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Biomarkers of glucose homeostasis as mediators of the relationship of body mass index and waist circumference with COVID-19 outcomes among postmenopausal women: Women's Health Initiative

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Abstract

Background & Aims: Systematic reviews, meta-analyses and Mendelian randomization studies suggest that cardiometabolic diseases may be associated with COVID-19 risk and prognosis, with evidence implicating insulin resistance (IR) as a common biological mechanism. As driving factors for IR, we examined body mass index (BMI) and waist circumference (WC) among postmenopausal women in association with COVID-19 outcomes (positivity and hospitalization), and the role of glucose homeostasis as a mediator of this relationship.

Methods: Associations of BMI and WC at baseline (1993–1998) with COVID-19 outcomes collected at Survey 1 (June-December, 2020) and/or Survey 2 (September-December, 2021) were evaluated among 42,770 Women's Health Initiative (WHI) participants (baseline age: 59.36 years) of whom 16,526 self-reported having taken ≥1 COVID-19 test, with 1,242 reporting ≥1 positive COVID-19 test and 362 reporting ≥1 COVID-19 hospitalization. We applied logistic regression and causal mediation analyses to sub-samples with available fasting biomarkers of glucose homeostasis (glucose, insulin, Homeostatic Model Assessment for Insulin Resistance, Homeostasis Model Assessment for β-cell function, Quantitative Insulin-sensitivity Check Index, Triglyceride-Glucose index (TyG)) at baseline, whereby 57 of 759 reported COVID-19 test positivity and 23 of 1,896 reported COVID-19 hospitalization.

Results: In fully adjusted models, higher BMI, WC and TyG were associated with COVID-19 test positivity and hospitalization. Glucose concentrations mediated associations of BMI and WC with COVID-19 positivity, whereas TyG mediated BMI and WC's associations with COVID-19 hospitalization.

Conclusions: Obesity and central obesity markers collected an average of 24 years prior were associated with COVID-19 outcomes among postmenopausal women. Glucose concentration and TyG partly mediated these associations.

Keywords

Coronavirus; Insulin Resistance; Menopause; Obesity; Triglyceride-Glucose index

INTRODUCTION:

The coronavirus disease 2019 (COVID-19) is an ongoing pandemic caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Although a substantial proportion of individuals infected with SARS-CoV-2 may be asymptomatic, symptomatic COVID-19 cases may exhibit a broad spectrum of clinical manifestations and disease severity (1), with both asymptomatic and symptomatic cases capable of SARS-CoV-2 transmission (1, 2). Evidence suggests that individuals who are older, immunocompromised

or having cardiometabolic or cardiorespiratory health concerns are more susceptible to SARS-CoV-2 infection and its complications (3). High-risk groups include men (4, 5), older adults (1, 4, 5), minorities (4, 6), obese individuals (7, 8) and those with pre-existing chronic conditions (1, 4, 5), including hypertension (5, 6), diabetes mellitus (6, 8), coronary artery disease (5, 6, 8), cerebrovascular disease (5, 6, 8), arrhythmias (8), heart failure (5, 8), and multimorbidities (7). These host characteristics have also been linked to COVID-19 disease severity (4), hospitalization (8, 9), intensive care unit (ICU) admission (5, 8), mechanical ventilation (6, 8) and mortality (4).

Among these host characteristics, systematic reviews and meta-analyses of observational studies suggest that obesity and its associated chronic conditions not only make individuals prone to COVID-19 infection but may also affect their prognosis (5). Mendelian Randomization (MR) studies evaluated the causal associations between biomarkers of body composition (4, 10, 11) (e.g. body mass index (BMI), waist circumference (WC), trunk fat ratio), cardiometabolic risk factors (4, 10, 12) (e.g. smoking, lipids/lipoproteins, glycemic traits), and chronic diseases (13, 14) (e.g. diabetes mellitus, coronary artery disease) and various COVID-19 outcomes (4, 13, 14) using genetic risk scores as instrumental variables. While most MR studies were conducted using UK Biobank data (4, 13, 14), only one study originated from the United States (11). These MR studies consistently identified a causal association between BMI and COVID-19 outcomes (4, 13). Of note, one study found that BMI, but not diabetes mellitus, was causally related to COVID-19 outcomes (11). Another study found that diabetes mellitus, but not coronary artery disease, stroke, chronic kidney disease or C-reactive protein, mediated the causal association between BMI and COVID-19 outcomes (13). While sex differences in COVID-19 outcomes have been attributed to cultural, behavioral and clinical characteristics, differences in diabetes mellitus burden among sexes could potentially explain the gap in COVID-19 risk and outcomes between men and women (15). Postmenopausal women may be at higher risk for COVID-19 outcomes since they are older and tend to experience cardiometabolic diseases more frequently than premenopausal women (16).

Current evidence suggests that insulin resistance may be a common biological mechanism reflecting the interplay between obesity, diabetes mellitus, dyslipidemia, hypertension and atherosclerosis leading to COVID-19 outcomes (17, 18). To date, few studies have explored blood-level biomarkers of glucose homeostasis as mediators of the association between obesity and COVID-19 outcomes, (16) and none of these studies focused on postmenopausal women. Clarifying the role of biomarkers of glucose homeostasis as mediators between obesity and COVID-19 outcomes will advance our understanding of COVID-19 pathophysiology and help identify potential targets for reducing the detrimental health impact of COVID-19 in postmenopausal women. In this study, data from the Women’s Health Initiative Clinical Trials and Observational Study (WHI-CTs and WHI-OS) were analyzed to (i) evaluate associations of baseline BMI, WC and biomarkers of glucose homeostasis with self-reported COVID-19 positivity and hospitalization occurring >20 years later and (ii) estimate mediating effects for glucose homeostasis measures on the associations between BMI and WC and COVID-19 outcomes.

MATERIALS & METHODS:

Data source:

The WHI study design, eligibility criteria, recruitment methods and measurement protocols were previously described (19, 20). Briefly, the WHI collected data longitudinally on a racially and ethnically diverse sample of postmenopausal women who were recruited and enrolled between 1993 and 1998 at 40 geographically diverse clinical centers (24 states and the District of Columbia) in the United States. The WHI-CTs (n=68,132) and WHI-OS (n=93,676) were two components of the WHI (n=161,808). WHI participants, 50–79 years of age at baseline, completed multiple baseline, self-administered questionnaires, covering demographics, general health, clinical and anthropometric characteristics, medical history, personal habits and medications. The CT and OS participants of WHI were followed initially from 1993 to 2005. Of 150,076 participants who were in active follow-up at the end of these studies, 76.9% participated in Extension Study 1 (2005–2010) and 86.9% of those eligible participated in Extension Study 2 (2010–2020) (21, 22). A total of 50,306 (78%) WHI participants in active follow-up completed the COVID-19 Survey 1 (June-December, 2020) and 37,289 (81%) WHI participants in active follow-up completed the COVID-19 Survey 2 (September-December, 2021). These two COVID-19 surveys were administered by mail, phone or online to assess the impact of the COVID-19 pandemic on older women, covering health and well-being, living situations, lifestyle, health care, and self-reported COVID-19 testing, treatment, and preventive behaviors (23–25). The WHI studies received Institutional Review Board approval at each participating clinical center, whereby each study participant completed a written informed consent. This study received an exempt determination for secondary use analyses of WHI data at Fort Belvoir Community Hospital.

Study population:

Of 43,795 WHI participants who completed COVID-19 Surveys 1 and/or 2 and had non-missing baseline data, 42,770 completed questions pertaining to COVID-19 status (**Sample 1**), with 16,526 reporting having taken ≥ 1 COVID-19 test, 1,242 reporting having ≥ 1 positive COVID-19 test, and 362 reporting ≥ 1 prior COVID-19 hospitalization (Supporting Figure 1). Among a sub-sample of 1,947 WHI participants with additionally available data on glucose, insulin and triglyceride concentrations, 1,896 completed questions regarding COVID-19 status (**Sample 2**), with 759 reporting having taken ≥ 1 COVID-19 test, 57 reporting having ≥ 1 positive COVID-19 test, and 23 reporting ≥ 1 prior COVID-19 hospitalization (Supporting Figure 1). The mean (± standard deviation [SD]) baseline age for **Sample 1** and **Sample 2** were 59.36 (±5.75) and 59.57 (±6.07) years, respectively. Also, the mean (±SD) follow-up durations for **Sample 1** and **Sample 2** from study baseline (1993–1998) to the date of the COVID-19 questionnaires were 24.51 (±1.10) years and 24.44 (±1.03) years, respectively.

