facultad de Medicina, Universidad Diego Portales, Santiago, Chile, [e] Faculty of Public Health, Chalermphrakiat Sakon Nakhon Province Campus, Kasetsart University, Sakon Nakhon, Thailand and [f] Education, Physical Activity and Health Research Unit, Universidad Catolica del Maule, Talca, Chile.

Abstract: Obesity is causally associated with multiple cardiovascular outcomes but effective population measure to control obesity is limited. This study aims to decipher to which extent excess atherosclerotic cardiovascular diseases (ASCVD) and heart failure (HF) risk due to obesity can be explained by conventional risk factors. This is a prospective cohort study of 404,332 White UK Biobank participants. Participants with

[1] Joint-senior authors.

PW reports grant income from Roche Diagnostics, Boehringer Ingelheim, Novartis, Astrazeneca and lectures fees from Novo Nordisk and Benecol. NS has received research grant from AstraZeneca, Boehringer Ingelheim, Novartis and Roche Diagnostics; personal fees from Abbott Laboratories, Afimmune, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Hanmi Pharmaceuticals, Merck Sharp and Dohme, Novartis, Novo Nordisk, Pfizer, Roche Diagnostics, Janssen; consulting fees from Amgen and Sanofi. PM declares grant funding from Boehringer Ingelheim; consulting fees from Astellas, Astrazeneca, Napp, GSK, Boehringer Ingelheim; personal fees from Napp, Astrazeneca, Pharmacosmos; meetings and travel fees from Napp, Pharmacosmos. All other authors declare no conflicts of interest.

*Corresponding author: Frederick K. Ho, School of Health and Wellbeing, University of Glasgow, Glasgow, UK E-mail: Frederick.Ho@glasgow.ac.uk

Curr Probl Cardiol 2023;48:101715
0146-2806/$ – see front matter
https://doi.org/10.1016/j.cpcardiol.2023.101715

prior CVDs or other chronic diseases at baseline, or body mass index <18.5 kg/m^2 were excluded. Data were collected at the baseline assessment between 2006 and 2010. Linkage to death registrations and hospital admission records was used to ascertain ASCVD and HF outcomes up to late 2021. Obesity was defined as body mass index ≥30 kg/m^2. Candidate mediators included lipids, blood pressure (BP), glycated hemoglobin (HbA1c), and liver and kidney function markers, which were chosen based on clinical trials and Mendelian randomization studies. Cox proportional hazard models were used to estimate hazard ratios (HR) and their 95% confidence intervals (CIs). Mediation analysis based on g-formula was used to separately estimate the relative importance of mediators for ASCVD and HF. Compared with people without obesity, obese people had an increased risk of ASCVD (HR 1.30, 95% CI, 1.26-1.35) and HF (HR 2.04, 95% CI, 1.96-2.13) after adjusting for sociodemographic and lifestyle factors and medications for cholesterol, BP and insulin. The strongest mediators for ASCVD were renal function (eGFR: mediation proportion: 44.6%), BP (SBP: 24.4%; DBP: 31.1%), triglycerides (19.6%), and hyperglycemia (HbA1c 18.9%). These mediators collectively explained more excess risk of ASCVD than that of HF. Interventions that help obese individuals to maintain healthy lipid concentrations, BP, glycemic control, and kidney function could potentially alleviate a sizable proportion of the ASCVD burden. However, HF burden could not be meaningfully reduced without weight management. (Curr Probl Cardiol 2023;48:101715.)

Introduction

Obesity is associated with elevated mortality risk and account for over one-third of morbidity worldwide, most notably cardiovascular disease (CVD).[1,2] By 2025, it is estimated that obesity will affect more than 18% of men and more than 21% of women across the globe. There is emerging evidence that obesity may be a modifiable

risk factor for multiple types of CVD, such as heart failure (HF), and atrial fibrillation.[3,4]

Obesity is thought to cause CVD through multiple mechanisms and pathways.[5,6] Most widely established, obesity is known to increase triglyceride-rich lipoproteins, most notably very-low-density lipoprotein.[7] Secondly, obesity has also been found to induce chronic, low-grade inflammation,[8,9] which could interact with the circulating lipids to promote atherosclerosis.[9] More recently, it has been suggested that hemodynamic and renal function may play a role in obesity predisposing to CVD.[10] Nonetheless, most of the available evidence on how obesity could lead to CVD is based on animal experiments[11,12] or from piecewise clinical studies.[13,14] A meta-analysis attempted to systematically disentangle the mechanisms linking obesity to atherosclerotic CVD (ASCVD), including coronary artery disease and stroke,[15] and suggested that blood pressure (BP), cholesterol and blood glucose were all mediators. However, that study did not examine emerging factors, such as systemic inflammation and renal function, nor conducted formal mediation analysis which could have obviated biases.[16] Importantly, there is also scarce evidence of the mechanisms underpinning the association between obesity and HF, an increasingly prevalent CVD.[17]

Therefore, this study aims to systematically explore the mechanisms linking obesity with ASCVD and HF under a counterfactual framework. Specifically, this study aims to decipher to which extent excess ASCVD and HF risk due to obesity can be explained by traditional risk factors such as lipids, BP, and glycated hemoglobin (HbA1c), as well as emerging markers of liver,[18] kidney function,[19] and systemic inflammation.[20]

Method

Study Design

The UK Biobank is a prospective cohort that recruited over 500,000 participants from the general population who were aged 37-73 years and were registered with NHS general practitioners between 2006 and 2010.[21] Participants attended 1 of 22 assessments centers across England, Scotland, and Wales, where they completed a self-administered, touchscreen questionnaire and face-to-face interview to collect information on their lifestyle, health and socioeconomic characteristics, and trained research staff measured their height, weight, and BP and obtained blood samples. The UK Biobank obtained ethical approvals from the Northwest Multicenter Research Ethics Committee, the Community Health Index

Advisory Group, the Patient Information Advisory Group, and the National Health Service National Research Ethics Service. All participants provided informed consent to participate and be followed up through data linkage.

