Contribution of obesity and cardiometabolic risk factors in patients with cardiovascular disease: A population based cohort study

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Abstract

Background

The mechanisms linking adiposity to associated clinical conditions such as type 2 diabetes, cardiovascular disease, and related metabolic and inflammatory disturbances. are poorly understood. This study aimed to identify sex-specific direct and indirect effects of central and general adiposity on cardiovascular disease, mediated by cardiometabolic risk factors and how much is independent of these factors.

Methods

We analyzed data from the TLGS cohort study with 6280 participants aged ≥ 30 years, free of cardiovascular disease at baseline with a median follow-up of 13.9 years. The total effects were broken down into natural direct and indirect effects using a 2-stage regression model in the context of the survival model. We also calculated the proportion mediated by systolic blood pressure, total serum cholesterol, and fasting plasma glucose as mediators.

Results

There was no interaction between BMI and its mediators in the multiplicative scale ($P > 0.05$ for all). Blood pressure was the most important mediator for general (HR_{NIE} : 1.11, 95% CI: 1.17–1.24) and central obesity (HR_{NIE} : 1.11, 95% CI: 1.07–1.15) with proportion mediated of 60% and 36% respectively in the total population. The percentage mediated through all three metabolic risk factors together was 46% (95% confidence interval = 31%–75%) for overweight, 66% (45%–100%) for general obesity and 52% (39%–87%) for central obesity. Blood pressure was the most important mediator for overweight and central adiposity in male population with 29% and 36% proportion mediated respectively while in female population percentage mediated through all three metabolic risk factors together was 23% (95% confidence interval = 13%–50%) for overweight, 36% (21%–64%) for general obesity and 52% (39%–87%) for central obesity.

Conclusions

Metabolic mediators explain more than 60% of the adverse effects of high BMI on CVD in the male population. Also, managing these metabolic mediators in women does not effectively contribute to reducing CVD risks without decreasing weight.

1. Background

Cardiovascular disease (CVD) is the leading cause of death worldwide (1). Mortality and morbidity from CVDs are expected to rise in low and middle income countries as well as high income countries over the next few decades (2). The combination of socio-economic and life style changes has contributed to development of CVDs over the past decades (3). Likewise, economic growth, industrialization, increased sedentary lifestyle and nutritional transition lead to, the prevalence of being overweight and obese have doubled and even quadrupled over the last 30 years (4). It has been shown that overweight and obese individuals had an elevated risk of developing CVD, particularly those with central obesity (5). Increased prevalence of being overweight and obese worldwide followed by elevated risk of CVDs has raised concerns in many countries(6).

The association of obesity with dyslipidemia, hypertension, diabetes, insulin resistance and systemic inflammation which is accompanied with elevated risk of CVDs, have also been documented (5). However, the mechanisms linking body mass index (BMI) to CVDs have not been clearly understood. A major clinical question is: what proportion of the adverse effects of high BMI will directly affect cardiovascular disease and how much of it by metabolic mediators? In order to clarify this question, we need to understand how much the effects of obesity could be mediated per se or through other metabolic factors e.g. blood pressure, glucose, cholesterol together or separately. The mediated effect of BMI on CVD events, blood pressure, cholesterol, and diabetes together have been examined in some previous studies (7). However, the effects of individual mediator or possible combination are important issue which is neglected in these studies.

In this study, we quantified how much the effect of overweight and obesity i.e. general and abdominal adiposity on CVDs are mediated through blood pressure, cholesterol, and blood glucose individually or in varying combinations, while assessing an interaction between BMI and mediators. In this study we also assessed whether sex specific analyses could alter overall findings.

2. Methods

2-1.Study population

Current research was performed in the frame work of The Tehran Lipid and Glucose Study (TLGS). The TLGS was a population-based longitudinal cohort study conducted in Tehran,Iran, to determine the prevalence and incidence of risk factors for non-communicable diseases. In the TLGS, patients were recruited in two phase including the first exam (1999- 2001) and the second exam (2002- 2005)(8).

The eligibility criteria for the current analyses were as follows 1) aged ≥ 30 years; 2) having at least 1 year follow up; 3) those with anthropometric and metabolic measurements (blood pressure, serum cholesterol, and blood glucose) at baseline; 4) and those with CVD event ascertained during follow-up.

