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Racial and ethnic disparities of type 2 diabetes in the United States: examination through social determinants of health, exercise, and visceral fat

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Racial and ethnic disparities of type 2 diabetes in the United States: examination through social determinants of health, exercise, and visceral fat

A dissertation submitted in partial satisfaction of the

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by

Tong Xia

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ABSTRACT OF THE DISSERTATION

Racial and ethnic disparities of type 2 diabetes in the United States: examination through social determinants of health, exercise, and visceral fat

by

Tong Xia

Doctor of Philosophy in Epidemiology

University of California, Los Angeles, 2024

Professor Liwei Chen, Co-Chair

Professor Roch Arnaud Kibsa Nianogo, Co-Chair

Diabetes is a prevalent chronic disease associated with elevated risks of cardiovascular disease (CVD) and premature mortality. In 2021, 38.4 million individuals in the United States (US), accounting for 11.6% of the population, had diabetes, with 95% of them having type 2 diabetes (T2D). T2D is a multifaceted metabolic disorder characterized by both impaired insulin action and secretion. Projections indicate that the number of people with T2D in the US will rise to 48 million by 2050. Meanwhile, racial disparities of T2D in the US have been well documented and are persistent over time. National Diabetes Statistics Report indicated that, in 2017–2018, the age-adjusted incidence of diagnosed T2D was highest among Hispanic (9.7 per 1000 persons), followed by non-Hispanic Black (8.2 per 1000 persons), non-Hispanic Asian (7.4 per 1000 persons) and non-Hispanic White (5.0 per 1000 persons) populations. These groups also

experience more severe complications and higher mortality rates related to T2D. Thus, it is crucial to find determinants of T2D contributing to the racial disparities.

Various risk factors contribute to the development of T2D and many of them are modifiable such as socioeconomic status (SES), behaviors (e.g., exercise), and obesity. Factors SES such as education and income, which impacts downstream behaviors and obesity, may be the upstream cause of developing T2D and its disparities among racial and ethnic groups. Meanwhile, associations of personal and neighborhood SES with T2D are deeply intertwined. A composite measurement encompassing personal and neighborhood, social and environmental conditions, which is social determinants of health (SDOH), is essential for comprehensively understanding how interconnected social conditions relate to T2D risk. Meanwhile, racial and ethnic minorities may experience worse SDOH than Whites due to systemic racism. However, up to now, no studies have yet examined the associations between SDOH integrating several domains and T2D. In addition, it is well-known that exercise could reduce T2D risk. Obesity, particularly the accumulation of visceral fat, has been hypothesized to be a primary risk factor for T2D. Meanwhile, compared to Whites, some racial and ethnic minorities (e.g., Hispanics, Blacks and Asians) have lower levels of exercise, and some minorities (e.g., Hispanics and South Asians) have higher levels of visceral fat, which may explain the racial disparities in T2D. Additionally, there are sex differences in visceral fat. Nonetheless, no studies have examined to what extent the association of race and ethnicity with T2D is mediated by exercise, or visceral fat. Thus, the dissertation investigated SDOH integrating several domains to determine associations between comprehensively assessed social disadvantages and T2D as well as if the associations varied by race and ethnicity (Objective 1). In addition, the dissertation examined whether and to what extent the association of race and ethnicity with T2D can be explained by

exercise (Objective 2), and examined to what extent the association of race and ethnicity with T2D can be explained by visceral fat within sex subgroups (Objective 3).

To address these objectives, this dissertation used the data from the Multi-Ethnic Study of Atherosclerosis (MESA), a prospective longitudinal cohort study including multiple racial and ethnic groups. We assessed SDOH comprehensively from several domains and applied modern casual mediation analysis to examine mediation effects of exercise and visceral fat. We found that disadvantaged SDOH was associated with increased T2D risk in a dose-response manner in all participants, and the associations existed in Whites and Hispanics when stratified by race and ethnicity. In addition, exercise accounted for one-tenth of racial differences in T2D comparing Hispanics or Chinese to Whites. Furthermore, visceral fat explained one-fifth of the racial disparities in T2D comparing Hispanic females to White females. As T2D is largely preventable, these findings highlight modifiable pathways that could inform future interventions for higher T2D risks among racial and ethnic minorities and promoting health equity. Specifically, prioritizing resources for populations with social disadvantages may reduce the T2D burdens, particularly among at-risk Hispanics to decrease T2D disparities. Additionally, interventions on increasing exercise are needed for each racial and ethnic group, and especially important among Hispanics and Chinese to lower their higher T2D risks. Furthermore, understanding the role of visceral fat in contributing to racial disparities in T2D among Hispanic females enhances our comprehension of the biological factor at play.

The dissertation of Tong Xia is approved.

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4. **Xia, T**., Lopes, S., Chen, L., Roth, R., Zinzow, H., Jones, K., ... & Jindal, M. (2022). A Feasibility Study on Low-dose Mindfulness-based Stress Reduction Intervention Among Prediabetes and Diabetes Patients. Complementary Therapies in Medicine, 102810.

5. **Xia, T**., Zhao, F. & Nianogo, R.A. (2022). Interventions in hypertension: systematic review and meta-analysis of natural and quasi-experiments. Clinical Hypertension, 28, 13.

6. Chen, L., Li, J., **Xia, T**., Matthews, T. A., Tseng, T. S., Shi, L., ... & Su, D. (2021). Changes of Exercise, Screen Time, Fast Food Consumption, Alcohol, and Cigarette Smoking during the COVID-19 Pandemic among Adults in the United States. Nutrients, 13(10), 3359.

