Global Epidemiology 9 (2025) 100193

Contents lists available at ScienceDirect

Global Epidemiology

journal homepage: www.sciencedirect.com/journal/global-epidemiology

Time-varying confounders in association between general and central obesity and coronary heart disease: Longitudinal targeted maximum likelihood estimation on atherosclerosis risk in communities study

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ARTICLE INFO

Keywords:
Time-varying confounders
Obesity
Coronary heart disease
Longitudinal targeted maximum likelihood estimation

ABSTRACT

Aim: This study examines the association between general and central obesity and the risk of cardiovascular diseases, utilizing the Targeted Maximum Likelihood Estimator (TMLE) method to account for time-varying covariates and also we compares the findings with those derived from conventional regression methods in the Atherosclerosis Risk in Communities (ARIC) cohort study.

Methods: We considered 15,792 participants 45–75 years of age registered in the Atherosclerosis Risk in Communities study, visit 1 and followed to visit 4. General obesity defined as body mass index and central obesity defined as Waist Circumference (WC), Waist-Hip-Ratio (WHR), Waist-Height-Ratio (WHtR), Body Shape Index (BSI) and Body Roundness Index (BRI). The effect of obesity on Coronary Heart Disease (CHD) was estimated and compared by Longitudinal Targeted Maximum Likelihood Estimation (LTMLE) and generalized linear model.

Results: The effects of BMI, adjusted for baseline and time-varying confounders, was 1.15 (95 %CI =1.00, 1.34). About the gender groups, the effect of BMI for males and females was 1.17 (95 %CI =0.97,1.40) and 1.19 (95 % CI =0.94,1.52), respectively. Considering age groups, the effect of BMI was 1.21 (95 %CI =0.95, 1.53) and 1.13 (95 %CI = 0.93, 1.36) for age $\leq$ 54 years and age $>$ 54 years, respectively. With regards to central obesity, the BSI and WC were shown the strongest effects, respectively. Among females and age group$\leq$54 years, WHtR was associated with a higher incidence of CHD.

Conclusions: According to the results, the appropriate index for obesity varies based on gender and age. Knowledge about this difference will help to experts to implement appropriate interventions.

Introduction

Obesity, a potentially modifiable risk factor, increases the risk of several chronic and debilitating diseases [1,2]. However, regarding to the definition of obesity and the type of anthropometric index, the direct and magnitude of obesity effects remain controversial. Body Mass Index (BMI), as a general obesity index, is the most habitual index for obesity [3]. Although, BMI often has a limited capacity to discriminate between fat mass and other body masses which results in misclassification [4]. Central obesity index as a predictor of cardiovascular diseases (CVDs) could be used to decrease some limitations of BMI [5]. Furthermore, due to time-varying characteristics of obesity and other covariates in the association between obesity and CVDs, the conventional methods have limited capacity to correctly adjust for them, and using the conventional regression methods will result in bias in estimation [6,7]. In longitudinal studies that measure time-varying covariates at several points in time, we need advanced analysis methods to consider these changes. Targeted Maximum Likelihood Estimator (TMLE) as a two-stage estimator was introduced to reduce the bias for the target parameter when one of the exposure or outcome models has been estimated consistently [8]. In the

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https://doi.org/10.1016/j.gloepi.2025.100193
Received 25 July 2024; Received in revised form 23 February 2025; Accepted 4 March 2025
Available online 6 March 2025

present study, we aimed to examine the association between general and central obesity and the risk of CVDs using the TMLE method to consider time-varying covariates and to compare the results with those of conventional regression methods, to demonstrate the limitations of conventional methods, in Atherosclerosis Risk in Communities (ARIC) cohort study.