This study included 404,332 white UK Biobank participants and who were free from CVDs, and any other chronic diseases (including cancer and chronic obstructive pulmonary disease) at baseline and had a body mass index (BMI) $\geq$18.5 kg/m^2 (Fig 1). Other ethnic groups were excluded because they may have different BMI cut-offs for obesity.[22] Participants with chronic health problems at baseline or conditions and who were underweight were excluded to minimize reverse causation.

Exposures

Obesity was defined as general obesity and central obesity. BMI was calculated as weight/height^2. Standing height (cm) was measured by a Seca 202 device (SECA). Weight and bioimpedance were measured by the Tanita BC-418MA body composition analyzer (Tanita Corporation of America). Waist and hip circumference were measured in centimeters. Trained nurses did all measurements following a standardized protocol. Wessex nonstretchable sprung tape measurements were used to determine waist and hip circumferences.[23] By dividing the waist circumference by the hip circumference, the waist-to-hip ratio was obtained.[23] General obesity was defined as BMI $\geq$ 30 kg/m^2. Central obesity was classified as waist-to-hip ratio (WHR) $>$0.95 and $>$0.85 for males and females, respectively.[24]

Outcomes

The outcomes measured were incident ASCVD, and incident HF ascertained from hospital admissions and deaths. Date and cause of hospital admissions were obtained through record linkage to Health Episode Statistics (England and Wales) and Scottish Morbidity Records (Scotland). Date and cause of death were obtained from death certificates held by the National Health Service Information Centre (England and Wales) and the National Health Service Central Register (Scotland). Dates and causes of hospital admissions were obtained through record linkage to Health Episode Statistics (England and Wales) and Scottish Morbidity Records (Scotland). Comprehensive details regarding the linkage procedures are at http://content.digital.nhs.uk/services. At the time of analysis, death records were available up to the end of September 2021 for

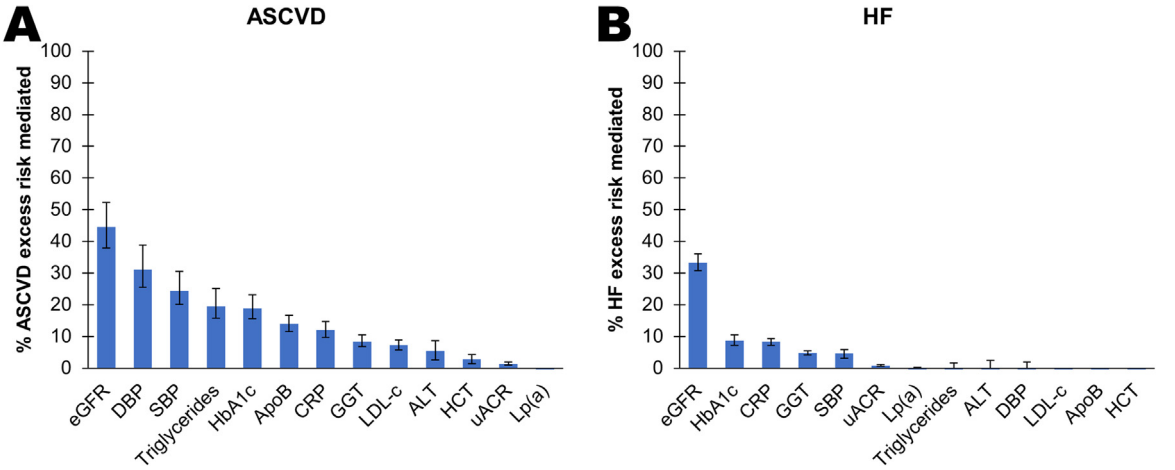

FIG 1. Proportion of mediation estimated independently for each mediator. Overlaps and sequential mediations were not accounted.

England and Wales and the end of October 2021 for Scotland. Hospital admission data were available up to September 30, 2021 for England, July 31, 2021 for Scotland and February 28, 2018 for Wales. ASCVD was defined, in accordance with the American College of Cardiology definition,[25] as fatal CAD (ICD-10 codes: I10-25), fatal/nonfatal myocardial infarction (MI) (I21), and fatal/nonfatal stroke (I60-64). HF was defined as either a hospitalization or death record with ICD-10 codes: I11.0, I42.0, I42.6-42.7, I42.9, or I50.

Mediators

This study included 14 candidate mediators in 6 categories based on clinical trials and Mendelian randomization studies. The 6 categories included (1) lipids: low density lipoprotein cholesterol (LDL-c),[26] triglycerides (TG),[27] apolipoprotein B (ApoB),[28] and lipoprotein(a)[29]; (2) BP: systolic BP (SBP) and diastolic BP (DBP)[30]; (3) metabolic marker: HbA1c[31]; (4) liver function marker: alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT)[32]; (5) kidney function: estimated glomerular filtration rate (eGFR),[33] urine albumin-to-creatinine ratio (uACR)[34]; (6) others: C-reactive protein (CRP),[35] and hematocrit (HCT).[36]