7. Liu, X., Chen, L., Fei, Z., Zhao, S. K., Zhu, Y., **Xia, T**., ... & Zhang, C. (2022). Physical activity and individual plasma phospholipid SFAs in pregnancy: a longitudinal study in a multiracial/multiethnic cohort in the United States. The American Journal of Clinical Nutrition, 116(6), 1729-1737.

8. Chen, L., Zhu, Y., Fei, Z., Hinkle, S. N., **Xia, T**., Liu, X., ... & Zhang, C. (2020). Plasma Phospholipid n-3/n-6 Polyunsaturated Fatty Acids and Desaturase Activities in Relation to Moderate-to-Vigorous Physical Activity through Pregnancy: A Longitudinal Study within the NICHD Fetal Growth Studies. Nutrients, 12(11), 3544.

9. Zhang, Y., Francis, E. C., **Xia, T**., Kemper, K., Williams, J., & Chen, L. (2020). Adherence to DASH dietary pattern is inversely associated with osteoarthritis in Americans. International Journal of Food Sciences and Nutrition, 1-7.

Manuscripts in preparation

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3. **Xia, T**., Nianogo, R.A., Yu, Q., Horwich, T., Srikanthan, P., Inoue, K., Allison, M., Zhang, Z., Watson, K.E., & Chen, L. Racial and ethnic disparities of type 2 diabetes in the United States: the pathways through exercise in the Multi-Ethnic Study of Atherosclerosis. Submitted to American Journal of Public Health.
4. **Xia, T**., Nianogo, R.A., Yu, Q., Horwich, T., Srikanthan, P., Inoue, K., Allison, M., Zhang, Z., Szklo, M., Watson, K.E., & Chen, L. Racial and ethnic disparities of type 2 diabetes: the pathways through visceral fat in the Multi-Ethnic Study of Atherosclerosis. Prepare to submit to Diabetes Care.

Oral presentation

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1. Chapter one: Introduction

1.1. Overview

Diabetes is a major chronic disease, affecting 38.4 million individuals in the United States (US) in 2021. This disease heightens the risk of cardiovascular disease (CVD), kidney and nerve disease, disability and impaired quality of life, and premature mortality[1,2]. Projections indicate that by 2050, one in three Americans will have diabetes, presenting substantial healthcare costs[3]. In 2022, the national expenditure on diabetes treatment reached $412.9 billion[4]. In addition, diabetes ranked as the eighth leading cause of death in the US in 2021[2,5]. Among people having diabetes, 95% have type 2 diabetes (T2D), which is characterized by insulin resistance and impairment of β-cell function[1,2]. Meanwhile, racial and ethnic disparities in T2D persist in the US[6–9]. According to the National Diabetes Statistics Report in 2017–2018, the age-adjusted incidence of diagnosed T2D was highest among Hispanic (9.7 per 1000 persons), followed by non-Hispanic Black (8.2 per 1000 persons), non-Hispanic Asian (7.4 per 1000 persons) and non-Hispanic White (5.0 per 1000 persons) populations[1]. Thus, identifying T2D risk factors contributing to these disparities is crucial to promoting health equity.

Both non-modifiable (e.g., aging, genetics) and modifiable [e.g., socioeconomic status (SES), psychological stress, behaviors and obesity (particularly visceral fat)] risk factors play roles in the development of T2D[10–16]. Our focus is on modifiable factors to provide implications for interventions on the elevated risk of T2D among racial and ethnic minorities. Systemic racism is a fundamental cause of racial health disparities in T2D, perpetuating discrimination and influencing policymaking[13,17–21]. Interlinked and mutually reinforcing, systemic racism and public policy significantly lead to minorities' undesired neighborhood environments, social

factors, and SES (e.g., neighborhood and physical environment influenced by racial residential segregation)[13,17–21].

The comprehensive experience of societal disadvantage, stemming from structural or systems-level root inequities, may be one important contributor of racial disparities in T2D[13,21,22]. Previous studies that assessed personal SES[23–27] and neighborhood environmental and social factors[28–31] with T2D separately failed to capture the cumulative social disadvantages individuals experienced comprehensively, as these personal SES and neighborhood factors are likely intertwined[13,22]. Thus, a composite measure encompassing personal, neighborhood, social, and environmental conditions, collectively referred to as social determinants of health (SDOH)[13,22], is essential for a thorough understanding of how interconnected social conditions relate to T2D risk. Although no studies have examined the relationship between SDOH and T2D, research assessing CVD risk through a composite of SDOH factors found it provide a more comprehensive understanding than evaluating SDOH elements individually and exposure to a higher SDOH score was associated with elevated CVD risk[32,33]. These studies support examining SDOH in relation to T2D to incorporate SDOH into a T2D prevention framework, thereby identifying people facing unfavorable social and environmental conditions for interventions. Thus, we aimed to examine associations of the SDOH, a comprehensive measurement of social profile, with T2D in the US. Given that racial and ethnic minorities may experience higher undesired SDOH[13,22,34,35] and have higher T2D risk[1,2,7], we also examined if the above associations varied by racial and ethnic groups (Objective 1), providing insights for prioritizing resources to vulnerable groups to enhance health equity.

Persons subjected to higher levels of undesired SDOH are likely to perceive higher stress levels[36,37]. Psychological stress may elevate the risk of T2D through the promotion of unhealthy

behaviors (e.g., increased smoking, poor diet, reduced exercise), as well as through impacts on obesity and fat distribution[15,16,38]. Meanwhile, racial and ethnic minorities, who are often exposed to more stressors (e.g., higher levels of disadvantaged SDOH), tend to experience higher psychological stress compared to White population[39–45]. Thus, psychological stress may be a contributing factor to the increased risk of T2D among minorities. Whereas, modifiable lifestyles (e.g., diet and exercise) are more well-recognized and important risk factors for T2D.