Methods

Participants and outcome

The ARIC study, a population-based prospective cohort study, which registered 15,792 participants, males and females 45–64 years of age at baseline, recruited from 4 United States communities (Washington County, Maryland; Jackson, Mississippi; Forsyth County, North Carolina; and the suburbs of Minneapolis, Minnesota) More details are available at ARIC website: https://www2.cscc.unc.edu/aric/. The aims of this study are identifying the risk factors for CVDs. Besides the baseline examination (1987–1989), this Study has conducted 3 follow-up examinations at 3-year intervals (1990–1992, 1993–1995, and 1996–1998). In addition, annual telephone calls were conducted to determine participant's status and get information on hospitalizations and interested outcomes. The outcome of interest was registered to the end of 2014. The outcome of interest in present study was coronary heart disease (CHD) events (ICD-9: 410–414) that ascertained through 31 December 2014. The incidence of CHD considered as definite or probable myocardial infarction or fatal CHD based on the ARIC study protocol. This study was a secondary data analysis on the ARIC study that was performed in accordance with the declaration of Helsinki; this included permission to use anonymized quotations in publications according to the ethics committee. This study was a secondary analysis on the ARIC study data that was performed in accordance with the declaration of Helsinki; this included permission to use anonymized quotations in publications according to the ethics committee (IR.SBMU.RETECH.REC.1401.022).

Exposures

The main exposures of interest are general and central obesity. General obesity defined as BMI and central obesity defined as waist circumference (WC), waist-hip-ratio (WHR), waist-height-ratio (WHtR), body shape index (BSI) and body roundness index (BRI). In ARIC the trained and certified technicians measured anthropometric measures on fasting participants wearing hospital standard scrub suit. The BMI index considered as general obesity, and participants were defined as obese with BMI $\geq$30 kg/m2. For central obesity, we considered three anthropometric measures that all participants were defined as obese with WC $\geq$102 cm in men and $\geq$ 88 cm in women, WHR $\geq$ 0.9 in men and $\geq$ 0.85 in women, and WHtR$\geq$0.5. In addition, BSI as BSI=WC/(BMI2/3 $\times$ height1/2) and BRI as BRI = 364.2-(365.5*square root(1-((WC/2π)^2)/(0.5*Height)^2))) equation. All participants were defined as obese with BSI and BRI $\geq$ 0.08 and $\geq$ 4, respectively. In this study, in order to highlighting the limitations of BMI, in addition to the main models, we aimed to display the association of BMI and CHD adjusted for other obesity indices. These models were only run to determine changes in the effect size of BMI.

Potential time-fixed and time-varying confounders

We identified outcome and exposure models with a list of time-fixed and time-varying confounders. The potential confounders were included in three demographic, behavioral and biologic categories that were presented in Table 1. Age (added in models as continues variable), gender, race, education level, occupation, marital status, family history of CVDs, and total calorie intake were included as fixed and others as time-varying. Age is considered as a time-fixed variable because its value can be predicted deterministically and for all visits is known at baseline [9]. The confounding effect of variables was measured based on the following conditions. 1. The variable must be statistically associated (causal or non-causal) with the exposure. 2. The variable must cause the outcome. 3. The variable must not be on a causal pathway.

Table 1
Baseline characteristics, by outcome occurrence (CHD), of participant in the ARIC Study, 1987–2014.

Characteristic		CHD occurrence	
		Yes	No
Categorical variables		No. %	No. %
Gender	female	663 (41.03)	5989 (57.21)
	male	953 (58.97)	4480 (42.79)
Race	white	1208 (74.75)	8167 (78.01)
	black	408 (25.25)	2302 (21.99)
Education	Basic	479 (29.64)	2093 (19.99)
	Intermediate	650 (40.22)	4393 (41.96)
	Advanced	487 (30.14)	3983 (38.05)
Family Income (per year)	Less than $16,000	444 (27.48)	2037 (19.46)
	$16,000 –$50,000	845 (52.29)	5545 (52.97)
	More than $50,000	327 (20.24)	2887 (27.58)
Drinker Status	Current drinker	835 (51.67)	6200 (59.22)
	Former drinker	374 (23.14)	1781 (17.01)
	Never drinker	407 (25.19)	2488 (23.77)
Cigarette smoking status	Current smoker	558 (34.53)	2557 (24.42)
	Former smoker	523 (32.36)	3346 (31.96)
	Never smoker	535 (33.11)	4566 (43.61)
Health insurance	No	182 (11.26)	878 (8.39)
	Yes	1434 (88.74)	9591 (91.61)
Family history of CVD	No	642 (39.73)	4556 (43.52)
	Yes	974 (60.27)	5913 (56.48)
Hypertension	No	988 (61.14)	7997 (76.39)
	Yes	628 (38.86)	2472 (23.61)
Antihypertensive medicine	No	1015 (62.81)	7997 (76.39)
	Yes	601 (37.19)	2472 (23.61)
Diabetes mellitus	No	1301 (80.51)	9758 (93.21)
	Yes	315 (19.49)	711 (6.79)
BMI	Non-obese	1116 (69.06)	7925 (75.70)
	Obese	500 (30.94)	2544 (24.30)
WC	Non-obese	734 (45.42)	5095 (48.67)
	Obese	882 (54.58)	5374 (51.33)
WHR	Non-obese	189 (11.70)	2531 (24.18)
	Obese	1427 (88.30)	7938 (75.82)
WHtR	Non-obese	155 (9.59)	1844 (17.61)
	Obese	1461 (90.41)	8625 (82.39)
BSI	Non-obese	479 (29.64)	4146 (39.60)
	Obese	1137 (70.36)	6323 (60.40)
BRI	Non-obese	383 (23.70)	3566 (34.06)
	Obese	1233 (76.30)	6903 (65.94)
Continues variables		Mean (SD)	Mean (SD)
Age, years		55.69 ± 5.52	53.78 ± 5.72
Physical activity (work)		2.20 ± 0.99	2.20 ± 0.99
Physical activity (sport)		2.37 ± 0.78	2.46 ± 0.80
Physical activity (leisure time)		2.28 ± 0.56	2.39 ± 0.56
Total energy intake (Kcal)		1666.2 ± 623.6	1611.1 ± 599.6
Saturated fatty acid (%Kcal)		12.38 ± 3.02	12.04 ± 2.97
Total cholesterol mg/dl		5.83 ± 1.13	5.50 ± 1.05
Triglyceride mg/dl		1.76 ± 1.18	1.42 ± 0.94
HDL cholesterol mg/dl		1.18 ± 0.38	1.36 ± 0.44