BP was measured by a nurse using an automated machine (or manually if unavailable), and the mean of available measurements was derived. LDL-c, TG, ApoB, Lp(a), HbA1c and CRP were measured in dedicated central laboratories with acceptable external validation correlations between 2014 and 2017.[37,38] The enzymatic selective protection method was used to analyze LDL-c and TG; and the immune-turbidimetric method was used to analyze ApoB, Lp(a), and CRP (Randox Laboratories; Crumlin, County Antrim, United Kingdom using a Beckman Coulter AU5800 Platform).[39] levels were used by the immunoturbidimetric method. Circulating concentrations of ALT, GGT were determined using the enzymatic rate method (Beckman Coulter AU5800), and urinary albumin was used in reagents and calibrators sourced from Randox Bioscience. eGFR was computed using the 2009 Chronic Kidney Disease Epidemiology Collaboration equation based on single serum cystatin C measurements taken during baseline assessment center visits by using linear regression to estimate the logarithm of measured GFR from standardized creatinine levels, sex, race, and age.[40] In our study, it is chosen over the estimation based on serum creatinine and cystatin C because it has better power in predicting CVD.[19,41] Within 24 hours of the blood draw,

reticulocyte parameters were assessed on a COULTER LH 750 System and the blood contents on a Beckman-automated hematology sanalyses.[42] HCT was reported from the instrument by mean (red blood cell volume (MCV) × red blood cell count (RBC)) /10.[42] The urine albumin-creatinine ratio (uACR) is a recognized indicator of urine albumin excretion that urine samples were collected at baseline in all UK Biobank participants.[43,44] A random urinary spot was used as a measure of electrolyte excretion.[44]

Covariates

Ethnicity, dietary intake, television viewing, smoking, and alcohol consumption were self-reported. The validated International Physical Activity Questionnaire was used to assess self-reported physical activity.[45] Townsend area deprivation index was obtained from the postcode of residence and is derived using aggregated data on unemployment, car and home ownership, and household overcrowding.[46] Baseline prevalent conditions were self-reported in a nurse-led interview.

Statistical Analyses

The characteristic of participants stratified by the general obesity categories (nonobese and obese) were summarized using means (standard deviations [SDs]) and frequencies (percentages) for quantitative and categorical variables, respectively. All biomarkers were standardized to sex-specific SD in regression analysis to compare the β coefficients. Multiple linear regressions were performed to evaluate the relationship between general obesity and biomarkers. Cox proportional hazards models were used to analyze the associations between general obesity and CVD. Deaths from other causes were censored at the date of death to eliminate the effect of competing risk. All models were adjusted for age, sex, deprivation, physical activity, TV viewing, dietary intake, alcohol consumption, and smoking, as well as medications for cholesterol, BP and insulin were adjusted in the corresponding factors. The g-formula-based mediation analyses[47] were fitted to identify significant mediators, and their associations with ASCVD and HF separately. As a sensitivity analysis, central obesity was used as exposure instead of general obesity. All analyses were conducted using R version 4.2.1 with the packages survival and CMAverse.[48]

Results

Of the more than 500,000 UK Biobank participants, 404,332 with complete data available on the exposures, mediators, and covariates were included in this study (Supplementary Fig 1). The overall prevalence of general obesity was 23.5%. Compared with participants without general obesity, those with general obesity were older, more likely to be deprived, watched more television, performed less physical activity, and were more likely to be male and nonvegetarians (Table 1).

Following adjustment for sociodemographic and lifestyle factors, all associations between obesity and the sex-standardized biomarkers were significant. The strongest associations were found for TG (β 0.47; 95% CI 0.47-0.48), eGFR (β -0.47; 95% CI, −0.48, −0.47), DBP (β 0.44; 95% CI, 0.44-0.45), uACR (β 0.09; 95% CI, 0.09, 0.10), and ALT (β 0.44; 95% CI, 0.44-0.45) (Table 2).

Table 3 shows the associations between obesity and CVDs outcomes by adjustment models. Adjusted for sociodemographic and lifestyle factors, obesity was associated with an increased risk of incident ASCVD (HR 1.30, 95% CI, 1.26-1.35) and incident HF (HR 2.04, 95% CI, 1.96-2.13). The associations were attenuated when candidate mediators were additionally adjusted. The largest attenuation for ASCVD was observed when DBP, SBP, eGFR, triglycerides, and HbA1c were included in the model. For HF attenuation was greatest when eGFR, SBP, and DBP were included in the model (Table 3).

Mediation analyses are shown in Table 4 and Figure 1. Without adjusting for each other, the mediators that potentially explained over 10% of the excess ASCVD risk were eGFR (44.6%), BP (SBP: 24.4%; DBP: 31.1%), TG (19.6%), HbA1c (18.9%), ApoB (14.0%), and CRP (12.0%). Only 1 mediator (eGFR [33.3%]) explained more than 10% of the excess HF risk. The causal structures between candidate mediators were not modelled; therefore, the proportion mediated could not be summed.

The sensitivity analyses using central obesity are shown in the supplementary materials. The distribution of participants by central obesity was generally similar to that identified using general obesity (Supplementary Table 1). The associations between central obesity and candidate mediators also followed similar patterns as for general obesity (Supplementary Table 2). Adjusted for sociodemographic and lifestyle factors, central obesity was associated with a similarly elevated risk of incident ASCVD (HR 1.33, 95% CI, 1.29-1.37) but a lower magnitude of elevated risk of incident HF (HR 1.67, 95% CI, 1.57-1.71). After adjusting for candidate mediators, there was less attenuation than was observed for general