Personas facing more challenging SDOH and elevated stress levels are prone to adopting more undesired behaviors. Unhealthy lifestyles, such as smoking[46–49] and poor diet[50–53], are risk factors for T2D through their impact on obesity and fat distribution. Meanwhile, racial and ethnic minorities (e.g., Native Americans and Blacks) may have a higher prevalence of smoking[54,55] and poorer dietary quality[56–60] compared to Whites. Thus, smoking and diet are considered as mediators for racial and ethnic differences in T2D, however, even after controlling for smoking and diet, the racial disparities still existed[56].

In addition to smoking and diet, exercise is a recognized modifiable factor for reducingT2D risk[61,62], by decreasing obesity and promoting favorable fat distribution. Meanwhile, previous studies showed that minorities tended to engage in less exercise than Whites[63–67]. Thus, exercise may explain the racial and ethnic difference in T2D. However, up to now, most studies relied on qualitative assessments without quantifying the mediation effect of exercise[34,35,68,69], or adjusted for multiple mediators (e.g., alcohol intake, smoking, and exercise) simultaneously, which obscuring the mediation contribution of exercise[63,64]. Thus, we aimed to examine whether exercise is a potential mediator of racial and ethnic (Hispanic, Black, Asian vs. White) differences in T2D and to quantify the extent to which these disparities are mediated by

exercise, using a multi-racial and ethnic cohort study with longitudinal measures of exercise in the US (Objective 2).

Personas with more adverse SDOH, greater stress, and unhealthy behaviors are likely to exhibit higher obesity and altered fat distribution. Obesity, particularly the accumulation of visceral fat (i.e., fat located around the vital organs), has been hypothesized as the most critical risk factor for T2D[11,70,71], which may be due to high lipolysis rate of visceral fat increasing the flux of free fatty acid (FFA) to the liver by the portal circulation[72] and visceral fat is more metabolically active, with adipocytes releasing adipocytokines[73–75] that link visceral fat to insulin resistance, leading to the development of T2D. Meanwhile, previous studies found that some racial and ethnic minorities (e.g., Hispanics[76–79] and South Asians[80,81]) have higher levels of visceral fat than White individuals. However, no studies have examined to what degree racial differences in T2D are explained by visceral fat. In addition, there are sex differences in visceral fat[82–84] and there may be sex and race interactions in visceral fat[79,85–87]. Therefore, we aimed to examine whether and to which degree the association of race and ethnicity (Hispanic, Black, Asian vs. White) with T2D can be explained by visceral fat within sex subgroups, using data from a cohort study including multiple racial and ethnic groups (Objective 3).

In summary, racial disparities in T2D represent a significant public health issue in the US and understanding the determinants of these disparities is crucial. Although studies indicated personal and neighborhood SES associated with T2D, no studies examined the comprehensive SDOH with T2D, so it is important to investigate the relationship between SDOH and T2D to provide insights for incorporating SDOH into T2D screening, thereby prioritizing resources for vulnerable groups affected by social disadvantages. Additionally, the mediation effects of exercise and visceral fat on racial disparities in T2D have not been quantified. It is critical to

understand to which degree the association of race and ethnicity with T2D can be explained by exercise and visceral fat. This knowledge can inform interventions targeting exercise and improve understanding of the biological factor, visceral fat, in contributing to racial disparities in T2D.

1.2. Conceptual framework

We illustrated the conceptual framework for determinants of racial and ethnic disparities of T2D in **Figure 1.1**, adapted from the proximal-distal framework[35,88–90]. The framework outlines multiple pathways between race and ethnicity and T2D. Systemic racism is a fundamental cause of racial health disparities in T2D, which may influence policymaking. In addition, systemic racism and public policy interlink and mutually reinforce, leading to minorities' disadvantaged SDOH[13,17–21]. The associations between SDOH and T2D need to be examined. Psychological factors, behavioral factors (e.g., exercise), obesity and fat distribution (e.g., visceral fat) are associated with development of T2D. Meanwhile, there are also racial differences in these risk factors, which may contribute to the racial disparities of T2D. This dissertation aimed to examine associations between SDOH and T2D and whether the associations varied across race and ethnicity subgroups (Objective 1), as well as whether and to what degree the association of race and ethnicity with T2D was mediated by exercise (Objective 2), and visceral fat (Objective 3).