* ARIC, atherosclerosis risk in communities study; SD, Standard deviation; NO. %, number and percentage of participants in each group; HDL, High-density lipoprotein cholesterol; LDL, Low density lipoprotein cholesterol, CVD, cardiovascular disease; BMI, body mass index; WC, waist circumference; WHR, waist to hip ratio; WHtR, waist to height ratio; BSI, body shape index; BRI, body roundness index; Kcal, kilocalorie; %Kcal, percentage of kilocalorie; mg/dl, milligrams per deciliter.

Causal diagram and notations

A directed acyclic graph (DAG) in Fig. 1 representing the causal structure between the obesity and CHD, with consideration to

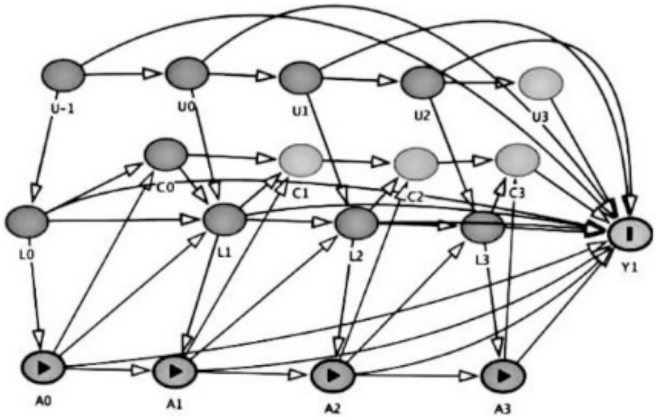

Fig. 1. A directed acyclic graph (DAG) representing the causal structure between the obesity and coronary heart diseases.

missingness mechanism and potential time-fixed and time-varying confounders. In this graph, there are 4 visits, K = 0,1,2, and 3 that A_k, L_k, C_k and U_k denote exposure (obesity), time-varying covariates, missingness mechanism and unmeasured confounders, respectively. A_0 and L_0 are the obesity status and baseline values of time-varying variables and covariates only measured at baseline visit, respectively. In longitudinal design, the overbars are used to denote the history of a variable. The outcome is denoted by Y_1 to Y_4 that in TMLE method the Y nodes are the components of L nodes other than the time-varying covariates.

Statistical analysis

Longitudinal targeted maximum likelihood estimation (LTMLE) model was used to analyze the association between obesity and CHD. LTMLE, as a double-robust estimator, use both outcome and exposure models. The missing mechanism, for each phase, considered both of the competing event (total mortality of all other causes, stroke, and heart failure (HF)) or lost to follow [10]. Obesity as exposure was considered dichotomously; "obese" for the values above the defined cut-off point and the other ones as "non-obese".