There was 9560 study participants aged ≥ 30 years. Subjects with prevalent CVD (n=602), baseline history of cancer (n=57), history of hospitalization at the baseline (n=109), pregnancy (n=43), BMI<18.5 (n=113), no follow-up (n=772), missing data in BMI, waist circumference (WC), fasting plasma glucose

(FPG) and 2-hour post-challenge plasma glucose (2 h-PCPG) (n=988), missing data of other covariates including baseline systolic blood pressure (SBP), diastolic blood pressure (DBP), total cholesterol (TC), physical activity, smoking status, educational status, and family history of CVDs (n=596) were excluded from the study. Among final analyses were performed on 6280 individuals (5357 individuals from exam 1 and 923 new participants from exam 2), who were followed till March 20, 2014. Sequential imputation using chained equations were used to manage missing data in the main variables such as exposure, mediator, and covariates used in the models.(9).

Ethical approval for this study was obtained from the Research Institute for Endocrine Sciences. All participants provided written informed consent.

2-2.Clinical and Laboratory Measurements:

Data related to demographic characteristics, medical history, medication use, and smoking habits were obtained through interviews by trained physicians (10). The SBP and DBP was measured twice at an interval of 15 minutes on the right arm in the seated position using a standardized mercury sphygmomanometer; the mean of the two measurements was regarded as the subjects' blood pressure. The WC was measured using a tape meter at the umbilical waist in light clothing to the nearest 0.1 cm. Venous blood specimens were withdrawn after overnight fasting (12-14 hours) between 07:00 and 09:00 AM and centrifugation was performed within 30-45 minutes of collection. Serum TC was measured using the enzymatic colorimetric method with cholesterol esterase and cholesterol oxidase. The methods of other metabolic measurements including FPG and 2hPG, high density lipoprotein cholesterol (HDL-C), and triglyceride (TG) have been reported elsewhere (11).

2-3.Definition of Terms:

Study variables definition has been detailed elsewhere(10). Subjects were classified as current smokers, who smoked either daily or occasionally, and non-smoker who had never smoked or stopped smoking. Education levels was categorized into 3 groups as follows: illiterate/primary school, below diploma/diploma, and university education. Central adiposity was defined by WC of ≥ 90 cm for both men and women based on the Iranian National Committee of Obesity reports (12). In addition, general adiposity was categorized into three groups: normal weight ($BMI \leq 25.0 \text{ kg/m}^2$), overweight ($25.0 < BMI < 30.0 \text{ kg/m}^2$) and obese ($BMI \geq 30.0 \text{ kg/m}^2$). Metabolic equivalent task (MET) less than 600 or exercising less than three days a week was considered as low-intensity physical activities.

2-4.Mediators and Potential Confounders

Metabolic factors including SBP, TC, and FPG was regarded as mediators (13). Age, gender, smoking status, educational status, family history of CVDs, and physical activity were regarded as potential factors which confound the association between BMI and CVDs, BMI and mediator, and mediator and CVDs. The same mediators were regarded for the association between the central adiposity and CVDs'

event. These variables were chosen as minimal set of confounders for association between the BMI or WC, mediators, and CVDs (14, 15).

2-5.Statistical analysis

The t-test and chi-square test were respectively used to compare the mean value and proportions of the baseline variables between the men and women participants. To specify the relationship between variables and their appropriate scale to be included in the final model, a fractional polynomial model was used(16). To account for selection bias due to censoring during the study (loss to follow-up or competing risk), an inverse probability-of-censoring weighting (IPW) in which the contribution of each uncensored subject is weighted by the inverse of his/her probability of not being censored at the end of the follow-up was used.

A pooled logistic regression model was used to estimate the inverse probability of loss to follow-up censoring weights, with the censoring variable as the outcome and all other covariates as predictors(17).The effect of unmeasured mediator-outcome confounding on direct and indirect effects were specified (18). The effect of unmeasured mediator-outcome confounding in the setting of mild and strong confounding was evaluated. Detailed description of this sensitivity analysis was published recently(15).

A2-stage regression method proposed by VanderWeele was used to estimate the direct and indirect effects(19). To evaluate the influence of violations to the no-unmeasured-confounding assumption, a sensitivity analysis was undertaken. The model will provide valid estimates of direct and indirect effects if the outcome is relatively rare,there is no unmeasured confounding and no model misspecification.(18, 20).