Measures:

Obesity: Trained staff collected anthropometric data, including weight [kg], height [cm] and WC [cm] at enrollment (1993–1998) (26) and BMI was calculated as (weight (kg) ÷ (height^2 (m^2)). Weight was measured to the nearest 0.1 kg on a balance beam scale with the participant dressed in indoor clothing without shoes, while height was measured

to the nearest 0.1 cm using a wall-mounted stadiometer. Similarly, WC was determined using tape measures at the natural waist or narrowest part of the torso to the nearest 0.5 cm (27). These exposures were also defined as categorical variables (BMI: <25.0 kg/m^2 [underweight/normal weight]; 25.0–29.9 kg/m^2 [overweight]; and ≥30 kg/m^2 [obese]; WC: ≤88 cm [normal]; >88 cm [high]) (28). Using a simple random sample of 1,000 WHI participants, we estimated intraclass correlation coefficients of 0.97 for repeated BMI and WC measurements at baseline and 3 years of follow-up. Besides baseline BMI and WC, sensitivity analyses were performed using (i) directly measured BMI and WC (Form 80) at the 3-year follow-up visit and the latest follow-up visit before WHI Extensions 1 and 2, and (ii) BMI calculated using self-reported weights at the earliest and latest visits ≥ 20 years of follow-up (Form 159) as well as the COVID-19 Survey 2 (Form 191).

Glucose homeostasis: Fasting blood samples were collected from each participant at study enrollment by trained phlebotomists and immediately centrifuged and stored at −70°C (28). Nearly 6% of WHI-CT and 1% of WHI-OS participants had core laboratory data, which included glucose, insulin and triglyceride measurements at baseline. Approximately 24,000 WHI participants also had biomarkers relevant to cardiometabolic diseases at baseline through a core set of WHI studies, which included blood levels of lipids, glucose, insulin, creatinine and C-reactive protein. Serum glucose concentration was determined using the hexokinase method on a Hitachi 747 analyzer (Boehringer Mannheim Diagnostics), with a coefficient of variation of 1.6% and a correlation coefficient of values of 0.99 (28). Serum insulin testing was conducted using the Sandwich Immunoassay on a Roche Elecsys 2010 analyzer (Roche Diagnostics), with a coefficient of variation of 4.9% and a correlation coefficient of values of 0.99 (28). All lipids and lipoprotein sub-fractions were analyzed from ethylenediaminetetraacetic acid-treated plasma, and triglyceride concentration was measured enzymatically (29). Biomarkers of glucose homeostasis were defined as circulating fasting levels of glucose [mg/dl] and insulin [μIU/ml] as well as indices of insulin resistance (Homeostatic Model Assessment for Insulin Resistance[HOMA-IR]), β-cell function (HOMA for β-cell function [HOMA-β]), insulin sensitivity (Quantitative Insulin-sensitivity Check Index [QUICKI]), and the Triglyceride-Glucose (TyG) index (30–32). Below is a detailed formula for calculating each biomarker. All biomarkers were analyzed as continuous variables, with HOMA-IR further categorized as > 2.5 versus ≤2.5.

- HOMA-IR = [fasting insulin (μIU/mL) x fasting glucose (mg/dl)/405]
- HOMA-β = [360 x fasting insulin (μU/mL) / (fasting glucose (mg/dL) - 63)]
- QUICKI = 1/[log(fasting insulin (μU/ml))+log(fasting glucose (mg/dl))]
- TyG = ln [fasting triglycerides (mg/dl) x fasting plasma glucose (mg/dl)] / 2

COVID-19 outcomes: Two cumulative COVID-19 outcomes (positivity and hospitalization) were defined using available COVID-19 Survey 1 and 2 data. COVID-19 positivity was identified in WHI participants who reported at least one positive test (Responded “Yes” to “Did any of these tests come back positive for a COVID-19 infection?”) among those who took part in a COVID-19 survey and received at least one

COVID-19 test (Responded “Yes” to “Have you been tested for COVID-19?”). Furthermore, COVID-19 hospitalization was defined as self-reported hospitalization (Responded “Yes” to “Were you ever hospitalized for COVID-19?”) among WHI participants who took part in at least one COVID-19 survey. Follow-up questions on length of stay, ICU admission and therapies received were asked of survey respondents who reported being hospitalized for COVID-19. WHI participants who completed both COVID-19 surveys were labeled as being COVID-19 positive if they reported at least one COVID-19 positive test, and as being hospitalized for COVID-19 if they reported at least one COVID-19 hospitalization. Moreover, the completion of COVID-19 surveys (i.e., 1, 2 or both) was added as a covariate in the context of multivariable modeling.

Covariates: Covariates collected at the baseline visit included WHI component (WHI-CT, WHI-OS), socio-demographic characteristics (age [in years], race [Black, White, Asian, Other], ethnicity [Hispanic, non-Hispanic, Unknown/Not reported], education [less than high school, high school, some college, completed college or higher level], household income [< $20,000, $20,000-$49,999, $50,000-$99,999, ≥$100,000], marital status [Married/Partnered, Single, Divorced, Widowed]), lifestyle characteristics (smoking status [Never Smoker, Past Smoker, Current Smoker], alcohol consumption [Non-Drinker, Former Drinker, < 1 drink/week, ≥ 1 drink/week], physical activity [Metabolic equivalent-hours/week]), and health characteristics, namely, comorbid conditions (cardiovascular disease [Yes, No], hypertension [Yes, No], hyperlipidemia [Yes, No], diabetes [Yes, No], number of conditions [0–4]) and self-rated health [Excellent/Very Good/Good, Fair/Poor]). History of cardiovascular disease was defined in terms of previous coronary heart disease, angina, aortic aneurysm, carotid endarterectomy or angioplasty, atrial fibrillation, congestive heart failure, cardiac arrest, stroke, or transient ischemic attack. History of hypertension was defined as self-reported diagnosis or treatment for hypertension or evidence of high blood pressure based on SBP and DBP measurements. History of diabetes was defined as physician-diagnosed diabetes or use of diabetes medications. History of hyperlipidemia was defined as using lipid-lowering medications or having been told of high cholesterol by a physician. Covariates were analyzed as confounders based on their putative relationships with the exposure, mediator and/or outcome variables of interest (11, 33).

Statistical analysis:

All statistical analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC) and STATA version 17 (StataCorp, College Station, TX). Summary statistics included mean ± standard deviation or median ± interquartile range (IQR) for continuous variables and frequencies with percentages for categorical variables. Bivariate associations were examined using the Chisquare test, independent samples t-test, one-way Analysis of Variance (ANOVA), Pearson’s correlation coefficient or their non-parametric counterparts, as appropriate. Univariate and multivariable logistic regression models were constructed to estimate odds ratios (OR) and their 95% confidence intervals (CI) for predictors of COVID-19 outcomes. A two-stage Heckman selection strategy was applied using the SAS QLIM procedure to adjust for sample selectivity due to missing data on biomarkers of glucose homeostasis. Specifically, an indicator of selection was predicted using baseline covariates in a probit model yielding an inverse mills ratio (IMR), a function