The TMLE method was implemented in three steps. Then, for LTMLE method, we repeated these steps up to phase one. In each step after step one, the updated estimate regressed on history of exposure and confounder until that time [11–13]. In this study, the intervention nodes (treatment regimens) defined by a sequence of treatments that all participant were obese in four phases against when all participant were non obese. This intervention regimen was defined as static regimen.

We fit the super learner algorithms (Bayesian GLM, SL.xgboost, Generalized linear model) for each of the exposure and outcome models. In these models, we considered all covariates that measured at baseline as predictors and also the obesity as binary exposure. We used absolute error (mean absolute error) and mean root square error for assessing the performance of models.

Finally, the risk ratios (RR) with influence-curve based confidence intervals, totally and for age (categorized based on the mean value as age $\leq$ 54 years and age $>$ 54 years) and gender subgroups, were calculated. Cross-validation in super learner model was used as internal validation. LTMLE analysis was performed using the ltmle package in R version 3.6.2.

In addition, the results from LTMLE were compared with four statistical models TMLE, g-computation, inverse probability of treatment-weighting (IPTW) and generalized linear model (GLM)).

Results

Participant characteristics

Out of 14,983 participants at baseline, 12,085 participants with no history of any heart disorder and complete data (with no missing data at baseline) were included in phase one. During a median 27 years of follow-up, in the following phases (2–4, and) 1028, 1199 and 1189 of participants experienced loss to follow up and 327, 367, 341 experienced competing risk, respectively. In addition, to end of this study, in each phase, 269, 272, 281 and 1535 of participants experienced CHD, respectively. Baseline characteristics are presented in Table 1. Obese participants, based on BMI definition, were more likely to be female, black, have lower education and annual family income, and less likely to have health insurance compared to non-obese individuals. Obese participants, based on WHR and BSI definition, were more likely to be male, white, have lower education and annual family income, and less likely to have health insurance compared to non-obese individuals.

Coronary heart disease

Table 2 shows the effect of both general and central obesity with 95 % confidence intervals, stratified by gender and age, on CHD. The effects of BMI on CHD, considering confounding effect of baseline and time-varying factors, was 1.15 (95 %CI =1.00, 1.34). About the gender groups, the effect of BMI for males and females was 1.17 (95 %CI =0.97,1.40) and 1.19 (95 %CI =0.94,1.52), respectively. About the age groups, the effect of BMI was 1.21 (95 %CI =0.95, 1.53) and 1.13 (95 % CI = 0.93, 1.36) for age $\leq$ 54 years and age $>$ 54 years, respectively. Totally, considering gender and age groups, BMI had a positive role in higher incidence of CHD.

Considering the age and gender groups, the WHtR has risk factor effect in females (RR =1.78, 95 %CI = 1.09, 2.92) and in age group equal or less than 54 years (RR = 1.77,95 %CI = 1.01, 3.12) on CHD. Also, the BSI for males (RR =1.23, 95 %CI = 0.95, 1.60) and age group over 54 years (RR = 1.15, 95 %CI = 0.88, 1.51) had a positive role in higher incidence of CHD.

Table 3, shows the adjusted effect of general obesity with 95 % confidence intervals on CHD adjusted for baseline and time-varying confounders. Results showed that the direction and magnitude of estimated effects of BMI, adjusted for measures of central obesity (WC or hip circumference) was different. For males, the effect of BMI, adjusted for all confounders and both waist and hip circumference, was 1.20 (95 % CI = 0.79, 1.84). This effect was close to the value obtained in model 3 (only adjusted for the confounders). On the other hand, this effect was wakened to 1.08 (95 %CI = 0.69, 1.69) after adjusting for all confounding factors and WC. For females, the effect of BMI, adjusted for both waist and hip circumference was attenuated (Table 3).

In addition, Fig. 2 compared the direction and magnitude of estimated effects for five statistical methods. Regarding the BMI, the greatest increase in risk ratios was observed in g-computation model 1.20 (95 %CI:1.02,1.38). This effect was observed for all age and gender groups. For central obesity, the greatest increase in risk ratios was observed in IPTW model for BSI index 1.36 (95 %CI:1.02,1.81). Regarding the age and gender groups, the greatest increase in risk ratios for BMI was observed in TMLE (for females) 1.29 (95 %CI:1.14,1.45), G-computation 1.20 (95 %CI:1.01,1.42) and LTMLE 1.17 (95 % CI:0.97,1.40) for males). For central obesity, the greatest increase in risk ratios was observed in IPTW 4.74 (95 %CI:2.80,8.03) (WHtR for females), G-computation 1.25 (95 %CI:0.98,1.58) (BSI for males) and LTMLE 1.78 (95 %CI:1.09,2.92) and 1.77 (95 %CI:1.01,3.12) (WHtR for females and age group equal or less than 54 years, respectively).