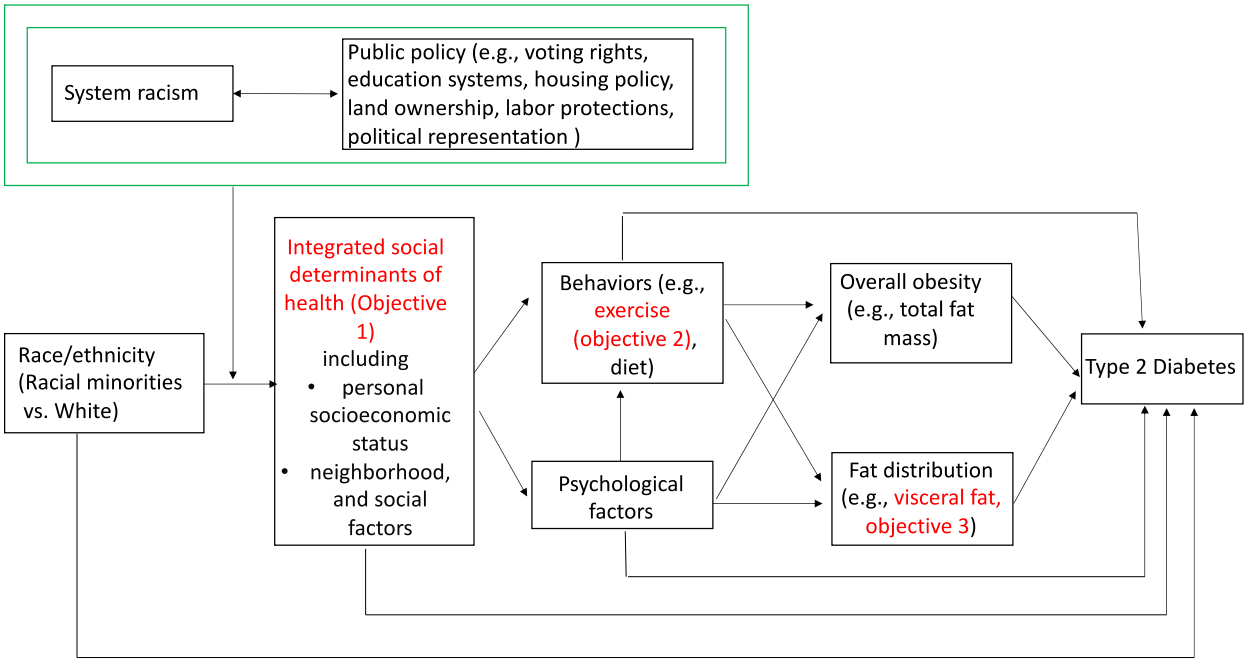


Figure 1.1. Conceptual framework for determinants of racial and ethnic disparities in type 2 diabetes

2. Chapter two: Literature review and research gaps

2.1. Epidemiology of type 2 diabetes

2.1.1. Prevalence, incidence, and trends

Diabetes is a prevalent chronic disease that imposes significant burdens and challenges on patients and healthcare systems[1,2]. It is associated with an elevated risk of CVD and premature mortality[1,2]. According to the Center for Disease Control and Prevention (CDC), there has been a long-term trend of increased age-adjusted diabetes prevalence, rising from 10.3% to 13.2% between 2001 and 2020[91]. In the US, 38.4 million people (11.6% of the Americans) were living with diabetes in 2021, with 1.2 million new cases diagnosed each year[1,2]. The age-adjusted incidence of diabetes increased from 6.5 to 8.5 cases per 1,000 adults from 2000 to 2009, followed by a decline to 5.3 cases per 1,000 adults from 2009 to 2021, and a slight increase to 6.4 cases per 1,000 adults from 2021 to 2022[92]. The decline in incidence of diabetes has previously been reported[93] and may reflect prevention of diabetes efforts. Moreover, diabetes ranked as the eighth leading cause of death in the US in 2021, with annual deaths expected to rise from 146,604 to 385,800 between 2015 and 2030[2,5]. In 2022, the total cost of diagnosed diabetes in the US was $412.9 billion, representing a 26.3% increase since 2017[1,2]. T2D accounts for about 95% of all diabetes cases[2]. In addition, the case number of T2D is rapidly increasing, with projections indicating that the number of cases will rise to 48 million by 2050[94]. Furthermore, persistent racial disparities in T2D have long been recognized in the US[1,7].

2.1.2. Racial and ethnic disparities of type 2 diabetes in the United States

Persistent racial and ethnic disparities in T2D are a significant public health concern in the US. Minority groups, such as Hispanics, Blacks, and Asians, exhibit a higher risk and prevalence of T2D compared to Whites[1,8,91,92,95]. For instance, CDC reported in 2022 that the age-adjusted

incidence rate of diagnosed T2D was the highest among Blacks (10.1 per 1,000 persons), followed by Hispanics (9.0 per 1,000 persons), Asians (8.4 per 1,000 persons) and Whites (5.2 per 1,000 persons)[92]. Data from the National Health and Nutrition Examination Survey (NHANES) for the years 2017-2020 revealed that the age- adjusted prevalence of diabetes was 17.6%, 16.8%, 16.4%, and 11.2% among Hispanics, Blacks, Asians, and Whites, respectively[91].

Based on the evidence presented, identifying the determinants of T2D that contribute to racial and ethnic disparities is essential. The next section reviewed the risk factors for T2D and the underlying causes of these disparities in the US.

2.1.3. Risk factors for type 2 diabetes and their roles in disparities

The development of T2D is influenced by both non-modifiable factors (e.g., age, genetics) and modifiable factors [e.g., SES, psychological stress, behaviors, obesity, and fat distribution (particularly visceral fat)][10–16]. Differences in some modifiable risk factors among racial groups may explain the disparities in T2D[22,34,35,56,63,64,68,96–99]. Therefore, this section mainly focus on modifiable factors to give information for interventions on the excess risk of T2D among racial and ethnic minorities.

Non-modifiable factors, aging and genetics

Aging is a recognized risk factor for T2D[96,100], with older adults (aged 65 and older) exhibiting a higher prevalence of T2D compared to younger individuals[12,101]. However, there are no racial differences in aging, and racial disparities in T2D persist even after controlling for age[1,8,9,56,63]. For instance, research involving postmenopausal women from the Women's Health Initiative (WHI) in the US revealed that, after adjusting for age, Blacks (HR: 2.40, 95% CI: 2.30-2.52), Hispanics (HR: 2.19, 95% CI: 2.05-2.35) and Asians (HR: 1.44, 95% CI: 1.30-1.59) still

exhibited higher risks of T2D compared to Whites[56]. Thus, aging is not considered as a contributor to racial difference in T2D.