of the probability of being selected given these characteristics. Then, logistic regression models were adjusted for the IMR along with other predictors (34). A directed acyclic graph that displays the hypothesized relationships among exposures, mediators, outcomes and covariates is shown in Supporting Figure 2. First, we examined the association of baseline socio-demographic, lifestyle and health characteristics with BMI, WC and COVID-19 outcomes using **Sample 1**. Second, we generated the IMR by comparing baseline socio-demographic, lifestyle and health characteristics of **Sample 1** participants included in **Sample 2** to those excluded from **Sample 2**. Third, we used **Sample 2** data to examine differences in biomarkers of glucose homeostasis among diabetic and non-diabetic participants and correlations of BMI and WC with biomarkers of glucose homeostasis overall and according to diabetes status. Fourth, we examined associations of BMI and WC (**Sample 1**) as well as biomarkers of glucose homeostasis (**Sample 2**) with COVID-19 outcomes, before and after controlling for baseline characteristics and IMR. Using Form 80, we performed sensitivity analyses to evaluate the relationships of COVID-19 outcomes with BMI and WC at the 3-year follow-up visit and the latest follow-up visit before WHI Extensions 1 and 2 whereby weight, height and WC were directly measured within an average of 19 and 20 years from COVID-19 Surveys 1 and 2, respectively. Using self-reported weight data from Forms 159 and 191, we also performed sensitivity analyses to evaluate the relationship of COVID-19 outcomes with BMI at the earliest and latest follow-up visits ≥ 20 years post-baseline, as well as the cross-sectional relationship between these outcomes and BMI within COVID-19 Survey 2. Both the earliest and latest Form 159 follow-up visits were, on average, within 1.8 and 2.9 years from COVID-19 Surveys 1 and 2, respectively. Finally, using **Sample 2**, we applied the *paramed* and *med4way* STATA commands to estimate the impact of each z-transformed biomarker of glucose homeostasis (continuous mediator variables M) on the associations of z-transformed baseline BMI and WC (continuous treatment variables T) with COVID-19 outcomes (binary outcome variables Y), controlling for baseline characteristics (z-transformed continuous or categorical covariates C) (35–37). This causal mediation analysis is helpful in a counterfactual framework and in the context of observational data whereby two models are estimated, namely, a model for the mediator conditional on exposure and covariates and a model for the outcome conditional on the exposure, mediator and covariates (35–37). Assuming no unmeasured confounding and 2-way decomposition, the *paramed* command can facilitate estimation of the controlled direct effect [CDE], the natural direct effect [NDE], natural indirect effect [NIE] and the marginal total effect [MTE]. Assuming no unmeasured confounding and 4-way decomposition, the *med4way* command can also facilitate estimation of mediation but not interaction (pure indirect effect [PIE]), interaction but not mediation (reference interaction [IRF]), both mediation and interaction (mediated interaction [IMD]) and neither mediation nor interaction (controlled direct effect [CDE]), whereby NDE=CDE+IRF, NIE=PIE+IMD and the total effect (TE) can be calculated as follows: TE=NDE+NIE (35–37). Two-sided statistical tests were conducted at α=0.05.

RESULTS:

The mean (±SD) baseline measurements of BMI and WC were estimated at 27.19 (±5.46) kg/m^2 and 83.94 (±12.83) cm, respectively. As shown in Table 1, BMI and WC were highest among WH-CT participants, Blacks, past smokers, former alcohol drinkers, and those with a history of cardiovascular disease, hypertension, hyperlipidemia and/or diabetes. Whereas BMI was negatively correlated with age, it was positively correlated with physical activity. Conversely, WC was positively correlated with age and negatively correlated with physical activity. Both anthropometric measurements correlated positively with the number of cardiometabolic conditions. A graded relationship was observed whereby BMI and WC decreased with higher educational level and household income.

Table 2 displays differences in socio-demographic, lifestyle and health characteristics according to COVID-19 outcomes, whereby 1,242 women who tested positive for COVID-19 were compared to 15,284 women who tested negative for COVID-19, and 362 women who reported ≥ 1 COVID-19 hospitalization were compared to 42,408 women who did not report a COVID-19 hospitalization. In general, women who reported COVID-19 positivity and/or hospitalization were more frequently WHI-CT participants, non-White, less educated, while reporting lower income, alcohol consumption and/or physical activity; they were also more frequently hypertensive, with more chronic conditions and worse self-rated health. In addition, women who reported COVID-19 positivity were more frequently married or partnered and those who reported COVID-19 hospitalization were older than those who did not.

The median fasting levels of glucose, insulin, HOMA-IR, HOMA-β, QUCKI and TyG among the total population were 88.0 mg/dl, 12.1 μIU/ml, 2.37, −14.6, 0.10 and 6.64, respectively. In addition, 47.8% had HOMA-IR > 2.5. As shown in Supporting Tables 1 and 2, levels of the biomarkers differed significantly among diabetic and non-diabetic women, with absolute correlations of anthropometric measurements, with these biomarkers ranging between 0.04 and 0.32 without substantial differences by diabetes status. Table 3 presents bivariate associations of BMI, WC and biomarkers of glucose homeostasis with COVID-19 outcomes. WHI participants who reported positive COVD-19 tests had, on average, higher baseline BMI and WC. Similarly, WHI participants who reported COVID-19 hospitalizations had significantly higher baseline BMI, WC, HOMA-IR and TyG and significantly lower QUICKI compared to those not hospitalized for COVID-19.

Logistic regression models for BMI, WC and biomarkers of glucose homeostasis as predictors of COVID-19 outcomes are presented in Table 4. After controlling for baseline characteristics as well as IMR generated using a probit model (Supporting Table 3), a 1 kg/m^2 increase in BMI and 1 cm increase in WC at baseline was associated with 1–3% increased odds of COVID-19 positivity (Model II, BMI: OR=1.01, 95% CI: 1.00, 1.02; WC: OR: 1.01, 95% CI: 1.00, 1.01) and hospitalization (Model II, BMI: OR=1.03, 95% CI: 1.01, 1.05; WC: OR=1.02, 95% CI: 1.01, 1.03). In fully adjusted models, women with baseline BMI > 30 kg/m^2 were more likely to report COVID-19 positivity (Model II, OR=1.16, 95% CI: 0.99, 1.36) than those with BMI < 25 kg/m^2, although the relationship was of borderline significance. A dose-response relationship between baseline BMI and COVID-19

hospitalization was observed whereby the odds of COVID-19 hospitalization in the BMI 25–29.9 kg/m^2 (Model II, OR=1.34, 95% CI: 1.03, 1.75) and the BMI ≥30 kg/m^2 (Model II, OR=1.63, 95% CI: 1.22, 2.17) groups were significantly higher than among the BMI < 25 kg/m^2 group. Similarly, women with baseline WC > 88 cm (vs. WC ≤ 88 cm) were more likely to report COVID-19 positivity (Model II, OR=1.27, 95% CI: 1.12, 1.45) and hospitalization (Model II, OR=1.78, 95% CI: 1.42, 2.23) in fully adjusted models. Similar results were obtained in the context of sensitivity analyses whereby COVID-19 outcomes were examined in relation to BMI and WC assessments at later follow-up times prior to or after the WHI Extensions 1 and 2, using WHI Forms 80, 159 and 191. These associations became slightly stronger as time duration between anthropometric measurements and COVID-19 outcomes became shorter (Supporting Table 4). Furthermore, a 1 mg/dl increase in glucose concentration at baseline was associated with <1% increase in odds of COVID-19 positivity, whereas a 1-unit increase in TyG at baseline was associated with 80% increased odds of COVID-19 positivity (Model II, OR=1.80, 95% CI: 1.03, 3.15) and approximately 4-fold increased odds of COVID-19 hospitalization (Model II, OR=3.92, 95% CI: 1.42, 10.83), after controlling for confounders.