First, we fit three linear regression models, one for each mediator (M), conditional on BMI categories (A) and confounders (C):

$$E [M | A, C] = \beta_0 + \beta_1 A + \beta_2 C \quad (1)$$

We then fit a Cox proportional hazards regression model for CVD risk on BMI categories (A), mediators (M), a BMI-by-mediator interaction term, and confounders (C) using age as the time scale:

$$\lambda (t | A, M, C) = \lambda_0 (t) \exp (\theta_1 A + \theta_2 M + \theta_3 AM + \theta_4 C) \quad (2)$$

Where in the equation, $\lambda_0(t)$ is the baseline hazard at age t for a normal weight participant when all the mediators and confounders are set to 0 and θ_3 is the vector of coefficients for the interaction between overweight/obesity and its mediators. The natural direct and indirect effects were estimated using the coefficients of the above regressions. The detailed expression was provided by Lu et, al (13).

Following convention, the direct and indirect effects at the mean level of confounders in TLGS cohort was estimated and a measure of the “proportion mediated” based on the natural direct and indirect effects,

using the formula $(HR_{TE} - HR_{NDE}) / (HR_{TE} - 1)$ was calculated, where HR_{TE} is the total effect hazard ratio and is calculated as $HR_{TE} = HR_{NDE} \times HR_{NIE}$ (21). In the final step, a bootstrap with 1000 samples was used for the total, direct, and indirect effects. Stata 13.0 MP (Stata corp, College Station, Texas, USA) and R 3.04 were used for conducting statistical analyses.

3. Results

In this study, we have used the information of 6280 people, of them 710 had CVD as an outcome. the study population had an average age of 46.2 ± 11.7 years old and included 2859 males (45.53%) and the remaining (54.47%) females. The results suggest that men and women do not exhibit meaningful statistical difference only in waist circumference, systolic & diastolic blood pressure ($P > 0.05$) and are otherwise different. In general, women in the study were more overweight and had higher blood cholesterol levels than men and their level of education was also lower than men.

Table 1
Baseline characteristics of participants according to gender status, Tehran Lipid and Glucose Study
(1999–2015)

Variable	Men (n = 2859)	Women (n = 3421)	Total Population (n = 6280)	P-value*
Age (years)	47.1 ± 12.5	45.5 ± 10.9	46.2 ± 11.7	< 0.001
Body mass index (Kg × m ²)	26.3 ± 3.7	28.6 ± 4.6	27.5 ± 4.4	< 0.001
Waist circumference(cm)	90.9 ± 10.3	90.4 ± 11.9	90.6 ± 11.2	0.095
Systolic blood pressure (mmHg)	120.9 ± 18.4	120.1 ± 19.3	120.5 ± 18.9	0.08
Diastolic blood pressure (mmHg)	78.5 ± 11.2	78.8 ± 10.6	78.6 ± 10.9	0.43
Fasting plasma glucose (mg/dl)	5.29 ± 1.17	5.21 ± 1.1	5.25 ± 1.13	0.009
Triglycerides (mmol/L)	2.19 ± 1.56	1.91 ± 1.18	2.04 ± 1.37	< 0.001
Total cholesterol (mmol/L)	5.38 ± 1.1	5.63 ± 1.2	5.51 ± 1.16	< 0.001
HDL-cholesterol (mmol/L)	0.98 ± 0.24	1.15 ± 0.28	1.07 ± 0.27	< 0.001
Family history of CVDS (%)	417 (14.59)	606 (17.71)	1023(16.29)	0.001
Low physical activity (%)	2061 (72.09)	2402 (70.21)	4463(71.07)	0.10
Education (%)				
Illiterate/primary school	824 (28.82)	1563 (45.6)	2387(38.01)	< 0.001
Below diploma/diploma	1497 (52.36)	1595 (46.62)	3092(49.24)	
Higher than diploma	538 (18.82)	263 (7.69)	801(12.75)	
Smoking (%)				
Never	1528 (53.45)	3196 (93.42)	4724(75.22)	< 0.001
Past	453 (15.84)	68 (1.99)	521(8.3)	

*Differences in continuous and categorical variables between males and females were assessed using the independent *t*-test and Chi-square test, respectively.

Variable	Men (n = 2859)	Women (n = 3421)	Total Population (n = 6280)	P-value*
Current	878 (30.71)	157 (4.59)	1035(16.48)	
*Differences in continuous and categorical variables between males and females were assessed using the independent <i>t</i> -test and Chi-square test, respectively.				

The estimations from the parametric model showed 61% of increased risk of CVDs by overweight is independent of intermediate cardiometabolic risk factors. According to the estimates of model, High cholesterol levels had indirect hazard ratio of 1.09 (1.06–1.12) and a mediated proportion of 22 percent which has been regarded as the most important intermediate risk factor in the relation between the overweight and CVDs.