Genetics play a role in T2D development, as demonstrated by numerous genome-wide association studies (GWAS)[102–105]. However, common genes related to T2D are similar across racial and ethnic groups[34,35,102,106–109]. For example, large GWAS studies identified T2D-associated genes (e.g., PPARG, CDKN2B, TCF7L2, KCNJ11, CDC123, THADA, IGF2BP2, CDKAL1, SLC30A8) in Whites that are also relevant for Hispanics, Blacks, and Asians[106,107].

Beyond non-modifiable factors, several modifiable risk factors for T2D warrant attention, which were illustrated as follows. Understanding these factors may give implications for interventions on the excess T2D risk observed in racial and ethnic minority groups.

The historical context of slavery, colonization, and genocide in the United States has led to the establishment of social, political, and economic systems that systematically afford advantages to white Americans while excluding other racial groups, exemplifying systemic racism[17–20]. Recent research suggests that systemic racism is a fundamental cause of racial health disparities[13,17–21]. Deeply embedded within systems, laws, and established cultural beliefs, values, and attitudes, systemic racism perpetuates discrimination throughout society, influencing policymaking (e.g., voting rights, education systems, housing policy, land ownership, labor protections, political representation). Moreover, systemic racism and public policy are interlinked and mutually reinforcing, significantly leading to minorities' undesired neighborhood environments, social factors, and SES[13,17–21].

2.1.3.1. Social determinants of health

Social determinants of health as a contributor for racial disparities in T2D

Previous studies have found personal SES (e.g., education and income)[23–27] and neighborhood environmental and social factors (e.g., such as the availability of exercise resources, educational level of neighborhood adults, and housing status)[28–31] were risk factors for T2D. In addition, research showed positive associations between neighborhood SES and T2D diminished after further controlling for personal SES[30,31], suggesting an interconnection between personal and neighborhood SES in relation to T2D risk[13,22]. So, only investigating these factors separately may fail to capture their cumulative or interactive effects, thus not reflecting the full scope of societal disadvantage. Therefore, a composite measurement including personal, neighborhood, social and environmental conditions, which is SDOH[13,22], is essential for a comprehensive understanding of how these interconnected social conditions influence T2D risk. The World Health Organization (WHO) defines SDOH as the conditions in which people live, work, and play, and the broader social structures and economic systems that shape these conditions of daily living[110].

To date, no studies have examined the associations between a comprehensive SDOH measure integrating several domains and T2D. Two studies—one cross sectional study using NHANES data among 10,276 US participants[27] and one cohort study involving 3,467 participants in Finland[31]—reported positive associations between cumulative personal sociodemographic variables[27] or cumulative neighborhood factors[31] and T2D. These studies did not, however, assess the combined influence of personal and neighborhood factors[27,31]. While comprehensive SDOH measures have not been specifically examined in relation to T2D, previous research has found positive associations between SDOH and both obesity and CVD[32,33,111,112], with higher SDOH scores linked to increased CVD risk[32,33]. Building on this body of work, we prospectively examined SDOH integrating several domains with T2D. Given

that racial and ethnic minorities often experience more adverse SDOH [13,22,34,35] and higher T2D risk[1,2,7], we also examined if the above associations varied across racial and ethnic groups (**Objective 1**). This would provide insights for incorporating SDOH into T2D prevention frameworks, targeting individuals in adverse social and environmental conditions with effective interventions.

Stress as a contributor for racial disparities in T2D

Individuals with higher adverse SDOH are likely to experience increased stress levels[36,37]. Psychological stress has been identified as a risk factor for T2D[15,16,38]. For instance, a review of longitudinal studies found a positive association between physiological stressors (e.g., stressful work or life events) and the risk of developing T2D[16]. Meanwhile, racial and ethnic minorities, who are often exposed to more stressors (e.g., higher level of disadvantaged SDOH), report greater psychological stress than White population[39–45]. For instance, one cross-sectional Chicago Community Adult Health Study (CCAHS) involving 3,105 adults found Blacks (7%) reported higher percentages of received high level of stressors than Whites (3%)[40]. The other cross-sectional study among 3,015 middle-aged women from the Study of Women's Health Across the Nation (SWAN) in the US found that the prevalence of very high perceived stress was higher among Hispanics (43.8%) compared to Whites (15.8%)[42]. Thus, psychological stress may be a potential contributor for minorities' higher risk of T2D. Although no studies examined stress as a mediator for racial differences in T2D, research found that stress partially explained racial differences in poor self-rated health[40]. For instance, the association between race and ethnicity (Black vs. White) and poor self-rated health decreased but persisted after adjusting for stress [estimate (SE): 0.13 (0.05)][40], based on a model that also accounted for age, gender,

language, education, and income. Nevertheless, modifiable lifestyles, such as smoking, diet, and exercise, remain more well-known and significant risk factors for T2D.

2.1.3.2. Lifestyles and exercise

Undesired lifestyles (e.g., smoking, unhealthy diet, and lack of exercise), contribute significantly to the development of T2D[34,46–49,108].

Smoking as a contributor for racial disparities in T2D

Smoking is as an independent risk factor for T2D[46–49]. A meta-analysis of 88 cohort studies involving 5,898,795 participants revealed that current smokers have a 37% higher risk of T2D compared to non-smokers, with a dose-response relationship observed between light, moderate, and heavy smoking and T2D[46]. Evidence from a Mendelian randomization study among 898,130 participants also indicated a causal relation between smoking and T2D[48]. Meanwhile, some racial and ethnic minorities, such as Blacks and Native Americans, have a higher prevalence of smoking compared to Whites[54,55]. Consequently, smoking may explain racial and ethnic minorities' higher T2D risk. However, smoking does not fully account for the disparities; racial differences in T2D persist even after controlling for smoking, suggesting that while smoking contributes to the disparities, it does not entirely eliminate them[56].