Discussion

In this large study, the association of six obesity indices with the risk

Table 2
Estimates of causal effects (RR (95 %CI)) of general and central obesity on coronary heart disease using LTMLE in the atherosclerosis risk in communities (ARIC) study (1987–2014).

Groups	BMI	WC	WHR	WHtR	BSI	BRI
Total	1.15 (1.00,1.34)	1.12 (0.97,1.31)	0.93 (0.74,1.16)	0.92 (0.73,1.17)	1.19 (0.97,1.45)	1.00 (0.84,1.20)
Males	1.17 (0.97,1.40)	1.16 (0.99,1.36)	0.83 (0.59,1.19)	0.74 (0.56,0.98)	1.23 (0.95,1.60)	1.05 (0.85,1.30)
Females	1.19 (0.94,1.52)	1.01 (0.73,1.73)	1.00 (0.73,1.38)	1.78 (1.09,2.92)	1.13 (0.83,1.55)	1.06 (0.75,1.48)
$\leq$ 54 years	1.21 (0.95,1.53)	1.28 (0.93,1.77)	1.43 (0.91,2.25)	1.77 (1.01,3.12)	1.28 (0.96,1.70)	1.35 (0.94,1.93)
$>$ 54 years	1.13 (0.93,1.36)	1.02 (0.85,1.24)	0.76 (0.58,0.99)	0.65 (0.50,0.84)	1.15 (0.88,1.51)	0.84 (0.69,1.02)

BMI, body mass index; WC, waist circumference; WHR, waist to hip ratio; WHtR, waist to height ratio; BSI, body shape index; BRI, body roundness index. $\leq$ 54, age group equal or less than 54 years at started of study; $>$ 54, age group over 54 years at started of study.

Table 3
Estimates of causal effects (RR (95 %CI)) of general obesity controlled for central obesity on coronary heart disease using LTMLE in the atherosclerosis risk in communities (ARIC) study (1987–2014).

Groups	Total	Males	Females	$\leq$ 54 years	$>$ 54 years
Model 1	1.08 (0.77,1.52)	1.20 (0.79,1.84)	0.89 (0.48,1.67)	0.89 (0.44,1.79)	1.24 (0.84,1.81)
Model 2	–	1.08 (0.69,1.69)	0.89 (0.50,1.59)	–	–
Model 3	1.15 (1.00,1.34)	1.17 (0.97,1.40)	1.19 (0.94,1.52)	1.21 (0.95,1.53)	1.13 (0.93,1.36)

Model 1: Adjusted for all time-fixed and time-varying confounders and central obesity (waist circumference and hip circumference).
Model 2: Adjusted for all time-fixed and time-varying confounders and central obesity (waist circumference for males and hip circumference for females).
Model 3: Adjusted for all time-fixed and time-varying confounders.

of CHD were evaluated using the LTMLE method. In addition, these relationships were evaluated using four statistical methods including TMLE, G-computation, IPTW and GLM. Considering the limitations of observational studies, which are more prone to confounding factors leading to biased estimations of causal effects, researchers are actively seeking methods to enhance the accuracy of estimating causal effects. In general, the results of our study demonstrate that the appropriate index for definition of obesity varies based on gender and age. Moreover, compared to conventional GLM models, which are unable to consider the time-varying covariates, results of LTMLE approach present different effect measures for some obesity definition in some subcategories. Another major finding was the limitation of BMI to classify the participants as obese and non-obese. In this instance, the association between BMI and CHD demonstrates varying degrees of attenuation within each subgroup, after adjusting for central obesity. According to the limitation of BMI in distinguishing the body masses, the results of adjusted models for central obesity and biologic variables showed the limited capacity of this index to classify obese and non-obese in both gender and age subgroups (Table 3).