Table 5 presents causal mediation analyses for each biomarker of glucose homeostasis assessed at baseline on the association of baseline BMI and WC with COVID-19 outcomes, controlling for covariates identified as confounders in Table 1 and 2. Taking sample size into consideration, key covariates, namely, WHI component, age, White race, College education, household income <$50000, current alcohol drinking, physical activity, hypertension, hyperlipidemia and sample selectivity, were added to all models. These covariates were fixed at their mean values in the context of 2-way and 4-way decomposition analyses. Overall, results suggested no significant natural direct effects based on the 2-way decomposition. By contrast, significant natural indirect effects were observed in the context of TyG as a mediator between BMI and COVID-19 hospitalization (Estimate=1.21, standard error (SE) = 0.07, P=0.010) and between WC and COVID-19 hospitalization (Estimate=1.24, SE=0.09, P=0.017). Furthermore, the 4-way decomposition revealed no significant mediation and/or interaction effects of insulin, HOMA-IR, HOMA-β, QUICKI or TyG in the associations of BMI and WC with COVID-19 outcomes. By contrast, significant pure indirect effects were observed for glucose concentration as a mediator of the associations between BMI and COVID-19 positivity (Estimate=0.11, SE=0.053, P=0.038) and between WC and COVID-19 positivity (Estimate=0.18, SE=0.08, P=0.020). Finally, a significant mediated interaction was observed for glucose when examining the relationship between WC and COVID-19 positivity (Estimate=−0.14, SE=0.07, P=0.041).

DISCUSSION:

In this study involving over 40,000 postmenopausal women, BMI and WC measured at baseline were associated with COVID-19 positivity and hospitalization after over two decades of follow-up. A unique aspect of this study is that anthropometric data were collected 24 years prior to COVID-19 surveys, providing an opportunity to examine whether midlife obesity can render aging women more vulnerable to detrimental outcomes associated with COVID-19 infections. The odds of reporting these COVID-19 outcomes were significantly higher among postmenopausal women with obesity (BMI ≥ 30 kg/m^2)

or central obesity (WC ≥ 88 cm) at baseline. Notably, COVID-19 hospitalization showed a dose-response relationship with overweight and obese postmenopausal women by 34% and 63% (respectively) compared with their normal/underweight counterparts based on BMI at baseline. Study results also suggested that baseline TyG was strongly associated with future COVID-19 outcomes and that baseline glucose concentration and TyG were significant mediators of relationships between anthropometric characteristics and future COVID-19 outcomes. Consistent with published studies that have hypothesized a link between atherogenic dyslipidemia and COVID-19 severity of outcomes during hospitalization (38–45), this study found a direct association between TyG index and COVID-19 hospitalization implying that high triglyceride levels may also be linked to COVID-19 hospitalization and reflecting the potential pathophysiological role of insulin resistance in contributing to COVID-19 disease severity. These findings are consistent with current knowledge of COVID-19 pathophysiology as it relates to obesity (BMI) and central obesity (WC). This study significantly contributes to the literature by highlighting multiple metabolic risk factors predicting COVID-19 outcomes as mediators of obesity and central obesity in postmenopausal women.

The co-existence of the obesity and COVID-19 pandemics has been referred to as a ‘twindemic’ with major public health implications. This is due to the vulnerability of obese individuals – through a wide range of structural, immune and molecular mechanisms – to the deleterious health consequences of COVID-19 (46). Obesity affords a unique pathogenic microenvironment leading to greater COVID-19 severity and worse outcomes (47). Among obese individuals, pro-inflammatory cytokines and chemotactic factors increase insulin resistance leading to more systemic inflammation, thrombosis and hyperglycemia, with impairment in pulmonary, cardiac, hepatic and renal functions as well as glycemic control among people with diabetes or pre-diabetes (46). Major complications of COVID-19 such as acute respiratory distress syndrome, cytokine storm and coagulopathy were previously linked to high fat mass and obesity (48, 49).

The mediating effect of glucose and TyG suggest that overall and central obesity may be associated with COVID-19 outcomes through a biological mechanism that adversely affects glycemic control. A bidirectional relationship has been previously suggested whereby people with diabetes experienced SARS-CoV-2 infections and severe COVID-19 outcomes more frequently than those without diabetes, whereas COVID-19 patients were at increased risk for developing obesity, β-cell dysfunction, insulin resistance and diabetes at a later stage (50, 51). As such, anti-diabetics and insulin sensitizers are among several therapies targeting cardiometabolic disease in the context of COVID-19 (51). In the absence of universal access to vaccines and recurrent “breakthrough” infections, previous literature has highlighted the need to identify targets for the prevention of COVID-19 and to advance the understanding of pathways between obesity and COVID-19 with evidence pointing towards a potential role for β-cell insufficiency, insulin resistance and diabetes mellitus (17, 33). According to Wensveen *et al.*, glucose homeostasis is simultaneously controlled by the endocrine and immune systems, whereby the endocrine system attempts to maintain glucose levels within a narrow range and the immune system attempts to optimize its access to glucose in order to resolve local disturbances associated with infection, and this intricate balance is disrupted in the context of obesity and its associated cardiometabolic diseases (52).

The contribution of glucose homeostasis biomarkers to COVID-19 outcomes has not been comprehensively examined in epidemiologic studies (53, 54). In a cross-sectional study involving 131 hospitalized COVID-19 patients at a clinical center in France, excess body weight emerged as a stronger predictor of COVID-19 severity than several metabolic parameters including glucose, insulin, HOMA-IR and lipids (53). Given that SARS-CoV-2 may enter cells in blood vessels, lungs, heart, intestines, and kidneys through the Angiotensin-Converting Enzyme-2 (ACE-2) receptor, Li *et al.* examined changes in subcutaneous adipose ACE-2 mRNA expression among 143 adults (BMI ≥ 27 kg/m^2) before and after a 12-week weight reduction program and its impact on short-term and long-term improvements of glucose metabolism, including indices of liver (HOMA-IR) and muscle (ISIClamp) insulin sensitivity (54, 55). Their results suggested that ACE-2 mRNA expression was not affected by obesity, but was reduced in the context of insulin resistance, whereas weight loss resulted in a decline of ACE-2 mRNA expression, which in turn was associated with improved insulin sensitivity over time (54).

According to Nadolsky *et al.* it has become necessary to risk stratify COVID-19 patients not merely according to their BMI, but also according to insulin resistance, which is linked to diabetes mellitus, hypertension and cardiovascular disease (56). Previous studies have suggested that components of the metabolic syndrome as well as related conditions such as non-alcoholic fatty liver disease (NAFLD) and polycystic ovarian syndrome, which are similarly characterized by abdominal adiposity, excess body weight and insulin resistance, may influence outcomes of COVID-19 (4, 57). In a population-based case-control study, Cho *et al.* compared 4,070 patients with positive SARS-CoV-2 test results to 27,618 age- and sex-matched controls with negative SARS-CoV-2 test results, and found no significant association between metabolic syndrome and COVID-19 infection; by contrast, COVID-19 infection was associated with higher odds of central obesity (OR=1.17, 95% CI: 1.06, 1.28) and COVID-19 severity was associated with greater odds of pre-diabetic or diabetic state (OR= 1.61, 95% CI: 1.21, 2.13) with the frequency of severe COVID-19 linearly increasing as the number of metabolic components increased (57).

This study has many strengths. First, the WHI database has a large baseline sample and the scope of the data collected by the WHI enables the evaluation of hypothesized relationships taking into account key potential confounders. Second, the longitudinal study design of WHI allowed us to establish temporal relationships between variables of interest. Specifically, the availability of baseline information dated >20 years prior to the assessments of COVID-19 outcomes enabled us to examine exposure, mediating and covariate factors predisposing postmenopausal women to greater risks of future COVID-19 outcomes. However, there are several limitations of our study. First, missing data on biomarkers of glucose homeostasis may have resulted in selection bias, despite the application of the Heckman selection model. Given that COVID-19 outcomes were self-reported, the range of disease severity among COVID-19 survey participants is limited by the exclusion of those who died from competing risks as well as those who died from COVID-19. Second, biological specimens used to measure glucose, insulin and triglyceride concentrations were analyzed by multiple laboratories using distinct methods potentially leading to small measurement discrepancies. Third, residual confounding due to unmeasured or inadequately measured confounders (e.g. medication use, nursing home residence) remains a concern for causal

inference with observational study designs. Fourth, temporality may be a concern given the long latency period between baseline assessments and the two COVID-19 surveys and the fact that BMI, WC and biomarkers of glucose homeostasis were examined in a cross-sectional manner. These clinical parameters, particularly biomarkers of glucose homeostasis, which were assessed at a single time point (at enrollment) may have changed over time prior to assessment of COVID-19 outcomes > 20 years later. Physiological changes may have intervened during this latency period resulting in clinical events such as cancers, immunosuppressive states, autoimmune and neurodegenerative conditions that are known risk factors of COVID-19 outcomes. Whereas weight maintenance is likely a sign of robustness, dementia may lead to weight loss thereby complicating the relationship between BMI, WC and COVID-19 outcomes. Fifth, the role of chance cannot be ruled out since 1,947 individuals had available data at enrollment and completed COVID-19 surveys, representing a small subset of the initial sample of 161,808 WHI participants at enrollment. Also, a relatively small number of cases (57 positive test results and 23 hospitalizations) remained after eligibility criteria were applied for each COVID-19 outcome. Specifically, it is plausible that the limited number of individuals with COVID-19 outcomes may have impacted the results of regression analyses. Finally, due to limited genome-wide association studies data that overlap with measurements of interest in this study, our initial plan for MR analysis was underpowered and could not be moved forward.