Diet as a contributor for racial disparities in T2D

Dietary intake plays a crucial role in influencing the risk of T2D. Various randomized controlled trials (RCTs) and cohort studies have demonstrated that adherence to healthy dietary patterns, such as the Mediterranean diet and Dietary Approaches to Stop Hypertension (DASH), as well as a high Alternative Healthy Eating Index (AHEI) score, can significantly reduce the risk of T2D[50–53]. Additionally, increased consumption of healthy foods like vegetables, fruits, whole grains, and fiber, coupled with reduced intake of processed red meat and sugar-sweetened

beverages, is associated with a lower risk of T2D[113–115]. Moreover, racial and ethnic minorities, such as Hispanics and Blacks, often exhibit lower adherence to these healthy dietary patterns, score lower on diet quality, and consume more carbohydrates and saturated fats compared to Whites[56–60]. Thus, this dietary behavior may contribute to the higher risk of T2D observed among minority groups. Despite the importance of diet, it does not fully explain the disparities in T2D risk. Even after adjusting for dietary factors, racial disparities in T2D persist, though they are somewhat reduced[56,63]. For instance, a cohort study in the US found that although Hispanics (32.92) and Blacks (33.19) had lower dietary quality score than Whites (36.94), racial differences in T2D persisted even after accounting for diet and diet explained 7% of racial differences (Hispanic vs. White; Black vs. White) in T2D[56].

Exercise as a contributor for racial disparities in T2D

In addition to smoking and diet, exercise is a well-recognized modifiable factor for T2D[61,62]. Evidence from RCT[61,62] and a meta-analysis of cohort studies[116] has indicated the protective effect of exercise against T2D. Meanwhile, previous studies showed that minorities tended to engage in less exercise compared to Whites[63–67]. For example, a cohort study among 78,419 women aged 30–55 years from the Nurses' Health Study (NHS) in the US found that Asians (3.4) and Blacks (3.4) had lower moderate/vigorous exercise (hours/week) than Whites (4.0)[63]. Exercise may thus contribute to explaining the racial and ethnic differences in T2D risk.

Nevertheless, most studies to date relied on qualitative assessments without quantifying the mediation effect of exercise[34,35,68,69], or adjusted for multiple mediators (e.g., alcohol intake, smoking, and exercise) simultaneously, which obscures the specific mediation contribution of exercise[63,64]. For instance, in one cohort study using NHS data among 78,419 women aged 30–55 years, further adjustment for exercise, family history of diabetes, smoking and alcohol

drinking based on the age- and body mass index-controlled model revealed that the T2D risk for Hispanics and Asians decreased compared to Whites[63]. In the other cohort study using Atherosclerosis Risk in Communities Study data among 12,107 participants aged 45–64 years, further adjusting or exercise, smoking, alcohol drinking, and dietary energy based on the age- and family history- adjusted model reduced the T2D risk for Blacks compared to Whites[64]. However, because exercise and other factors were adjusted simultaneously in these studies, it remains unclear whether the reduced T2D risk was due to exercise or other factors[63,64]. Only one cohort study did examine combined exercise and household activities as the mediator for racial disparities in T2D among postmenopausal US women in the WHI Study[56]. This study found that Blacks and Hispanics had lower combined exercise and household activities than Whites, which explained approximately 6% of the racial differences in T2D for Blacks and Hispanics compared to Whites[56]. However, limitations of this study included focusing only on postmenopausal women, using combined exercise and household activities, and only assessing these activities at baseline which may have changed during follow-up[56]. Consequently, it remained unclear whether exercise played a mediating role in the racial and ethnic difference in T2D among men or younger women and whether the decreased risk of T2D was attributable solely to exercise. Therefore, we aimed to examine whether habitual exercise is a potential mediator of racial and ethnic differences (Hispanic, Black, Asian vs. White) in T2D and to what extent the disparities are mediated by exercise, using a cohort study with longitudinal measures of exercise including multiple racial and ethnic groups in the US (**Objective 2**).

2.1.3.3. Body fat and fat distribution

Obesity as a contributor for racial disparities in T2D

Evidence has shown that obesity is an important risk factor for T2D[10,11,117,118]. The body mass index (BMI) is commonly used to assess obesity, with T2D risk escalating substantially at BMI above 30 kg/m² [10–12,117,119,120]. The incidence of T2D can triple for individuals with BMI between 25 and 30 kg/m², and increase tenfold when BMI exceeds 30 kg/m²[121]. Meanwhile, some racial and ethnic groups, such as Hispanics and Blacks, had higher percentage of being obese than Whites[7,56,63,122]. For instance, data from NHANES 2011-2016 showed that Hispanics and Blacks had higher percentages of individuals with BMI ranges of 30-34.9 kg/m² (26.1%, 22.4% vs. 21.4%) and ≥35 kg/m² (17.7%, 23.6% vs.16.5%) compared to Whites, respectively[7]. Thus, BMI may explain racial and ethnic differences in T2D. However, these disparities persist even after adjusting for BMI[7,56,63,122]. For example, a cohort study among postmenopausal women in the US found that after adjusting for BMI, Hispanics still had a higher risk of T2D, with BMI accounting for about 10% of the racial and ethnic differences (Hispanic vs. White)[56]. Furthermore, BMI has its limitations; it does not distinguish between muscle mass and fat mass, which is critical since muscle and fat have different metabolic properties and contribute differently to the risk of developing T2D[123].