Considering the relation between general obesity and CVD, the estimations showed a 68% increase in the total effects. The intermediate variables of blood pressure, cholesterol, and blood sugar were responsible for 17, 14 and 5 percent increase risk respectively and had the most indirect effects. In obese people with all three metabolic risk factors together, the indirect risk increased to $HR_{NIE} = 1.33$ (1.26–1.42), conducting 66 percent of obesity effect through these mediators. Central obesity increased the risk of CVD for 59 percent. The results proved that 52 percent of total effects were exerted through the mediators. Scrutinizing the relationship between central adiposity and CVD showed that blood pressure, cholesterol, and blood glucose had the most indirect effects.

Table 2

Total, direct, and indirect effects of overweight and adiposity on cardiovascular diseases (CVDs) using a parametric method not considering exposure-mediator interaction.

exposures	Mediators	Total effect ^{a,b}	Natural direct effect	Natural indirect effect	Proportion mediated ^c
		HR (95% CI)	HR (95% CI)	HR (95% CI)	(95% CI)
overweight	Blood pressure (mmHg)	1.61 (1.34–1.95)	1.42 (1.18–1.73)	1.08 (1.06–1.11)	21 (14–37)
	Cholesterol (mmol/l)		1.5 (1.23–1.81)	1.09 (1.06–1.12)	22 (15–34)
	Glucose (mmol/l)		1.53 (1.27–1.86)	1.02 (1.03–1.04)	8 (5–15)
	Blood pressure, cholesterol, and glucose		1.29 (1.07–1.58)	1.19 (1.15–1.24)	46 (31–75)
General obesity	Blood pressure (mmHg)	1.68 (1.35–2.08)	1.37 (1.08–1.70)	1.17 (1.11–1.21)	38 (26–70)
	Cholesterol (mmol/l)		1.5 (1.21–1.85)	1.14 (1.10–1.18)	29 (20–45)
	Glucose (mmol/l)		1.58 (1.26–1.96)	1.05 (1.03–1.07)	12 (7–20)
	Blood pressure, cholesterol, and glucose		1.20 (0.96–1.52)	1.33 (1.26–1.42)	66 (45–100)
Visceral adiposity	Blood pressure (mmHg)	1.59 (1.33–1.85)	1.40 (1.18–1.63)	1.10 (1.07–1.13)	27 (18–43)
	Cholesterol (mmol/l)		1.44 (1.19–1.67)	1.09 (1.06–1.12)	23 (16–38)
	Glucose (mmol/l)		1.50 (1.25–1.74)	1.04 (1.02–1.06)	11 (8–19)
	Blood pressure, cholesterol, and glucose		1.25 (1.03–1.46)	1.22 (1.17–1.27)	52 (39–87)

MI: body mass index; CI: confidence interval; HR: hazard ratio; WC: waist circumference.

^aCompared with normal-weight participants for general adiposity and WC < 90 cm as a reference for central adiposity.

^bAll models were adjusted for age, gender, smoking, physical activity level, educational status, and family history of CVDs.

^cThe direct, indirect, and total effects were estimated for each bootstrap resample

The result of inverse probability weighting demonstrated that the censoring due to lost to follow-up for increased BMI, adiposity, and central adiposity was less than 5 percent (etable1). Also results of multiple imputation of missing data didn't show any significant differences (less than 5 percent) with observed estimates (results available upon the request).

Tables 3 and 4 show the results of the parametric model with differentiation for males and females. The results of this model for the male population shows that the general estimated effects for the studied exposures have been associated with a 10, 28 and 17 percent decrease compared to the whole population. Also, the results show that blood pressure, cholesterol and blood sugar with an intermediate share of 11, 24 and 29 percent have been the most important cardio-metabolic intermediate variables in the relation between the overweight and CVDs in males. Also, when all three cardiometabolic risk factors were present in the model simultaneously, about 60 percent of the harmful effects of being overweight on CVD was due to those three. The fact worth mentioning is that the same effect for the whole studied population was around 46 percent.

Table 3

Total, direct, and indirect effects of overweight and adiposity on cardiovascular diseases (CVDs) using a parametric method not considering exposure-mediator interaction in men.