CONCLUSION:

BMI and WC were associated with future risks of COVID-19 positivity and hospitalization among postmenopausal women, and these associations were partially mediated by levels of glucose concentration and TyG. The specificity of TyG as a biomarker of insulin resistance and other metabolic diseases such as NAFLD necessitates further elucidation. Identification of modifiable risk factors with the greatest impact on COVID-19 outcomes can inform preventive strategies whereby risk factors that precede COVID-19 outcomes can be addressed. Studies with larger sample sizes and repeated measures of obesity and biomarkers of glucose homeostasis are warranted for validating and extending these research findings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Mean distribution of body mass index and waist circumference of the study samples according to socio-demographic, lifestyle and health characteristics (n=42,770) [a]

	BMI [kg/m^2]		WC [cm]	
	Mean	**SD**	**Mean**	**SD**
Total	27.19	5.46	83.94	12.83
WHI component:	*P<0.0001*		*P<0.0001*	
WHI-CT	28.26	5.60	86.44	13.07
WHI-OS	26.41	5.22	82.11	12.32
Age (Years):	r=−0.020		r=+0.023	
	P<0.0001		*P<0.0001*	
Race:	*P<0.0001*		*P<0.0001*	
Black	30.10	6.19	88.75	13.26
White	27.03	5.35	83.72	12.73
Asian	25.18	4.78	79.13	11.44
Other	28.71	6.19	86.21	13.48
Ethnicity:	*P<0.0001*		*P=0.0016*	
Hispanic	28.08	5.48	84.61	12.63
Non-Hispanic	27.17	5.47	83.93	12.83
Unknown/not reported	25.76	5.18	79.82	12.15
Education:	*P<0.0001*		*P<0.0001*	
Less than High School	29.28	5.74	88.92	14.32
High School	28.17	5.55	85.13	13.02
Some college	27.71	5.56	85.13	13.02
Completed College or Higher	26.48	5.27	82.30	12.26
Household income ($):	*P<0.0001*		*P<0.0001*	
< 20,000	28.63	6.11	87.57	13.96
20,000–49,999	27.78	5.55	85.56	13.12
50,000–99,999	26.93	5.33	83.19	12.50
≥100,000	25.73	4.88	80.09	11.106
Marital status:	*P<0.0001*		*P<0.0001*	
Married / Partnered	27.03	5.30	83.49	12.51
Single	27.55	6.07	85.21	14.52
Divorced	27.57	5.93	84.74	13.56
Widowed	27.66	5.55	85.41	12.95
Smoking status:	P=0.11		*P<0.0001*	
Never	27.11	5.45	83.42	12.66
Past	27.32	5.52	84.55	13.02
Current	26.80	5.14	84.21	12.55
Alcohol consumption:	*P<0.0001*		*P<0.0001*	
Non-drinker	27.76	5.87	84.87	13.88
Former drinker	28.20	6.11	86.35	14.21

	BMI [kg/m^2]		WC [cm]	
	Mean	**SD**	**Mean**	**SD**
< 1 drink / week	27.94	5.69	85.35	13.20
≥1 drink / week	26.18	4.79	81.90	11.49
Physical activity	r=+0.028		r=−0.24	
(Met-hours/week):	*P<0.0001*		*P<0.0001*	
Chronic conditions:				
Cardiovascular disease:	*P<0.0001*		*P<0.0001*	
Yes	27.65	5.72	85.16	13.13
No	27.12	5.42	83.74	12.76
Hypertension:	*P<0.0001*		*P<0.0001*	
Yes	29.04	5.94	88.48	13.61
No	26.36	5.02	81.90	11.90
Hyperlipidemia:	*P<0.0001*		*P<0.0001*	
Yes	28.29	5.24	87.36	12.18
No	27.06	5.48	83.55	2.84
Diabetes:	*P<0.0001*		*P<0.0001*	
Yes	30.97	6.23	93.77	14.26
No	26.79	5.22	82.91	12.22
Number of conditions:	*P<0.0001*		*P<0.0001*	
r	+0.25		+0.27	
Self-rated health:	*P<0.0001*		*P<0.0001*	
Excellent/Very Good/Good	27.04	5.34	83.58	12.57
Fair/Poor	30.81	6.98	92.60	15.69
COVID-19 Survey:	*P<0.0001*		*P<0.0001*	
1	27.46	5.64	84.73	13.11
2	27.77	6.04	85.39	13.80
1+2	27.09	5.39	83.66	12.71

Note. *Abbreviations:* BMI = Body Mass Index; COVID-19 = Coronavirus disease 2019; r = Pearson's correlation coefficient; SD = Standard Deviation; WC = Waist Circumference; WHI = Women's Health Initiative; WHI-CT = Women's Health Initiative Clinical Trial; WHI-OS = Women's Health Initiative Observational Study.

[a] P values are based on general linear models or Pearson's correlation coefficients.

Table 2.

Distribution of the study sample according to baseline socio-demographic, lifestyle and health characteristics and COVID-19 outcomes (n=42,770)

	Total	COVID-19 positivity		COVID-19 hospitalization		P [a]	
		Yes	No	Yes	No	POS	HOSP
	N (%) Mean (SD)	N (%) Mean (SD)	N (%) Mean (SD)	N (%) Mean (SD)	N (%) Mean (SD)		
Total	**42,770**	**1,242**	**15,284**	**362**	**42,408**		
WHI component:						*0.0065*	*0.020*
WHI-CT	18,049 (42.20)	567 (45.65)	6,372 (41.69)	175 (48.34)	17,874 (42.15)		
WHI-OS	24,721 (57.80)	675 (54.35)	8,912 (58.31)	187 (51.66)	24,534 (57.85)		
Age (Years):						0.16	*0.001*
Mean (SD)	59.36 (5.76)	59.19 (6.01)	58.94 (5.77)	60.33 (5.78)	59.36 (5.75)		
Race:						*0.0044*	*0.0020*
Black	2,413 (5.64)	87 (7.00)	1,042 (6.82)	35 (9.67)	2,378 (5.61)		
White	38,388 (89.75)	1,121 (90.26)	13,534 (88.55)	313 (86.46)	38,075 (89.78)		
Asian	1,092 (2.55)	11 (0.89)	375 (2.45)	4 (1.10)	1,088 (2.57)		
Other	877 (2.05)	23 (1.85)	333 (2.18)	10 (2.76)	867 (2.04)		
Ethnicity:						0.60	0.27
Hispanic	1,257 (2.94)	42 (3.38)	464 (3.04)	15 (4.14)	1,242 (2.93)		
Non-Hispanic	41,422 (96.85)	1,199 (96.54)	14,794 (96.79)	347 (95.86)	41,075 (96.86)		
Unknown/not reported	91 (0.21)	1 (0.08)	26 (0.17)	0 (0.00)	91 (0.21)		
Education:						*<0.0001*	*<0.0001*
Less than High School	761 (1.78)	43 (3.46)	253 (1.66)	13 (3.59)	748 (1.76)		
High School	5,736 (13.41)	210 (16.91)	1,834 (12.00)	59 (16.30)	5,677 (3.39)		
Some college	14,944 (34.94)	465 (37.44)	5,214 (34.11)	160 (44.20)	14,784 (34.86)		
Completed College or Higher	21,329 (49.87)	524 (42.19)	7,983 (52.23)	130 (35.91)	21,199 (49.99)		
Household income ($):						*0.0002*	*0.0001*
< 20,000	3,058 (7.15)	98 (7.89)	1,048 (6.86)	37 (10.22)	3,021 (7.12)		
20,000–49,999	16,721 (39.10)	509 (40.98)	5,684 (37.19)	169 (46.69)	16,552 (39.03)		
50,000–99,999	16,219 (37.92)	474 (38.16)	5,890 (38.54)	120 (33.15)	16,099 (37.96)		
100,000	6,772 (15.83)	161 (12.96)	2,662 (17.42)	36 (9.94)	6,736 (15.88)		
Marital status:							
Married / Partnered	30,354 (70.97)	934 (75.20)	10,729 (70.20)	257 (70.99)	30,097 (70.97)	*0.0008*	0.39
Single	1,707 (3.99)	36 (2.90)	693 (4.53)	11 (3.04)	1,696 (4.00)		
Divorced	6,680 (15.62)	166 (13.37)	2,453 (16.05)	52 (14.36)	6,628 (15.63)		
Widowed	4,209 (9.42)	106 (8.53)	1,409 (9.22)	42 (11.60)	3,987 (9.40)		
Smoking status:						0.40	0.94
Never	22,562 (52.75)	656 (52.82)	7,772 (50.85)	191 (52.76)	22,371 (52.75)		
Past	18,234 (42.63)	529 (42.59)	6,765 (44.26)	153 (42.27)	18,081 (42.64)		
Current	1,974 (4.62)	57 (4.59)	747 (4.89)	18 (4.97)	1,956 (4.61)		
Alcohol consumption:						*<0.0001*	*<0.0001*