Studies have indicated that body fat is more closely correlated with T2D than BMI[123,124]. For example, one cohort study using data from Health Professionals Follow-up Study and the NHS in the US found that the association between predicted fat mass quintiles and T2D (HR: 1.00, 1.96, 2.96, 3.90, and 8.38 for men and 1.00, 2.20, 3.50, 5.73, and 12.1 for women) was higher than the association between BMI quintiles and T2D (1.00, 1.69, 2.45, 3.54, and 6.94 for men and 1.00, 1.76, 2.86, 4.88, and 9.88 for women)[124]. This finding suggested fat mass may better capture the risk of T2D than BMI. Meanwhile, some racial and ethnic groups (e.g., Hispanics) had higher fat mass or fat mass percentage than Whites[79,125]. Thus, fat mass may

explain racial differences in T2D. Whereas, fat mass does not account for fat distribution. Meanwhile, there are different physiological effects of these fat depots on the body's metabolism and therefore contribute differently to the risk of developing T2D.

Visceral fat as a contributor for racial disparities in T2D

Recent evidence has suggested that fat distribution, particularly central obesity, is a more critical factor in T2D risk due to its impact on insulin resistance[11,70,71]. Abdominal fat is classified into subcutaneous fat and visceral fat[126,127], with visceral fat—situated around vital organs—being more pathogenic and closely associated with T2D than subcutaneous fat[128–131]. The higher lipolysis rate of visceral fat increases the flux of free fatty acids (FFA) to the liver through the portal circulation[72], and visceral fat is more metabolically active, releasing adipocytokines[73–75] that contribute to insulin resistance and T2D development. Mendelian randomization analysis in the United Kingdom (UK) showed the positive association between visceral fat and T2D, implying a causal effect of visceral fat on T2D[132]. Several cohort studies in the US also found positive associations between visceral fat and T2D[133–137]. Previous studies have suggested that some racial and ethnic groups, such as Hispanics[76–79] and South Asians[80,81], may have higher levels of visceral fat compared to Whites.

However, few studies have examined to what extent visceral fat explains racial disparities in T2D. One cohort study in the US examined waist circumstance as a mediator for racial and ethnic differences in T2D[56]. It found that Blacks (58.78%) had higher percentages of high waist circumstance (≥ 88 cm) than Whites (39.96%), explaining 19% of the racial differences (Blacks vs. Whites) in T2D[56]. However, waist circumstance could not distinguish between visceral and subcutaneous fat, which may limit its accuracy in estimating visceral fat[75]. Thus, it was unclear to which degree the mediation proportion was attributed to visceral fat.

Moreover, there are sex differences in visceral fat[82–84] and potential sex and race interactions in visceral fat distribution[79,85–87]. Our study aimed to examine whether and to what degree the association between race and ethnicity and T2D can be explained by visceral fat in sex subgroups using data from a cohort study that included multiple racial and ethnic groups in **objective 3**.

In summary, the modifiable risk factors such as SDOH, psychological stress, lifestyles, body fat, and visceral adiposity play significant roles in the development and progression of T2D and may explain the higher risk of T2D among racial and ethnic minorities. However, the presence of these risk factors alone does not fully explain the intricacies of T2D development and the pronounced disparities among racial groups. The transition from a state of health to T2D involves complex interactions at the molecular levels, influenced by risk factors. To understand the full scope of how these risk factors contribute to the pathogenesis of T2D and the disparities seen across different racial and ethnic groups, a thorough examination of the underlying pathophysiology is essential. The next section, therefore, explored the etiology and pathophysiology of T2D, focusing on the intricate biological processes that the risk factors may influence racial disparities in T2D.

2.2. Etiology and pathophysiology of type 2 diabetes

The etiology of T2D encompasses a broad spectrum of genetic and environmental factors, each contributing to the disease's pathogenesis in unique ways. Building upon the factors we focused on in the previous section, we now turn our attention to the biological mechanisms that lead to T2D.

T2D is a multifaceted metabolic disorder characterized by impaired insulin action and secretion[10,11,117]. The pathophysiology of T2D primarily involves insulin resistance (i.e., reduced insulin-mediated glucose-update by tissues) in skeletal muscle, adipose tissue, and liver,

followed by a decrease in compensatory pancreatic β-cell response, ultimately leading to hyperglycemia and T2D[10,11,117]. Two major physiological abnormalities contribute to insulin resistance: 1) peripheral insulin resistance in muscle and adipose tissue, marked by increased adipose tissue lipolysis and reduced glucose uptake by these tissues and 2) hepatic insulin resistance, characterized by excessive hepatic glucose production during fasting[10,11,117]. The primary function of β-cells is to secrete insulin. When β-cell dysfunction occurs, insulin secretion is impaired[10,11,117].

Initially, insulin resistance is countered by increased insulin secretion, but over time, β-cells deteriorate, reducing insulin secretion and resulting in hyperglycemia[10,11,117]. Elevated plasma glucose concentrations further impair insulin target tissues, exacerbating insulin resistance and diminishing β-cell function, creating a vicious cycle that worsens hyperglycemia[10,11,117]. T2D is diagnosed when the pancreas can no longer compensate for insulin resistance in insulin-sensitive tissues by increasing insulin secretion[10,11,117].