TABLE 1. Participant characteristics

Characteristics	All participants	Nonobese (BMI < 30 kg/m^2)	Obese (BMI ≥ 30 kg/m^2)
Total N	404,332	309,229 (76.48%)	95,103 (23.52%)
Age, years, mean (SD)	56.19 (8.05)	56.11 (8.11)	56.46 (7.85)
Sex			
Female	221,074 (54.68%)	170,999 (55.30%)	50,075 (52.65%)
Male	183,258 (45.32%)	138,230 (44.70%)	45,028 (47.35%)
Deprivation index, mean (SD)	−1.51 (2.96)	−1.64 (2.89)	−1.09 (3.12)
Physical activity, MET min/week, mean (SD)	2495.35 (2244.31)	2579.39 (2272.42)	2222.10 (2127.58)
TV viewing (hours), mean (SD)	2.75 (1.53)	2.61 (1.49)	3.20 (1.63)
Diet type			
Vegetarians	5,618 (1.39%)	4,872 (1.58%)	746 (0.78%)
Fish eaters	8,554 (2.12%)	7,591 (2.45%)	963 (1.01%)
Fish and poultry eaters	3,896 (0.96%)	3,356 (1.09%)	540 (0.57%)
Meat-eaters	346,597 (85.72%)	265,660 (85.91%)	80,937 (85.10%)
Others	39,667 (9.81%)	27,750 (8.97%)	11,917 (12.53%)
Smoking status			
Never	223,839 (55.5)	174,629 (56.6)	49,210 (52.0)
Previous	138,356 (34.3)	101,854 (33.0)	36,502 (38.5)
Current	40,835 (10.1)	31,849 (10.3)	8986 (9.5)
Alcohol consumption, units/week, mean (SD)	17.00 (18.97)	16.88 (18.27)	17.40 (21.11)
BMI, kg/m^2, mean (SD)	27.35 (4.68)	25.34 (2.64)	33.89 (3.84)
Lipids			
LDL-c, mmol/L, mean (SD)	3.61 (0.85)	3.60 (0.84)	3.61 (0.89)
Triglycerides, mmol/L, mean (SD)	1.74 (1.03)	1.62 (0.94)	2.16 (1.18)
Lp(a), nmol/L, mean (SD)	49.28 (59.92)	49.54 (59.95)	48.41 (59.83)
ApoB, g/L, mean (SD)	1.04 (0.24)	1.04 (0.23)	1.07 (0.24)
Blood pressure			
SBP, mmHg, mean (SD)	137.89 (18.53)	136.55 (18.60)	142.27 (17.61)
DBP, mmHg, mean (SD)	82.40 (10.07)	81.20 (9.90)	86.31 (17.61)
Metabolic markers			
HbA1c, mmol/L, mean (SD)	35.67 (6.23)	34.99 (5.23)	37.87 (8.35)
Glucose, mmol/L mean (SD)	5.09 (1.16)	5.00 (0.98)	5.36 (1.59)
Liver function markers			
ALT, U/L, mean (SD)	23.51 (14.44)	21.88 (12.98)	28.83 (17.41)
GGT, U/L, mean (SD)	36.64 (42.15)	33.58 (39.12)	46.67 (49.50)
Kidney function markers			
ACR (urine), mg/mmol, mean (SD)	12.91 (60.08)	11.36 (49.79)	18.01 (85.39)
eGFR, mL/min, mean (SD)	92.66 (16.62)	94.75 (15.99)	85.80 (16.77)
Others			
CRP, mg/L, mean (SD)	2.53 (4.53)	2.07 (4.19)	4.04 (5.22)
HCT, L/L, mean (SD)	41.14 (3.51)	40.98 (3.49)	41.64 (3.51)

Numbers are n (%) unless otherwise specified. Some sub-categories, such as ethnicity, may not add up due to missing data.

Abbreviations: ALT, alanine transaminase; ApoB, apolipoprotein B; BMI, body mass index; CRP, C-reactive protein; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; LDL−C, low−density lipoprotein−cholesterol; Lp(a), lipoprotein(a); SBP, systolic blood pressure; uACR, urine albumin to creatinine ratio.

TABLE 2. Associations between general obesity and the biomarkers included in the analyses by group category

	β (95% CI)
Lipids*	
LDL-c	0.11 (0.11, 0.12)
Triglycerides	0.47 (0.47, 0.48)
Lp(a)	−0.04 (−0.04, −0.03)
ApoB	0.20 (0.19, 0.21)
Blood pressure*	
SBP	0.23 (0.22, 0.24)
DBP	0.44 (0.44, 0.45)
Metabolic markers*	
HbA1c	0.39 (0.39, 0.40)
Liver function markers	
ALT	0.44 (0.44, 0.45)
GGT	0.27 (0.26, 0.28)
Kidney function markers	
uACR	0.09 (0.09, 0.10)
eGFR	−0.47 (−0.48, −0.47)
Others	
CRP	0.40 (0.39, 0.40)
HCT	0.14 (0.14, 0.15)

All biomarkers were standardised to sex-specific SD so that the beta coefficients are comparable. All results are statistically significant ($P < 0.0001$).
All analyses adjusted for age, sex, ethnicity, deprivation, physical activity, sedentary behaviour, dietary intake, alcohol consumption, and smoking.
*Medications for cholesterol, blood pressure and insulin were adjusted in the corresponding factors.

obesity (Supplementary Table 3). The mediation analysis results were largely similar but with a lower proportion of the associations explained by the mediators (Supplementary Table 4).

Discussion

Principal Findings

This study investigated the underlying mechanisms between 2 types of obesity—general obesity and central obesity, and 2 main types of CVD outcomes—ASCVD and HF. The results showed that while eGFR, BP, TG, and HbA1c were all significant mediators for ASCVD and HF, they explained a much higher proportion of excess ASCVD risk. To our knowledge, this is the first study which systematically, in a single cohort, showed that the excess ASCVD risk due to obesity could be mitigated

TABLE 3. Associations between general obesity and incident CVD outcome by adjustment models