	Total	COVID-19 positivity		COVID-19 hospitalization		P [a]	
		Yes	No	Yes	No	POS	HOSP
	N (%) Mean (SD)	N (%) Mean (SD)	N (%) Mean (SD)	N (%) Mean (SD)	N (%) Mean (SD)		
Non-drinker	3,350 (7.83)	131 (10.55)	1,042 (6.82)	48 (13.26)	3,302 (7.79)		
Former drinker	5,967 (13.95)	189 (15.22)	2,196 (14.37)	68 (18.78)	5,899 (13.91)		
< 1 drink / week	14,673 (34.31)	437 (35.19)	5,212 (34.10)	131 (36.19)	14,542 (34.29)		
≥1 drink / week	18,780 (43.91)	485 (39.05)	6,834 (44.71)	115 (31.77)	18,665 (44.01)		
Physical activity (Met-hours/week):							
Mean (SD)	13.75 (14.06)	12.55 (13.33)	13.87 (14.01)	10.86 (12.05)	13.77 (14.07)	*0.0009*	*<0.0001*
Chronic conditions:							
Cardiovascular disease:						0.97	0.25
Yes	5,959 (13.93)	184 (14.81)	2,259 (14.78)	58 (16.02)	5,901 (13.91)		
No	36,811 (86.07)	1,058 (85.19)	13,025 (85.22)	304 (83.98)	36,507 (86.09)		
Hypertension:						*0.009*	*0.003*
Yes	1,326 (30.99)	433 (34.86)	4,779 (31.27)	138 (38.12)	13,118 (30.93)		
No	29,514 (69.01)	809 (65.14)	10,505 (68.73)	224 (61.88)	29,290 (69.07)		
Hyperlipidemia:						0.091	*0.026*
Yes	4,291 (10.03)	142 (11.43)	1,518 (9.93)	49 (13.54)	4,242 (10.00)		
No	38,479 (89.97)	1,100 (88.57)	13,766 (90.07)	313 (86.46)	38,166 (90.00)		
Diabetes:							
Yes	4,055 (9.48)	129 (10.39)	1,489 (9.74)	42 (11.60)	4,013 (9.46)	0.46	0.17
No	38,715 (90.52)	1,113 (89.61)	13,795 (90.26)	320 (88.40)	38,395 (90.54)		
Number of conditions:							
Mean (SD)	0.64 (0.80)	0.71 (0.84)	0.66 (0.82)	0.79 (0.87)	0.64 (0.80)	*0.018*	*0.0013*
Self-rated health:						0.33	*0.0006*
Excellent/Very Good/Good	41,078 (96.04)	1,179 (94.93)	14,599 (95.52)	335 (92.54)	40,743 (96.07)		
Fair/Poor	1,692 (3.96)	63 (5.07)	685 (4.48)	27 (7.46)	1,665 (3.93)		
COVID-19 Survey:						*<0.0001*	*<0.0001*
1	11,145 (26.06)	82 (6.60)	1,998 (13.07)	28 (7.73)	11,117 (26.21)		
2	86 (0.20)	0 (0.0)	28 (0.18)	1 (0.28)	85 (0.20)		
1+2	31,539 (73.74)	1,160 (93.40)	13,258 (86.74)	333 (91.99)	31,206 (73.59)		

Note. *Abbreviations:* COVID-19 = Coronavirus disease 2019; HOSP = COVID-19 hospitalization; POS = COVID-19 positivity; SD = Standard Deviation; WHI = Women's Health Initiative; WHI-CT = Women's Health Initiative Clinical Trial; WHI-OS = Women's Health Initiative Observational Study.

[a] P values are based on independent samples t-tests or Chi-square tests.

Table 3.

Bivariate associations of COVID-19 outcomes with BMI, WC and biomarkers of glucose homeostasis [a]

	Total	COVID-19 Positivity		COVID-19 hospitalization	
		Yes	No	Yes	No
	N (%)	N (%)	N (%)	N (%)	N (%)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)
SAMPLE 1:		**N=16,526**		**N=42,770**	
Total	**42,770**	**1,242**	**15,284**	**362**	**42,408**
BMI [kg/m^2]:					
Mean (SD)	27.20 (5.50)	27.90 (5.50)	27.30 (5.50)	28.90 (5.30)	27.20 (5.50)
		P<0.0001		*P<0.0001*	
< 25.0 [underweight / normal weight]	17,160 (40.12)	438 (35.27)	6,067 (39.70)	98 (27.07)	17,062 (40.23)
25.0–29.9 [overweight]	15,007 (35.09)	427 (34.38)	5,371 (35.14)	134 (37.02)	14,873 (35.07)
≥30 [obese]	10,603 (24.79)	377 (30.35)	3,846 (25.16)	130 (35.91)	10,473 (24.70)
		P=0.0001		*P<0.0001*	
WC [cm]:					
Mean (SD)	83.90 (12.80)	85.80 (12.90)	84.10 (12.90)	88.70 (12.80)	83.90 (12.80)
		P<0.0001		*P<0.0001*	
≤88 [Normal]	29,162 (68.18)	749 (60.31)	10,361 (67.79)	182 (50.28)	28,980 (68.34)
> 88 [High]	13,608 (31.82)	493 (39.69)	4,923 (32.21)	180 (49.72)	13,428 (31.66)
		P<0.0001		*P<0.0001*	
SAMPLE 2:		**N=759**		**N=1,896**	
Total	**1,896**	**57**	**702**	**23**	**1,873**
Glucose,	88.00	90.00	88.00	94.00	88.00
Median (IQR) [mg/dl]	(67.00, 97.00)	(80.00, 106.00)	(62.00, 97.00)	(82.00, 110.00)	(67.00, 97.00)
		P=0.08		P=0.08	
Insulin,	12.10	14.10	12.60	17.00	12.00
Median (IQR) [μIU/ml]	(7.60, 29.10)	(8.20, 37.00)	(7.70, 30.10)	(11.90, 32.70)	(7.60, 29.00)
		P=0.5		P=0.06	
HOMA-IR,	2.37	3.20	2.50	3.30	2.40
Median (IQR)	(1.52, 4.17)	(1.70, 5.50)	(1.50, 4.30)	(2.40, 5.30)	(1.50, 4.10)
		P=0.1		*P=0.009*	
HOMA-IR > 2.5, %	47.84%	63.16%	49.86%	73.91%	47.52%
		P=0.05		*P=0.02*	
HOMA-β,	−14.60	−2.30	−12.50	3.60	−14.90
Median (IQR)	(−32.10, 297.00)	(−31.00, 297.00)	(−30.90, 297.00)	(−20.3, 297.00)	(−32.2, 297.00)
		P=0.9		P=0.23	
QUICKI,	0.10	0.090	0.10	0.090	0.10
Median (IQR)	(0.09, 0.11)	(0.08, 0.10)	(0.09, 0.10)	(0.09, 0.10)	(0.09, 0.10)
		P=0.1		*P=0.009*	
TyG,	6.64	6.70	6.60	6.80	6.60