exposures	Mediators	Total effect	Natural direct effect	Natural indirect effect	Proportion mediated (95% CI)
		HR (95% CI)	HR (95% CI)	HR (95% CI)	
overweight	Blood pressure (mmHg)	1.50 (1.22–1.86)	1.32 (1.07–1.64)	1.10 (1.06–1.14)	29 (16–62)
	Cholesterol (mmol/l)		1.40 (1.13–1.75)	1.09 (1.05–1.13)	24 (14–48)
	Glucose (mmol/l)		1.42 (1.15–1.77)	1.04 (1.02–1.05)	11 (6–26)
	Blood pressure, cholesterol, and glucose		1.17 (0.93–1.47)	1.23 (1.17–1.29)	60 (30–100)
General obesity	Blood pressure (mmHg)	1.40 (1.06–1.85)	1.12 (0.82–1.52)	1.11 (1.17–1.24)	60 (1–100)
	Cholesterol (mmol/l)		1.27 (0.95–1.67)	1.14 (1.08–1.22)	40 (22–99)
	Glucose (mmol/l)		1.28 (0.97–1.70)	1.06 (1.03–1.10)	22 (10–99)
	Blood pressure, cholesterol, and glucose		0.95 (0.70–1.28)	1.39 (1.29–1.51)	98 (10–100)
Visceral adiposity	Blood pressure (mmHg)	1.42 (1.16–1.73)	1.24 (1.02–1.56)	1.11 (1.07–1.15)	36 (19–83)
	Cholesterol (mmol/l)		1.30 (1.05–1.60)	1.09 (1.06–1.13)	29 (15–67)
	Glucose (mmol/l)		1.34 (1.11–1.66)	1.04 (1.02–1.06)	14 (7–30)
	Blood pressure, cholesterol, and glucose		1.11 (0.90–1.41)	1.25 (1.18–1.32)	71 (41–100)

Table 4

Total, direct, and indirect effects of overweight and adiposity on cardiovascular diseases (CVDs) using a parametric method not considering exposure-mediator interaction in women.

exposures	Mediators	Total effect	Natural direct effect	Natural indirect effect	Proportion mediated (95% CI)
		HR (95% CI)	HR (95% CI)	HR (95% CI)	
overweight	Blood pressure (mmHg)	1.91 (1.32–2.93)	1.76 (1.21–2.75)	1.05 (1.02–1.08)	10 (4–22)
	Cholesterol (mmol/l)		1.80 (1.26–2.81)	1.06 (1.03–1.10)	12 (1–25)
	Glucose (mmol/l)		1.83 (1.25–2.79)	1.02 (1.01–1.03)	5 (2–11)
	Blood pressure, cholesterol, and glucose		1.64 (1.13–2.56)	1.11 (1.07–1.17)	23 (13–50)
General obesity	Blood pressure (mmHg)	2.13 (1.44–3.20)	1.82 (1.23–2.79)	1.13 (1.07–1.19)	22 (11–41)
	Cholesterol (mmol/l)		1.96 (1.35–3.03)	1.08 (1.04–1.13)	14 (7–26)
	Glucose (mmol/l)		2.04 (1.39–3.04)	1.03 (1.01–1.03)	6 (3–14)
	Blood pressure, cholesterol, and glucose		1.70 (1.15–2.64)	1.21 (1.14–1.31)	36 (21–64)
Visceral adiposity	Blood pressure (mmHg)	1.72 (1.39–2.39)	1.59 (1.16–2.20)	1.08 (1.04–1.12)	18 (10–40)
	Cholesterol (mmol/l)		1.62 (1.19–2.27)	1.05 (1.02–1.08)	13 (5–25)
	Glucose (mmol/l)		1.64 (1.19–2.24)	1.03 (1.01–1.06)	9 (4–22)
	Blood pressure, cholesterol, and glucose		1.47 (1.07–2.06)	1.14 (1.09–1.21)	31 (18–69)

The results in the relationship between obesity and CVDs show that the estimated total effects were less in men than women. The results indicate that the presence of cardiometabolic risk factors in men has been associated with less harmful effects on the incidence of CVDs than women. In the male population none of the direct natural effects in the model do not exhibit meaningful statistical relations, also when an individual has all three cardiometabolic risk factors, approximately all of the harmful effects of obesity is conducted to the outcome from this causal route (intermediate share 98%)

The results for men with abdominal obesity shows that the most crucial intermediate variable was the same as the last two exposures, all the intermediated effects on the outcome from the intermediate variables were around 71%. The clinical result of this model's result shows that controlling intermediate risk factors in men with general obesity comes with better results in controlling and preventing CVDs rather than men with abdominal obesity.

The results of the parametric model in women show that overweight, general and abdominal obesity are associated with higher risks of the incidence of CVDs compared to men and they have their impact independently from cardiometabolic risk factors. The increased risk was 40 percent higher for overweight, 60 percent higher for general obesity and 30 percent higher than abdominal obesity compared to the male population. In the female population, the direct natural effects had a more significant proportion of the whole effects and the intermediate variables played a weaker role in conducting the harmful effects on the outcome. For example, the intermediate share of each of the three intermediate variables, if co-occurred, is 98 percent whereas the effect found in the female population was 36 percent.