	ASCVD	HF
Baseline model	1.30 (1.26-1.35)	2.04 (1.96-2.13)
Additionally adjusted for:		
Lipids*		
LDL-c	1.26 (1.22-1.31)	1.95 (1.86-2.04)
Triglycerides	1.22 (1.18-1.26)	1.95 (1.87-2.05)
Lp(a)	1.28 (1.23-1.33)	1.95 (1.86-2.04)
ApoB	1.25 (1.20-1.29)	1.96 (1.87-2.05)
Blood pressure*		
SBP	1.18 (1.14-1.22)	1.76 (1.69-1.84)
DBP	1.17 (1.12-1.21)	1.79 (1.71-1.88)
Metabolic markers*		
HbA1c	1.22 (1.18-1.27)	1.91 (1.82-2.00)
Liver function markers		
ALT	1.29 (1.24-1.33)	2.06 (1.97-2.16)
GGT	1.28 (1.24-1.33)	2.00 (1.92-2.10)
Kidney function markers		
uACR	1.30 (1.25-1.34)	2.02 (1.93-2.11)
eGFR	1.17 (1.13-1.21)	1.71 (1.64-1.79)
Others		
CRP	1.27 (1.23-1.32)	1.98 (1.89-2.07)
HCT	1.29 (1.25-1.34)	2.07 (1.98-2.16)

Numbers presented are HR (95% CI); all results are statistically significant ($P < 0.0001$).
All analyses adjusted for age, sex, ethnicity, deprivation, physical activity, sedentary behaviour, and dietary intake.
*Medications for cholesterol, blood pressure and insulin were adjusted in the corresponding factors.

through intervening intermediate risk factors, but the excess HF risk could not be.

Strengths and Limitations

This study has several key strengths compared with existing studies. Firstly, we were able to systematically examine an extensive range of mediators, including emerging risk factors, such as liver and kidney function markers, in relation to the 2 major types of CVDs. Secondly, the use of counterfactual-based analysis and the carefully selected covariates provided robustness in estimating the relative importance of the mediators. Using a single cohort, rather than meta-analysis,[44] also ensured the consistency of measurements and eliminated any between-study confounding. The exclusion of participants with other preexisting chronic diseases reduced the chances of reverse causation and confounding by other

TABLE 4. Mediation analysis for the association between general obesity and CVD

	ASCVD			HF		
	Natural indirect effect		Proportion mediated	Natural indirect effect		Proportion mediated
	HR (95% CI)	*P*-value	% (95% CI)	HR (95% CI)	*P*-value	% (95% CI)
Lipids*						
LDL-c	1.02 (1.01-1.02)	< 0.0001	7.3 (5.8, 8.9)	0.99 (0.99-0.99)	< 0.0001	−2.5 (−3.1, −1.7)
Triglycerides	1.04 (1.04-1.05)	< 0.0001	19.6 (15.8, 25.2)	1.00 (0.98-1.01)	0.57	−0.6 (−3.5, 1.7)
Lp(a)	1.00 (0.99-1.00)	< 0.0001	−1.8 (−2.5, −1.2)	1.00 (1.00-1.00)	< 0.0001	−0.4 (−0.6, −0.2)
ApoB	1.03 (1.03-1.04)	< 0.0001	14.0 (11.6, 16.7)	0.99 (0.98-0.99)	< 0.0001	−2.7 (−4.1, −1.7)
Blood pressure*						
SBP	1.05 (1.04-1.05)	< 0.0001	24.4 (20.2, 30.5)	1.02 (1.01-1.03)	< 0.0001	4.6 (3.2, 5.9)
DBP	1.06 (1.05-1.07)	< 0.0001	31.1 (25.5, 38.8)	1.00 (0.98-1.01)	0.47	−1.1 (−4.3, 2.0)
Metabolic markers*						
HbA1c	1.04 (1.04-1.05)	< 0.0001	18.9 (15.6, 23.2)	1.04 (1.04-1.05)	< 0.0001	8.7 (7.3, 10.5)
Liver function markers						
ALT	1.01 (1.01-1.02)	< 0.0001	5.5 (2.6, 8.7)	1.00 (0.98-1.01)	0.63	−0.9 (−4.1, 2.5)
GGT	1.02 (1.02-1.02)	< 0.0001	8.4 (6.8, 10.5)	1.03 (1.02-1.03)	< 0.0001	4.8 (4.2, 5.5)
Kidney function markers						
uACR	1.00 (1.00-1.00)	< 0.0001	1.4 (1.0, 2.0)	1.00 (1.00-1.01)	< 0.0001	0.8 (0.6, 1.2)
eGFR	1.12 (1.10-1.13)	< 0.0001	44.6 (37.9, 52.3)	1.21 (1.19-1.22)	< 0.0001	33.3 (30.8, 36.1)
Others						
CRP	1.03 (1.02-1.03)	< 0.0001	12.0 (9.8, 14.8)	1.04 (1.04-1.05)	< 0.0001	8.4 (7.2, 9.4)
HCT	1.01 (1.00-1.01)	< 0.0001	2.8 (1.5, 4.3)	0.99 (0.98-0.99)	< 0.0001	−2.9 (−4.0, −1.9)

All analyses adjusted for age, sex, ethnicity, deprivation, physical activity, sedentary behaviour, dietary intake, alcohol consumption, and smoking.
*Medications for cholesterol, blood pressure, and insulin were adjusted in the corresponding factors.

diseases. However, this study has several limitations. As with any observational studies, reverse causation, and residual confounding could not be ruled out completely, despite robust exclusion and a comprehensive set of covariates. Moreover, the mediation analyses did not model the complex causal relationship between candidate mediators; thus, the proportion mediated should not be summed. While we aim to include a comprehensive list of potential mechanisms, it is not possible to including some emerging risk factors such as troponin, broad metabolomic biomarkers, and cardiac imaging. Last but not least, the UK Biobank is not representative of the UK general population even though exposure-outcome associations have been shown to be consistent with those from representative cohorts.[49]

Comparison With Other Studies

Our results are generally consistent with mainly of existing studies. For instance, a meta-analysis study of 9 prospective cohort studies (n = 58,322) showed that BP was the largest mediator, accounting for 37% of the associations between obesity and CHD, with blood glucose and cholesterol also accounting for 17% and 6%, respectively.[50] These numbers are very close to our findings. Another collaborative analysis of 58 prospective studies investigated the separate and combined associations between BMI and WHR and the risk of incident CVD, and found that lipids, BP, and history of diabetes were the main mediators.[51] Also, a population-based study demonstrated that adjustment for CRP substantially attenuated the association between BMI and CVD substantially.[52] Interestingly, a Mendelian Randomization mediation study has estimated that genetically predicted diabetes (41%) was a stronger mediator than SBP (27%), even though LDL-c remained a weak mediator (3%).[53] However, this study only investigated risk factors for which there was a good genetic risk score. Similar to our findings, the ARIC study also found that obesity has a stronger association with HF than other CVDs, but the associations was largely unexplained by traditional risk factors.[54] Notably, this study included additional emerging risk factors, for example eGFR, which explained the obesity-HF associations, highlighting the potential importance of kidney function.