	Total	COVID-19 Positivity		COVID-19 hospitalization	
		Yes	No	Yes	No
	N (%)	N (%)	N (%)	N (%)	N (%)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)
Median (IQR)	(6.28, 6.93)	(6.50, 6.90)	(6.30, 6.90)	(6.50, 7.20)	(6.30, 6.90)
		0.07		*P=0.04*	

Note. *Abbreviations:* BMI = Body mass index; COVID-19 = Coronavirus disease 2019; HOMA-IR = Homeostatic Model Assessment for Insulin Resistance; HOMA-β = Homeostasis Model Assessment for β-cell function; IQR=Interquartile range; QUICKI = Quantitative Insulin-sensitivity Check Index; SD = Standard Deviation; TyG = Triglyceride-glucose index; WC = Waist circumference

[a]P values are based on independent samples t-tests and Chi-square tests for BMI and WC and on Wilcoxon's rank sum test for biomarkers of glucose homeostasis.

Table 4.

Logistic regression models for BMI, WC and biomarkers of glucose homeostasis as predictors of COVID-19 outcomes

	COVID-19 positivity		COVID-19 hospitalization	
	n	**OR (95% CI)**	**n**	**OR (95% CI)**
Model I: [a]				
BMI – Continuous [kg/m^2]	16,526	*1.02 (1.01, 1.03)*	42,770	*1.04 (1.02, 1.06)*
WC – Continuous [cm]	16,526	*1.01 (1.00, 1.01)*	42,770	*1.02 (1.01, 1.03)*
BMI – Categorical [kg/m^2]	16,526		42,770	
< 25.0 [underweight/normal weight]		Ref.		Ref.
25.0–29.9 [overweight]		1.07 (0.93, 1.23)		*1.50 (1.16, 1.95)*
≥30 [obese]		*1.28 (1.11, 1.49)*		*1.95 (1.49, 2.56)*
WC – Categorical [cm]	16,526		42,770	
≤88 [normal]		Ref.		Ref.
> 88 [High]		*1.33 (1.17, 1.50)*		*1.99 (1.62, 2.46)*
Glucose [mg/dl]	759	*1.01 (1.00, 1.01)*	1,896	1.00 (0.99, 1.01)
Insulin [μIU/ml]	759	1.00 (0.99, 1.01)	1,896	0.99 (0.96, 1.01)
HOMA-IR	759	1.01 (0.99, 1.02)	1,896	0.99 (0.96, 1.03)
HOMA-IR > 2.5	759	1.73 (0.98, 3.05)	1,896	*2.77 (1.07, 7.16)*
HOMA-β	759	0.99 (0.99, 1.00)	1,896	1.00 (0.99, 1.00)
QUICKI	759	--	1,896	--
TyG	759	*1.62 (1.02, 2.57)*	1,896	*2.44 (1.11, 5.36)*
Model II: [b]				
BMI – Continuous [kg/m^2]	16,526	*1.01 (1.00, 1.02)*	42,770	*1.03 (1.01, 1.05)*
WC – Continuous [cm]	16,526	*1.01 (1.00, 1.01)*	42,770	*1.02 (1.01, 1.03)*
BMI – Categorical [kg/m^2]	16,526		42,770	
< 25.0 [underweight/normal weight]		Ref.		Ref.
25.0–29.9 [overweight]		1.00 (0.87, 1.16)		*1.34 (1.03, 1.75)*
≥30 [obese]		1.16 (0.99, 1.36)		*1.63 (1.22, 2.17)*
WC – Categorical [cm]	16,526		42,770	
≤88 [normal]		Ref.		Ref.
> 88 [High]		*1.27 (1.12, 1.45)*		*1.78 (1.42, 2.23)*
Glucose [mg/dl]	759	*1.01 (1.00, 1.02)*	1,896	1.01 (0.99, 1.02)
Insulin [μIU/ml]	759	1.00 (0.99, 1.01)	1,896	0.99 (0.98, 1.01)
HOMA-IR	759	1.01 (0.99, 1.02)	1,896	0.99 (0.95, 1.04)
HOMA-IR > 2.5	759	1.51 (0.81, 2.83)	1,896	2.48 (0.91, 6.76)
HOMA-β	759	0.99 (0.99, 1.00)	1,896	0.99 (0.99, 1.00)
QUICKI	759	--	1,896	--
TyG	759	*1.80 (1.03, 3.15)*	1,896	*3.92 (1.42, 10.83)*

Note. *Abbreviations:* BMI = Body mass index; CI = Confidence Interval; COVID-19 = Coronavirus disease 2019; HOMA-IR=Homeostatic Model Assessment for Insulin Resistance; HOMA-β=Homeostasis Model Assessment for β-cell function; OR=Odds ratio; QUICKI=Quantitative Insulin-sensitivity Check Index; TyG=Triglyceride-Glucose index; WC=Waist circumference.

[a]Model I, Adjusted for sample selectivity only

[b]Model II, Adjusted for WHI component, age (in years), race (Black, White, Asian, Other), ethnicity (Hispanic, non-Hispanic, unknown/not reported), education (Less than High School, High School, Some College, Completed College or Higher), household income (< $20,000, $20,000-$49,999, $50,000-$99,999, ≥$100,000), marital status (Married/Partnered, Single, Divorced, Widowed), smoking status (Never Smoker, Past Smoker, Current Smoker), alcohol consumption (Non-Drinker, Former Drinker, < 1 drink/week, ≥ 1 drink/week), physical activity (Met-hours/week)), cardiovascular disease [Yes, No], hypertension [Yes, No], hyperlipidemia [Yes, No], diabetes [Yes, No]) and self-rated health (Excellent/Very Good/Good, Fair/Poor)) as well as sample selectivity.

Table 5.

Effects of each biomarker of glucose homeostasis on the association of BMI and WC with COVID-19 outcomes, controlling for socio-demographic, lifestyle and health characteristics [a, b]