According to previous literature, obesity has paradoxical relationship with CVD outcomes separately for males and females [14,15]. These different effects can be associated to the difference in fat distribution and accumulation between males and females. In this case, previous studies defined the apple and pear obesity for males and females, respectively [16,17]. Apple shape obesity was more related to central obesity and pear shape obesity was related to both central obesity and other fat accumulation [17]. In this case, our results indicated that the effects of obesity indices, which display different fatty mass, are different. Furthermore, based on subgroup analysis, for gender and age groups, these effects appear more inconsistent. Moreover, low capacity of BMI to distinguish between body masses (fat mass and fat-free mass) could be resulted in more paradoxical effects [18]. In a cohort study, was shown that WHR significantly associated with the risk of beginning the atrial fibrillation in males. For females, the risk of atrial fibrillation was more corelated with BMI when WHR was added to the multivariable model for BMI [19]. In addition, difference between the fat distribution and fat accumulation was verified in a study that explored the relationship of central fat distribution and epicardial fat accumulation with several non-communicable diseases [20]. Hence, considering the results highlighted in Table 3, which underscore the divergence in the effects of obesity indices between males and females, it is imperative for researchers and clinicians to define and investigate the varying impacts of fat distribution and accumulation in gender subgroups. Furthermore, elucidating the mechanisms linking obesity to CVDs is crucial. Previous studies on ARIC data showed that appropriate obesity index could be different for gender and age subgroups [21].

Moreover, the effect of confounding covariates could explain a part of this complication [22,23]. Time-varying confounders could add this complexity as the results of this study were showed. The time-varying confounders affected by previous exposure, could have a double role as both mediator and confounder. In addition, in this framework the time-varying confounder may share a common cause with the outcome and considered as collider. In these cases, the conventional methods of estimation could result in two important biases, over-adjustment and collider stratification biases [6,24,25]. Previous studies demonstrate that the major effect of obesity may mediated through insulin-resistance, dyslipidemia, and hypertension [26,27]. Therefore, these risk factors could be considered as both confounder and mediator. In addition, these risk factors, insulin-resistance, dyslipidemia, and hypertension, may share a common cause with the outcome, that adjusted method in conventional models may result in collider stratification bias.

Causal inference from observational studies needs to meet three assumptions include consistency, exchangeability and positivity. In this case, usually, the exchangeability and positivity assumption are given more attention than consistency. According to the importance of this assumption, Hernan and Taubman debate on the violations of consistency and its effect on exchangeability and positivity [28]. In the present study, despite the limitations of consistency assumption for association between the obesity and CHD, we were looking more to show the limitations of the conventional methods. Regarding to the ARIC studies, most of previous studies used the conventional estimation methods that may result in biased estimations [29–31].

Strengths and limitations

A major advantage of present study is that it is a longitudinal cohort study with a long follow-up. In addition, in this study a double robust method was used that consistently estimate the parameters in a semi-parametric model when at least one of exposure or outcome models are correctly specified, regardless of which. Additionally, we considered the time varying confounders and missing mechanism for better estimation of true effects. As limitation, this study is limited by the fact that this statistical method could only consider binary exposures, which need to extend for multinomial and continues exposures. In addition, the cardiorespiratory fitness data was not available and only the crude data of physical activity was available.