Table 5 shows the parametric model results this considers the interaction of the desired exposure, and the intermediate variables are not meaningful. The reason behind the little changes of the whole effects in this table compared to the results previously achieved (Table 2) was the existence of interactions in models. There were no interactions between any mediator and exposure in the models. The sensitivity analysis for unmeasured mediator-outcome confounding showed that in two scenarios showed the variations were less than 5 percent (eTable 2).

Table 5. Total, direct, and indirect effects of overweight and adiposity on cardiovascular diseases (CVDs) using a parametric method considering exposure-mediator interaction.

exposures	Mediators	Total effect	Natural direct effect	Natural indirect effect	Multiplicative interaction (95% CI)
		HR (95% CI)	HR (95% CI)	HR (95% CI)	
overweight	Blood pressure (mmHg)	1.50 (1.29-1.90)	1.46 (1.17-1.74)	1.08 (1.05-1.12)	1 (0.99-1.07)
	Cholesterol (mmol/l)	1.64 (1.35-1.94)	1.51 (1.24-1.82)	1.08 (1.04-1.12)	0.93 (0.83-1.04)
	Glucose (mmol/l)	1.57 (1.30-1.87)	1.53 (1.27-1.82)	1.03 (1.01-1.04)	0.95 (0.87-1.02)
	Blood pressure, cholesterol, and glucose	1.61 (1.30-1.94)	1.38 (1.10-1.67)	1.17 (1.12-1.22)	1 (0.99-1.007) 0.90 (0.80-1.10) 0.92 (0.85-1.01)
General obesity	Blood pressure (mmHg)	1.69 (1.36-2.07)	1.50 (1.20-1.91)	1.12 (1.05-1.19)	1 (0.99-1.00)
	Cholesterol (mmol/l)	1.67 (1.36-2.05)	1.42 (1.15-1.78)	1.17 (1.11-1.24)	0.93 (0.83-1.04)
	Glucose (mmol/l)	1.60 (1.31-1.94)	1.48 (1.21-1.79)	1.07 (1.04-1.11)	0.95 (0.87-1.02)
	Blood pressure, cholesterol, and glucose	1.66 (1.33-2.07)	1.20 (0.94-1.54)	1.37 (1.26-1.50)	1.08 (0.99-1.07) 0.90 (0.80-1.01) 1.02 (0.85-1.04)
Visceral adiposity	Blood pressure (mmHg)	1.59 (1.34-1.79)	1.41 (1.18-1.65)	1.07 (1.07-1.13)	1.01 (0.98-1.04)
	Cholesterol (mmol/l)	1.57 (1.31-1.82)	1.42 (1.17-1.67)	1.09 (1.06-1.15)	1.02 (0.97-1.08)
	Glucose (mmol/l)	1.60 (1.29-1.84)	1.51 (1.26-1.76)	1.05 (1.04-1.07)	1.00 (0.99-1.01)
	Blood pressure, cholesterol, and glucose	1.63 (1.35-1.83)	1.22 (1.03-1.42)	1.23 (1.16-1.23)	0.98 (0.99-1.002) 0.99 (0.96-1.03) 1.00 (0.99-1.01)

4. Discussion

This study shows that overweight and obesity both generally or viscerally increases the risk of cardiovascular diseases independent from the intermediate metabolic risk factors. The increased risk is more in women than in men. Cardiometabolic risk factors, including hypertension, blood sugar, and cholesterol, are respectively responsible for 46 percent, 66 percent, and 52 percent of the impact of being overweight or obese has on cardiovascular diseases. The most important variable that intermediated being overweight and CVD is cholesterol (22 percent), the most vital variable that mediate the effects of general obesity on CVD is Hypertension (38 percent). Hypertension is also the most important mediator variable between visceral obesity and CVD. The critical finding of this study is the differentiation of the direct and indirect natural effects of exposure on the outcome between men and women. In men a total of 60 percent of the impact due to overweight, 98 percent of the results due to general obesity, and 71 percent of the effect due to visceral obesity is conducted via cholesterol, blood sugar, and blood pressure mediators; in contrast to women, which the effects of obesity is mostly done directly through CVDs.