	BMI [kg/m^2]				WC [cm]			
	POS (n=759)		HOSP (n=1,896)		POS (n=759)		HOSP (n=1,896)	
Two-way decomposition (based on *paramed*)[c]								
Natural Direct Effect:	**Est (SE)**	**P**	**Est (SE)**	**P**	**Est (SE)**	**P**	**Est (SE)**	**p**
Glucose [mg/dl]	0.92 (0.17)	0.62	0.95 (0.22)	0.83	1.01 (0.21)	0.95	1.18 (0.21)	0.44
Insulin [μIU/ml]	0.99 (0.15)	0.96	1.00 (0.21)	0.94	1.09 (0.17)	0.63	1.24 (0.21)	0.32
HOMA-IR	0.92 (0.21)	0.71	0.99 (0.23)	0.99	0.99 (0.24)	0.98	1.23 (0.25)	0.39
HOMA-β	1.00 (0.15)	0.99	1.02 (0.21)	0.91	1.08 (0.16)	0.65	1.24 (0.20)	0.29
QUICKI	0.94 (0.22)	0.77	0.74 (0.51)	0.56	1.00 (0.24)	0.99	0.94 (0.48)	0.89
TyG	0.95 (0.16)	0.74	0.90 (0.29)	0.72	1.00 (0.18)	0.97	1.08 (0.24)	0.76
Natural Indirect Effect:	**Est (SE)**	**P**	**Est (SE)**	**P**	**Est (SE)**	**P**	**Est (SE)**	**P**
Glucose [mg/dl]	1.04 (0.03)	0.15	1.02 (0.045)	0.54	1.02 (0.04)	0.54	1.02 (0.05)	0.67
Insulin [μIU/ml]	1.02 (0.03)	0.42	0.97 (0.064)	0.67	1.01 (0.38)	0.79	0.95 (0.07)	0.47
HOMA-IR	1.03 (0.02)	0.11	0.98 (0.07)	0.79	0.98 (0.05)	0.81	0.95 (0.08)	0.48
HOMA-β	0.99 (0.01)	0.51	0.98 (0.02)	0.35	0.99 (0.01)	0.53	0.98 (0.02)	0.28
QUICKI	1.04 (0.08)	0.61	1.12 (0.14)	0.43	1.04 (0.08)	0.66	1.09 (0.13)	0.51
TyG	1.04 (0.05)	0.34	*1.21 (0.07)*	*0.010*	1.05 (0.06)	*0.42*	*1.24 (0.09)*	*0.017*
Four-way decomposition (based on *med4way*)								
Total Effect:	**Est (SE)**	**P**	**Est (SE)**	**p**	**Est (SE)**	**p**	**Est (SE)**	**p**
Glucose [mg/dl]	−0.04 (0.15)	0.80	−0.020 (0.21)	0.92	0.04 (0.18)	0.83	0.20 (0.25)	0.42
Insulin [μIU/ml]	0.01 (0.15)	0.93	−0.009 (0.21)	0.96	0.09 (0.18)	0.60	0.17 (0.24)	0.47
HOMA-IR	−0.06 (0.19)	0.77	−0.02 (0.21)	0.93	−0.03 (0.21)	0.89	0.16 (0.26)	0.53
HOMA-β	0.002 (0.15)	0.98	0.009 (0.21)	0.96	0.08 (0.17)	0.66	0.21 (0.24)	0.37
QUICKI	−0.08 (0.22)	0.72	−0.17 (0.31)	0.59	−0.02 (0.25)	0.93	0.024 (0.35)	0.94
TyG	0.0006 (0.15)	0.99	0.08 (0.25)	0.72	0.08 (0.18)	0.66	0.32 (0.29)	0.26
Pure Indirect Effect:	**Est (SE)**	**P**	**Est (SE)**	**p**	**Est (SE)**	**P**	**Est (SE)**	**P**
Glucose [mg/dl]	*0.11 (0.053)*	*0.038*	0.038 (0.06)	0.49	*0.18 (0.08)*	*0.020*	0.038 (0.068)	0.57
Insulin [μIU/ml]	0.037 (0.046)	0.79	0.012 (0.083)	0.88	0.07 (0.05)	0.14	0.089 (0.095)	0.71
HOMA-IR	0.073 (0.065)	0.26	0.0078 (0.12)	0.94	0.10 (0.06)	0.09	0.044 (0.098)	0.65
HOMA-β	−0.0037 (0.0075)	0.62	−0.0052 (0.013)	0.68	−0.0062 (0.009)	0.51	−0.0046 (0.015)	0.75
QUICKI	0.12 (0.10)	0.22	0.22 (0.16)	0.17	0.18 (0.15)	0.22	0.22 (0.19)	0.22
TyG	0.09 (0.05)	0.08	0.13 (0.071)	0.062	0.13 (0.076)	0.08	0.16 (0.09)	0.10
Reference Interaction:	**Est (SE)**	**P**	**Est (SE)**	**P**	**Est (SE)**	**P**	**Est (SE)**	**p**
Glucose [mg/dl]	−0.045 (0.14)	0.74	−0.0036 (0.018)	0.84	−0.079 (0.07)	0.26	−0.0032 (0.016)	0.84
Insulin [μIU/ml]	−0.0046 (0.017)	0.79	0.014 (0.036)	0.69	−0.018 (0.03)	0.54	0.034 (0.081)	0.68
HOMA-IR	−0.060 (0.11)	0.59	0.010 (0.05)	0.83	−0.097 (0.11)	0.39	0.042 (0.15)	0.77
HOMA-β	−0.0074 (0.016)	0.65	0.035 (0.065)	0.58	−0.01 (0.019)	0.61	0.055 (0.085)	0.52
QUICKI	−0.13 (0.20)	0.49	−0.23 (0.29)	0.43	−0.14 (0.21)	0.49	−0.20 (0.26)	0.43

	BMI [kg/m^2]				WC [cm]			
	POS (n=759)		**HOSP (n=1,896)**		**POS (n=759)**		**HOSP (n=1,896)**	
TyG	−.021 (0.03)	0.49	0.11 (0.11)	0.34	−0.021 (0.034)	0.54	0.10 (0.10)	0.32
Mediated interaction:	**Est (SE)**	**P**	**Est (SE)**	**P**	**Est (SE)**	**P**	**Est (SE)**	**p**
Glucose [mg/dl]	−0.062 (0.042)	0.15	−0.012 (0.042)	0.77	*−0.14 (0.07)*	*0.041*	−0.012 (0.052)	0.82
Insulin [μIU/ml]	−0.014 (0.036)	0.69	−0.039 (0.066)	0.55	−0.06 (0.05)	0.20	−0.098 (0.084)	0.24
HOMA-IR	−0.046 (0.060)	0.44	−0.025 (0.089)	0.77	−0.11 (0.075)	0.13	−0.11 (0.13)	0.39
HOMA-β	0.0012 (0.0036)	0.72	−0.010 (0.013)	0.43	0.0023 (0.0057)	0.68	−0.019 (.017)	0.26
QUICKI	−0.082 (0.09)	0.37	−0.14 (0.15)	0.37	−0.13 (0.13)	0.31	−0.14 (0.15)	0.35
TyG	−0.044 (0.044)	0.33	0.056 (0.073)	0.44	−0.074 (0.068)	0.27	−0.099 (0.096)	0.31
Controlled direct effect:	**Est (SE)**	**P**	**Est (SE)**	**P**	**Est (SE)**	**P**	**Est (SE)**	**p**
Glucose [mg/dl]	−0.045 (0.14)	0.74	−0.043 (0.21)	0.83	0.085 (0.17)	0.62	0.18 (0.25)	0.48
Insulin [μIU/ml]	−0.0037 (0.15)	0.98	0.0039 (0.22)	0.98	0.09 (0.18)	0.58	0.20 (0.24)	0.40
HOMA-IR	−0.022 (0.14)	0.87	−.010 (0.22)	0.96	0.079 (0.16)	0.63	0.19 (0.25)	0.44
HOMA-β	0.012 (0.15)	0.94	−0.010 (0.20)	0.96	0.091 (0.17)	0.59	0.18 (0.23)	0.44
QUICKI	0.0098 (0.14)	0.95	0.023 (0.19)	0.90	0.077 (0.17)	0.64	0.14 (0.20)	0.49
TyG	−0.026 (0.15)	0.86	−0.20 (0.18)	0.24	0.039 (0.17)	0.82	−0.028 (0.22)	0.89

Note. *Abbreviations:* BMI=Body mass index; CI=Confidence Interval; COVID-19=Coronavirus disease 2019; HOMA-IR=Homeostatic Model Assessment for Insulin Resistance; HOMA-β=Homeostasis Model Assessment for β-cell function; HOSP=COVID-19 hospitalization; QUICKI=Quantitative insulin-sensitivity check index; OR=Odds ratio; POS=COVID-19 positivity; TyG=Triglyceride-Glucose index; WC=Waist circumference.

[a]Covariates adjusted for in the causal mediation analyses are the following: WHI component, age (years) [z-transformed], race (White, non-White), education (Completed College or higher, Less than College), household income (<$50000, ≥$50000), alcohol consumption (Current drinker, Current non-drinker), physical activity (Met-hours/week) [z-transformed], hypertension (Yes, No), hyperlipidemia (Yes, No), sample selectivity

[b]BMI, WC and biomarkers of glucose homeostasis were z-transformed

[c]The paramed command also displays conditional direct effects and marginal total effects, not shown in this table.