Potential Mechanisms

While observational studies demonstrate association rather than causation, there is existing evidence that causation is biologically plausible.[55]

Generally, obesity indicates an excess amount of adipose tissue. Adipose tissue secretes inflammatory cytokines, such as CRP, and interleukin 6 (IL-6), which interacts with increased BP and LDL-c to cause endothelial dysfunction and, subsequently atherosclerosis.[56] Obesity can also cause elevated concentrations of LDL-c, which penetrate the subendothelial region to develop plaques.[57] One established mechanism is that obesity predispose for type 2 diabetes which could increase CVD risk substantially.[58] Obesity may also cause the renin-angiotensin-aldosterone pathway to become more active, increasing the synthesis of the aldosterone hormone.[10] However, it should be noted that the relationship between obesity and eGFR is complex and might be time dependent. Others, however, have proposed additional mechanisms for increased aldosterone synthesis in obese people, including greater direct aldosterone synthesis in adipose tissue and direct adrenal gland activation by the cytokine leptin, which is produced by adipocytes.[10] Aldosterone and leptin both activate pathways that result in sodium retention, plasma volume expansion, a rise in systemic inflammation, a rise in renal and cardiac fibrosis, a rise in arterial stiffness, and a reduction in the ability of the left ventricle to relax.[10] These pathophysiological deviations finally lead to hospitalization for symptomatic HF.[10,59] It should be noted that CRP might not be a causal factor per se[37] but could be a marker for other chronic upstream inflammatory markers, such as IL-6, a potential causal factor.[38]

Implications

The findings of this study suggest that controlling multiple intermediate outcomes of obesity could be effective in limiting the subsequent ASCVD burden in the population. The strength of eGFR as a mediator suggest that the current prevention efforts might be enhanced by monitoring and treating the kidney function of obese people.[60] Trials, for example, Dapagliflozin in Patients with Chronic Kidney Disease (DAPA-CKD)[61] which indicated that sodium-glucose co-transporter-2 (SGLT2) inhibitors happen to be the best eGFR drug,[62] to test this hypothesis are warranted. Further studies to examine whether suboptimal but clinical insignificant eGFR (eg, >60 mL/min) should indicate clinical action.

However, the study also illustrated that the underlying mechanisms for ASCVD and HF are very different and none of these mediators investigated could sustainably reduce the population burden of HF. For example, the glucagon-like peptide 1 receptor agonists (GLP1RA) could be a candidate to reduce ASCVD risk due to HbA1c being a much stronger mediator for ASCVD than for HF. Without strong mediators, prevention

efforts on HF would need to rely on obesity prevention, particularly since the association of obesity with HF is stronger than that with ASCVD.

Conclusion

Interventions that help individuals living with obesity to maintain healthy levels of lipids, BP, HbA1c, and kidney function could potentially alleviate some of the ASCVD burden. However, HF burden could not be meaningfully reduced without weight management.

Ethics Approval

UK Biobank received ethics approval from the Northwest Multi-Centre Research Ethics Committee (REC reference: 11/NW/03820). All participants gave written informed consent before enrolment in the study, which was conducted in accordance with the principles of the Declaration of Helsinki. Direct dissemination of the results to participants is not possible/applicable.

Funding

None.

Authors' Contribution

ZZ, NS, JPP, and FKH conceived the idea. ZZ and FKH conducted the analysis and wrote the first draft. All authors contributed to the interpretation of the findings. All authors critically revised the abstract for intellectual content and approved the final version of the abstract. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Acknowledgments

We thank UK Biobank participants. This research has been conducted using the UK Biobank Resource (application No 7155).

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.cpcardiol.2023.101715.