Waist circumference is a better index to show visceral fat deposition and consequently worsening one's metabolic profile than solely BMI. While BMI is an excellent index to show general obesity (22). Several studies have been conducted on the effects of central obesity on cardiovascular events (23, 24). It was seen in the Bogers et al. study that overweight can increase the effects of cholesterol and hypertension on cardiovascular diseases up to 45 percent(25). It was discovered in the Batty et al. study that overweight and obesity increase the mortality risk caused by CHDs in both patient groups that have previously diagnosed with CHD and patients who did not have a prior CHD history, although this effect is faster in the latter group (26). It was shown in the study conducted by Pekka Jousilahti et al. that a 1Kg increase in one's weight increases the mortality risk caused by CHD between 1 to 1.5 percent(27). In a study performed in 2011, it was shown that BMI, waist circumference and waist to gluteal ratio, either alone or in combination, will not increase the probability of cardiovascular diseases independent from hypertension, also will neither increase the risk of getting diabetic nor having elevated cholesterol levels (28).

In the study done by Kazem Poorardabili in 2018 on the + 65-year-old population of Tehran, the effects of general and visceral obesity and overweight on the incidence of cardiovascular diseases, considering cardiometabolic risk factors. The results showed that visceral obesity increases the risk of CVD incidence by 16 to 21 percent. No association between BMI and the increased risk of CVDs was seen in this study (29).

It seems like the small sample size and not using the standardized models of causal mediation analysis, which are currently receiving much attention from scientists, is the reason behind the different results between our study and the mentioned study. Both studies were held on the same population.

Unfortunately there has been an increase in the general and core obesity rate in Iranian adults in the recent years (30) and the unsuccessful interventions for controlling this health problem, has led the scientists to find other causal patterns to prevent this problem, including considering intermediate metabolic variables that already have some successful clinical trials performed on them (31). Understanding the causal patterns in which how and from what route does a cause delivers its protective or harmful effects to the outcome is called Mediation analysis (32). The primary purpose of these methods is purifying the interventions' effects with deleting components that do not have any impact on the outcome (33).

Lu et al. study performed in 2015 show that hypertension with a proportion mediated of 22 percent is the essential intermediate variable in CVD and overweight. As for obesity, hypertension did not show any indirect effects on the outcome, and elevated blood sugar levels accounting for 65% of all effects, is the most crucial intermediate variable. As for abdominal obesity, results showed that hypertension, with 36 percent of all effects, is considered the most critical risk factor. Also, the sum of all impact that overweight, obesity, and a waist circumference higher than 90 cm has on CVD through the three cardiometabolic risk factors of hypertension, blood sugar, and elevated cholesterol are 54, 81 and 62 percent respectively that are all greater in comparison to this study (13).

Lu et al. study in 2014, which was conducted using conventional methods on the data of 97 cohorts, showed that obesity and overweight increase the risk of CHDs independently from the metabolic risk factors of hypertension, blood sugar, and elevated cholesterol levels. Also, the results of this study show that respectively 50 and 44 percent of the effects of overweight and obesity are conducted to the outcome via the intermediate variables of hypertension, blood sugar and cholesterol (14).

Several studies have been done on the impact of visceral obesity on CVD. [2, 3] Bakhtiari et al. study have evaluated the relationship between obesity and CVD using nonparametric methods. In this study, the essential mediators concerning the relationship between overweight, general, and visceral obesity with CVD are hypertension (PM = 22), cholesterol (PM = 65), blood glucose (PM = 36), respectively. Also, this study showed that 81 percent of the effects caused by obesity are conducted to CVD via three mediators of hypertension, cholesterol, and blood glucose. It seems that the reason behind the different results of the Bakhtiari study and the current one is the fact that nonparametric methods were used in that study (15).

As mentioned before, the results of our study also show that general and central obesity indices accompany increased risk of CVD, independently from the previously mentioned cardiometabolic risk factors. This result contradicts the results achieved in Kazempour-Ardebili and Flegal and colleagues' studies (29, 34). Another point worth mentioning is that the insufficient control of the confounding variables in this study may be the reason behind differences between results (35). Another factor that may have influenced the results of this study is the population's age. With aging, BMI will not be a good index to show adiposity in the elderly, and this is due to the reduction in skeletal muscle mass and the increase of abdominal obesity as a matter of time (36).