Conclusion

In this large study, we used LTMLE with super learner models to

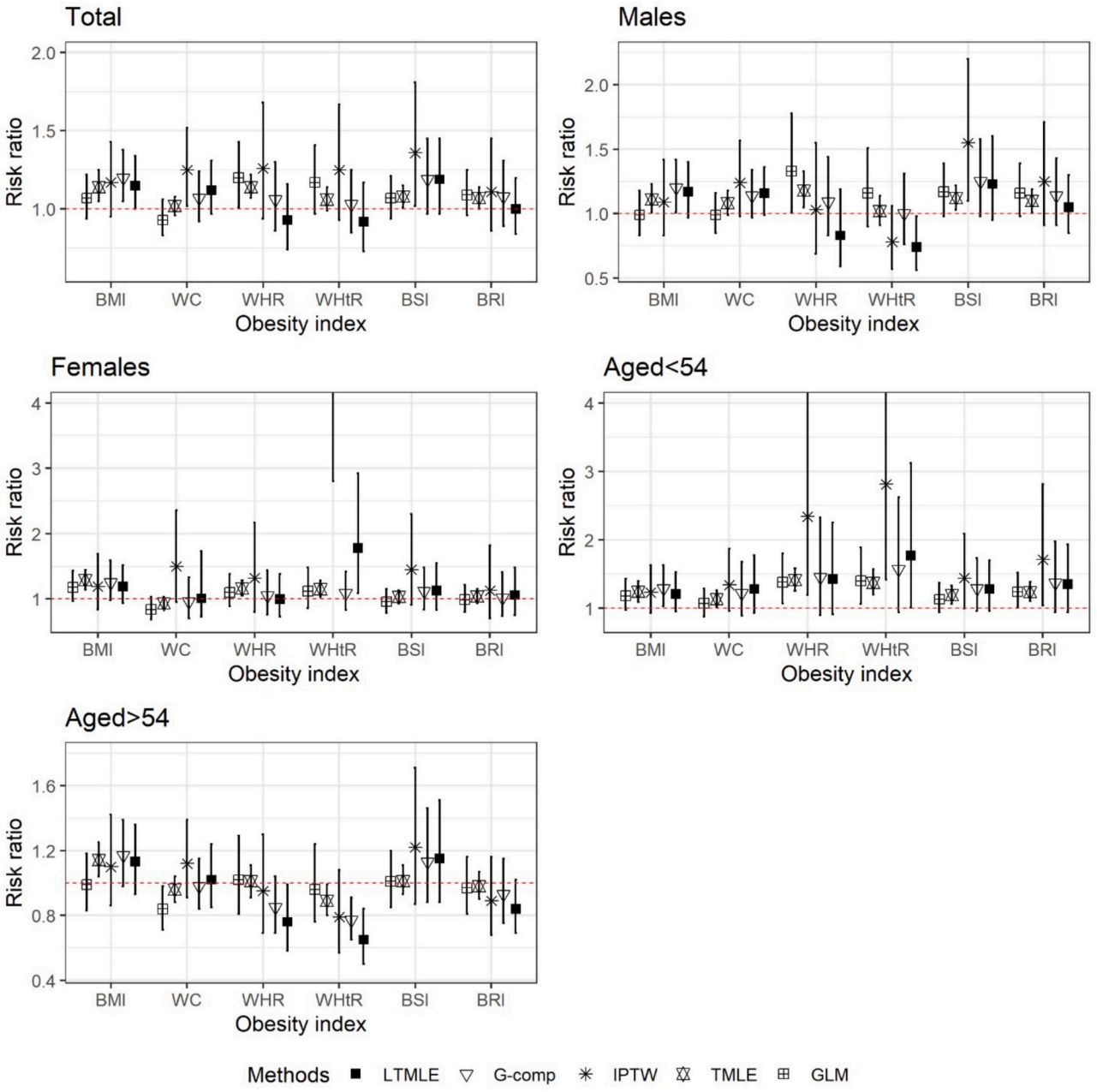

Fig. 2. comparison and direction of estimated effects for five statistical methods by gender and age groups.

calculate the association of obesity and CHD by adjusting for time-varying confounders and considering the missing mechanism. According to the results, the appropriate index for obesity varies based on gender and age. These results highlight the importance of selecting best obesity definition separately for each subgroups. Totally, among females and the age group under 54 years, WHtR index was associated with higher incidence of CHD. Also, in men and the age group over 54 years, the BSI had a positive role in higher incidence of CHD but further investigation may be needed to draw definitive conclusions about risk association of BSI with CHD.

Ethics approval and consent to participate

This study was a secondary analysis on the ARIC study data that was performed in accordance with the declaration of Helsinki; this included permission to use anonymized quotations in publications according to the ethics committee. Written informed consent was waived by review board of Deputy for Research Affairs, Shahid-Beheshti University of Medical Sciences, Tehran, Iran (IR.SBMU.RETECH.REC.1401.022) due to registry-based nature of the study.

Consent for publication

Not Applicable.

Availability of data and materials

The data that support the findings of this study are available for request. Data are available from https://biolincc.nhlbi.nih.gov/studies/aric/

Funding

None.

CRediT authorship contribution statement

Hossein Mozafar Saadati: Writing – original draft, Software, Formal analysis. **Niloufar Taherpour:** Writing – review & editing, Project administration. **Seyed Saeed Hashemi Nazari:** Writing – review & editing, Supervision, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgment

The authors thank the staff and participants of the ARIC Study for important contributions.

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