REFERENCES

1. Koliaki C, Liatis S, Kokkinos A. Obesity and cardiovascular disease: revisiting an old relationship. *Metabolism* 2019;92:98–107.
2. Wang Z, Nakayama T. Inflammation, a link between obesity and cardiovascular disease. *Mediators Inflamm* 2010;2010:535918.
3. Larsson SC, Back M, Rees JMB, Mason AM, Burgess S. Body mass index and body composition in relation to 14 cardiovascular conditions in UK Biobank: a Mendelian randomization study. *Eur Heart J* 2020;41(2):221–6.
4. Look ARG, Gregg EW, Jakicic JM, et al. Association of the magnitude of weight loss and changes in physical fitness with long-term cardiovascular disease outcomes in overweight or obese people with type 2 diabetes: a post-hoc analysis of the Look AHEAD randomised clinical trial. *Lancet Diabetes Endocrinol* 2016;4(11):913–21.
5. Douketis JD, Sharma AM. Obesity and cardiovascular disease: pathogenic mechanisms and potential benefits of weight reduction. *Semin Vasc Med* 2005;5(1):25–33.
6. Van Gaal LF, Mertens IL, De Block CE. Mechanisms linking obesity with cardiovascular disease. *Nature* 2006;444(7121):875–80.
7. Stadler JT, Marsche G. Obesity-related changes in high-density lipoprotein metabolism and function. *Int J Mol Sci* 2020;21(23).
8. 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(4):851–63.
9. Rocha VZ, Libby P. Obesity, inflammation, and atherosclerosis. *Nat Rev Cardiol* 2009;6(6):399–409.
10. Pandey A, Patel KV, Vaduganathan M, et al. Physical activity, fitness, and obesity in heart failure with preserved ejection fraction. *JACC Heart Fail* 2018;6(12):975–82.
11. Tamura N, Ogawa Y, Chusho H, et al. Cardiac fibrosis in mice lacking brain natriuretic peptide. *Proc Natl Acad Sci U S A* 2000;97(8):4239–44.
12. Nakagawa H, Oberwinkler H, Nikolaev VO, et al. Atrial natriuretic peptide locally counteracts the deleterious effects of cardiomyocyte mineralocorticoid receptor activation. *Circ Heart Fail* 2014;7(5):814–21.
13. Wang TJ, Larson MG, Levy D, et al. Impact of obesity on plasma natriuretic peptide levels. *Circulation* 2004;109(5):594–600.
14. Khan AM, Cheng S, Magnusson M, et al. Cardiac natriuretic peptides, obesity, and insulin resistance: evidence from two community-based studies. *J Clin Endocrinol Metab* 2011;96(10):3242–9.
15. Lu Y, Hajifathalian K, Ezzati M, et al. Metabolic mediators of the effects of body-mass index, overweight, and obesity on coronary heart disease and stroke: a pooled analysis of 97 prospective cohorts with 1.8 million participants. *Lancet* 2014;383:970–83.
16. Lapointe-Shaw L, Bouck Z, Howell NA, Lange T, Orchanian-Cheff A, Austin PC, et al. Mediation analysis with a time-to-event outcome: a review of use and reporting in healthcare research. *BMC Med Res Methodol* 2018;18(1):1–12.
17. Ebong IA, Goff DC, Jr., Rodriguez CJ, Chen H, Bertoni AG. Mechanisms of heart failure in obesity. *Obes Res Clin Pract* 2014;8(6):e540–8.

18. Ho FK, Ferguson LD, Celis-Morales CA, et al. Association of gamma-glutamyltransferase levels with total mortality, liver-related and cardiovascular outcomes: a prospective cohort study in the UK Biobank. *eClinicalMedicine* 2022;48:101435.
19. Lees JS, Welsh CE, Celis-Morales CA, et al. Glomerular filtration rate by differing measures, albuminuria and prediction of cardiovascular disease, mortality and end-stage kidney disease. *Nature Med* 2019;25(11):1753–60.
20. Lange LA, Carlson CS, Hindorff LA, et al. Association of polymorphisms in the CRP gene with circulating C-reactive protein levels and cardiovascular events. *Jama* 2006;296(22):2703–11.
21. Sudlow C, Gallacher J, Allen N, 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(3):e1001779.
22. Caleyachetty R, Barber TM, Mohammed NI, et al. Ethnicity-specific BMI cutoffs for obesity based on type 2 diabetes risk in England: a population-based cohort study. *Lancet Diabetes Endocrinol* 2021;9(7):419–26.
23. Ortega LS, Bradbury KE, Cross AJ, Morris JS, Gunter MJ, Murphy N. A prospective investigation of body size, body fat composition and colorectal cancer risk in the UK biobank. *Sci Rep.* 2017;7(1):17807.
24. Christakoudi S, Tsilidis KK, Muller DC, et al. A body shape index (ABSI) achieves better mortality risk stratification than alternative indices of abdominal obesity: results from a large European cohort. *Sci Rep.* 2020;10(1):14541.
25. Goff DC, Jr., Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014;63(25):2935–59.
26. Ridker PM, Pradhan A, MacFadyen JG, Libby P, Glynn RJ. Cardiovascular benefits and diabetes risks of statin therapy in primary prevention: an analysis from the JUPITER trial. *Lancet* 2012;380(9841):565–71.
27. Ye X, Kong W, Zafar MI, Chen LL. Serum triglycerides as a risk factor for cardiovascular diseases in type 2 diabetes mellitus: a systematic review and meta-analysis of prospective studies. *Cardiovasc Diabetol* 2019;18(1):48.
28. Zuber V, Gill D, Ala-Korpela M, et al. High-throughput multivariable Mendelian randomization analysis prioritizes apolipoprotein B as key lipid risk factor for coronary artery disease. *Int J Epidemiol* 2021;50(3):893–901.
29. Guertin J, Kaiser Y, Manikpurage H, et al. Sex-specific associations of genetically predicted circulating Lp(a) (lipoprotein(a)) and hepatic LPA gene expression levels with cardiovascular outcomes: mendelian randomization and observational analyses. *Circ Genom Precis Med* 2021;14(4):e003271.
30. Fuchs FD, Whelton PK. High blood pressure and cardiovascular disease. *Hypertension* 2020;75(2):285–92.
31. Mannucci E, Monami M, Lamanna C, Gori F, Marchionni N. Prevention of cardiovascular disease through glycemic control in type 2 diabetes: a meta-analysis of randomized clinical trials. *Nutr Metab Cardiovasc Dis* 2009;19(9):604–12.