Different mechanisms relate general and abdominal obesity to CVD via cardiometabolic risk factors. When excessive fat accumulates, even in the absence of systematic hypertension and underlying cardiac disease, remarkable changes in the structure and function of the heart occurs. To overcome the metabolic needs, circulating blood volume, plasma volume, and cardiac output increase. The increase in blood volume leads to an increase in the venous return to the left ventricle, which will lead to cardiac chambers diastolic compliance reduction and an increase in the left ventricle filling time and left ventricle enlargement. As long as left ventricular hypertrophy is synced with the left ventricle enlargement, the systolic activity of the heart is preserved. When LVH cannot keep up with the progressive increase in heart size, the pressure on the cardiac wall will have a more considerable increase and thus may lead to systolic dysfunction. An increase in systematic and pulmonary blood pressure (left ventricle failure and chronic hypoxia) and CHD can all occur due to the impact of obesity on the structure and function of the heart. Also, the risk of sudden cardiac death increases with obesity increase (37). Another mechanism is the release of bioactive mediators from the adipose tissue that, by acting on blood lipids, blood pressure, inflammation, and coagulation, will eventually lead to blood vessel dysfunction and atherosclerosis (38).

After analyzing sensitivity and considering (U) energy-adjusted glycemic load as an unmeasured confounder variable in this study, achieved results did not show a tangible change, and this is a support to the validity of the results achieved in this study. No difference was seen in the sensitivity analysis results obtained in Lu et al. study (14).

The advantage of the method of this study is that there is no restriction in exposure type, intermediate variable count, and outcome type, applicability in most basic regression equations, including survival models and existence assessment of any interaction between exposure and the mediator in these models.

A matter that must be noted in this study is the widening of confidence intervals for the proportion mediated estimated indices. One of the main reasons for the Confidence intervals' widening is the high variation and instability of these indices (39). The small sample size of this study compared to other held studies (13). Another encountered restriction in this study is the change in the levels of the basic measured risk factors, during follow up. Informational bias due to incomplete data recording was considered in this study. The assumption of "no correlation" between the risk factors of CVD was also considered. For example, an increase in patients' blood glucose levels led to an increase in their blood pressure, delivering an impact on the kidneys and changing serum cholesterol levels (40).

In order to achieve a valid estimation of the direct and indirect natural effects in this study, it was assumed that there is no confounding variable between the following relations; A: BMI (or waist circumference) and CVD, B: Mediator and CVD, C: BMI (or waist circumference) and Mediator, and D: No confounder is present in the relation between the mediator and CVD that is being affected by exposures. To avoid any confounding effects between BMI (or waist circumference) and CVD, persons with a BMI lower than 18.5 and patients with a history of hospital admission were excluded. No significant change in estimations was seen in the measurement of confounding effects in the relationship between the

mediators and CVD despite calculating a bias factor. Also, to assess the assumption “*C*,” the main reasons that relate to BMI and Mediators such as physical activity, smoking, education, and history of cardiovascular diseases were included in the analysis. Finally, to assess the assumption “*D*” was not upheld if, for example, physical activity was affected by obesity and itself affected both hypertension (diabetes) and CVD. In this setting, physical activity was once assumed as a new variable, and once estimated its direct effects using marginal structural and structural nested models which do not divide the effects into direct and indirect ones.

Obesity is considered a crucial risk factor for cardiovascular diseases. Behavioral interventions can lower one’s weight only for a short period, even if they cause a significant change (41). Also, drug interventions do not have sufficient efficacy and effectiveness. Surgical interventions such as sleeve surgery can be used for weight reduction, but this method is also short-term. Not to mention that these surgeries conduct significant morbidities to patients (42–44).

Conclusions

It can be concluded from this study that obesity mostly delivers its impacts via blood pressure, blood glucose, and cholesterol in men. Thus it can be assumed that managing these three factors can be treated with much more efficient and much less costly drug treatment methods which can significantly reduce CVD risks without reducing weight (45–47). In contrast to men, obesity delivers its impacts more directly to women.

Abbreviations

T2DM: Type 2 diabetes mellitus; HR: Hazard ratio; NIE: Natural indirect effect; HTN: Hypertension; FBS: Fasting blood sugar; CVD: Cardiovascular disease

Declarations

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None.

Authors’ contributions

MB, FH and MAM interpreted the data and drafted the manuscript. FA, SKA, FH, PM and NTG designed the study, interpreted the data, reviewed the article critically, and revised it for important intellectual content. AG, FA, MAM and MB analyzed and interpreted the data, reviewed the article critically, and revised it for important intellectual content.

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Availability of data and materials

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The research ethics committee of Shahid Beheshti University of Medical Sciences reviewed and approved the study protocol before the enrollment of patients. All procedures performed in studies involving human participants were in accordance with the ethics standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethics standards. All participants were informed of the details of the study and signed the corresponding consent forms.

Consent for publication

All data published here are under the consent for publication.

Competing interests

The authors declare that they have no competing interests.

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