32. Liu J, Au Yeung SL, Lin SL, Leung GM, Schooling CM. Liver enzymes and risk of ischemic heart disease and type 2 diabetes mellitus: a mendelian randomization study. *Sci Rep* 2016;6:38813.
33. Park S, Lee S, Kim Y, et al. Nonlinear causal effects of estimated glomerular filtration rate on myocardial infarction risks: mendelian randomization study. *BMC Med* 2022;20(1):44.
34. Haas ME, Aragam KG, Emdin CA, et al. Genetic association of albuminuria with cardiometabolic disease and blood pressure. *Am J Human Genet* 2018;103(4):461–73.
35. Lange LA, Carlson CS, Hindorff LA, et al. Association of polymorphisms in the CRP gene with circulating C-reactive protein levels and cardiovascular events. *JAMA* 2006;296(22):2703–11.
36. Zhong Y, Lin S, Schooling C. The effect of hematocrit and hemoglobin on the risk of ischemic heart disease: a Mendelian randomization study. *Prev Med* 2016;91:351–5.
37. Langlois MR, Chapman MJ, Cobbaert C, et al. Quantifying atherogenic lipoproteins: current and future challenges in the era of personalized medicine and very low concentrations of LDL cholesterol. A consensus statement from EAS and EFLM. *Clin Chem* 2018;64(7):1006–33.
38. Jacobson TA, Ito MK, Maki KC, et al. National lipid association recommendations for patient-centered management of dyslipidemia: part 1—executive summary. *J Clin Lipidol* 2014;8(5):473–88.
39. Patel AP, Wang M, Pirruccello JP, et al. Lp(a) (Lipoprotein[a]) concentrations and incident atherosclerotic cardiovascular disease: new insights from a large national biobank. *Arterioscler Thromb Vasc Biol* 2021;41(1):465–74.
40. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009;150(9):604–12.
41. Inker LA, Eneanya ND, Coresh J, et al. New creatinine- and cystatin C-based equations to estimate GFR without race. *N Engl J Med* 2021;385(19):1737–49.
42. Watts EL, Perez-Cornago A, Kothari J, Allen NE, Travis RC, Key TJ. Hematologic markers and prostate cancer risk: a prospective analysis in UK biobank. *Cancer Epidemiol Biomarkers Prev* 2020;29(8):1615–26.
43. Casanova F, Tyrrell J, Beaumont RN, et al. Corrigendum to: a genome-wide association study implicates multiple mechanisms influencing raised urinary albumin-creatinine ratio. *Hum Mol Genet* 2022;31(9):1544.
44. Zanetti D, Bergman H, Burgess S, Assimes TL, Bhalla V, Ingelsson E. Urinary albumin, sodium, and potassium and cardiovascular outcomes in the UK biobank: observational and mendelian randomization analyses. *Hypertension* 2020;75(3):714–22.
45. Craig CL, Marshall AL, Sjostrom M, et al. International physical activity questionnaire: 12-country reliability and validity. *Med Sci Sports Exerc* 2003;35(8):1381–95.
46. Health and deprivation P Townsend P Phillimore a Beattie health and deprivation published by Croom Helm 212pp pound19.95 0-7099-4351-2 [Formula: see text]. *Nurs Stand* 1988;2(17):34.
47. Keil AP, Edwards JK, Richardson DB, Naimi AI, Cole SR. The parametric g-formula for time-to-event data: intuition and a worked example. *Epidemiology* 2014;25 (6):889–97.

48. Shi B, Choirat C, Coull BA, VanderWeele TJ, Valeri L. CMAverse: a suite of functions for reproducible causal mediation analyses. *Epidemiology* 2021;32(5):e20–e2.
49. Batty GD, Gale CR, Kivimäki M, Deary IJ, Bell S. Comparison of risk factor associations in UK Biobank against representative, general population based studies with conventional response rates: prospective cohort study and individual participant meta-analysis. *BMJ* 2020:368.
50. Lu Y, Hajifathalian K, Rimm EB, Ezzati M, Danaei G. Mediators of the effect of body mass index on coronary heart disease: decomposing direct and indirect effects. *Epidemiology* 2015;26(2):153–62.
51. Emerging Risk Factors C, Wormser D, Kaptoge S, et al. Separate and combined associations of body-mass index and abdominal adiposity with cardiovascular disease: collaborative analysis of 58 prospective studies. *Lancet* 2011;377(9771):1085–95.
52. Seven E, Husemoen LL, Sehested TS, et al. Adipocytokines, C-reactive protein, and cardiovascular disease: a population-based prospective study. *PLoS One* 2015;10(6):e0128987.
53. Gill D, Zuber V, Dawson J, et al. Risk factors mediating the effect of body mass index and waist-to-hip ratio on cardiovascular outcomes: Mendelian randomization analysis. *Int J Obes (Lond)* 2021;45(7):1428–38.
54. Ndumele CE, Matsushita K, Lazo M, et al. Obesity and subtypes of incident cardiovascular disease. *J Am Heart Assoc* 2016;5(8):e003921.
55. Gianicolo EAL, Eichler M, Muensterer O, Strauch K, Blettner M. Methods for evaluating causality in observational studies. *Dtsch Arztebl Int* 2020;116(7):101–7.
56. Gualillo O. Mediators of inflammation in obesity and its comorbidities. Hindawi; 2010;2010:239126.
57. Klop B, Elte JW, Cabezas MC. Dyslipidemia in obesity: mechanisms and potential targets. *Nutrients* 2013;5(4):1218–40.
58. Piche ME, Tchernof A, Despres JP. Obesity phenotypes, diabetes, and cardiovascular diseases. *Circ Res* 2020;126(11):1477–500.
59. Schefold JC, Filippatos G, Hasenfuss G, Anker SD, von Haehling S. Heart failure and kidney dysfunction: epidemiology, mechanisms and management. *Nat Rev Nephrol* 2016;12(10):610–23.
60. Tsimihodimos V, Mitrogianni Z, Elisaf M. Dyslipidemia associated with chronic kidney disease. *Open Cardiovasc Med J* 2011;5:41–8.
61. Heerspink HJL, Stefansson BV, Correa-Rotter R, et al. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med* 2020;383(15):1436–46.
62. Bailey CJ, Day C, Bellary S. Renal protection with SGLT2 inhibitors: effects in acute and chronic kidney disease. *Curr Diab Rep* 2022;22(1):39–52.