Previous studies have indicated that, compared to Whites, Hispanics exhibit higher hepatic and peripheral insulin resistance[138,139]. This dual resistance means that both the liver and peripheral tissues are less responsive to insulin, leading to increased glucose production and impaired glucose uptake, resulting in significant metabolic dysregulation[138,139]. Additionally, Hispanics show higher insulin secretion as a compensatory response to insulin resistance[138,140,141]. Despite this mechanism, the increased insulin demand may eventually exhausts β-cells, leading to β-cell dysfunction and T2D development[138,140,141]. Blacks show higher peripheral insulin resistance, leading to impaired glucose uptake, but similar hepatic insulin resistance[142–145] compared to Whites. They also exhibit higher insulin secretion[146–148]. However, this hyperinsulinemia may not be sufficient to overcome the significant peripheral

resistance, ultimately leading to β-cell failure and the onset of T2D. Asians present both higher hepatic and peripheral insulin resistance[149,150] along with lower β-cell function[148,149,151–154]. The reduced β-cell function means their pancreatic cells are less capable of producing adequate insulin in response to blood glucose levels. This combination of high insulin resistance and poor β-cell function significantly increases the risk of T2D in Asian populations. Furthermore, the extent of insulin resistance varies among Asian subgroups[149,150,155]. For instance, Chinese individuals exhibit higher hepatic insulin resistance and similar peripheral insulin resistance compared to Whites, leading to increased glucose production by the liver and elevated fasting glucose levels. South Asians display higher hepatic and peripheral insulin resistance compared to Whites, making them highly susceptible to T2D due to compounded insulin resistance in both the liver and peripheral tissues[149,150,155]. These pathophysiological differences among racial and ethnic groups highlight the need to investigate specific determinants of T2D that explain the variations in insulin resistance and β-cell function across these populations.

T2D is a complex and multifactorial disease influenced by a myriad of genetic, environmental, and behavioral factors. Among these, we focus on SDOH, exercise, and visceral fat in the dissertation, especially in the context of racial and ethnic disparities. Here, we explore how these elements contribute to the etiology and pathophysiology of T2D, with a focus on their interplay and implications for different racial and ethnic groups.

SDOH and T2D

The link between SDOH and T2D is multifaceted. Adverse SDOH including lower socioeconomic status and unfavorable neighborhood and social conditions can lead to unhealthy behaviors, such as low exercise and poor diet, which subsequently contribute to obesity and higher visceral fat levels[36,37]. Moreover, individuals experiencing adverse SDOH often perceive

higher levels of stress, which can increase T2D risk through both unhealthy behaviors (e.g., increased smoking, unhealthy diet, reduced exercise) and activation of the hypothalamic-pituitary-adrenal (HPA) axis. This activation leads to dysregulation of cortisol and the metabolic system[36,37], resulting in higher obesity and visceral fat levels. These factors, in turn, elevate hepatic and peripheral insulin resistance, impair β-cell function, and increase the risk of T2D[36,37]. Given that racial and ethnic minorities (Hispanic, Black and Asian) often experience worse SDOH compared to Whites due to systems-level root inequities[13,22,34,35], adverse SDOH may contribute to Hispanics' higher peripheral and hepatic insulin resistance, Blacks' higher peripheral insulin resistance, Asians' higher peripheral and hepatic insulin resistance, and impaired β-cell function, thereby increasing the T2D risk among these minority groups.

Exercise and T2D

Regular exercise is crucial for maintaining healthy blood glucose levels and reducing insulin resistance. It enhances glucose uptake into muscles, reduces overall adiposity, and specifically decreases visceral fat, which is associated with lower levels of FFA and circulating inflammatory cytokines, further improving hepatic and peripheral insulin resistance and β-cell function[156–159]. Meanwhile, minorities (e.g., Hispanics, Blacks, Asians) tend to exercise less than Whites which may be due to due to undesired SDOH (e.g., unsafe neighborhoods, lack of recreational facilities, and time constraints related to SES) and higher stress[63–67]. Consequently, they may experience higher levels of obesity, visceral fat and inflammation, which exacerbates insulin resistance and impairs insulin secretion. This lower level of exercise could explain the higher hepatic and peripheral insulin resistance in Hispanics, the higher peripheral insulin resistance in Blacks, and the higher hepatic and peripheral insulin resistance and lower β-cell function in Asians, contributing to the higher T2D risk in minority groups.

Visceral fat and T2D

Visceral fat, is a critical factor in T2D development due to physiological effects of the fat depots on the body's metabolism[128–131]. Visceral fat has a direct effect on liver circulation due to its high lipolysis rate[72], and it is more metabolically active, releasing adipocytokines[73–75] and altering hormone secretion, which links visceral fat to hepatic and peripheral insulin resistance, leading to T2D.

There are two mechanisms by which visceral fat accumulation causes insulin resistance. The first mechanism is the "portal theory", which suggests that visceral adipose tissue has a high lipolysis rate, increasing the flux of FFAs from visceral fat depots to the liver, leading to hepatic insulin resistance and hepatic steatosis[72]. The second mechanism involves the secretion of adipocytokines and hormones[73–75]. Visceral fat accumulation increases the secretion of adipocytokines involving in inflammation (e.g., IL-6, IL-8, IL-10, TNF-α] and the acute-phase response [e.g., plasminogen activator inhibitor (PAI)-1], which increases insulin resistance. Secreted hormones (e.g., leptin, adiponectin, resistin and visfatin) also regulate insulin resistance. For example, visceral fat accumulation decreases adiponectin secretion, resulting in increased peripheral insulin resistance[73–75]. Overall, these two mechanisms promote both hepatic insulin resistance and peripheral insulin resistance, ultimately leading to T2D[160,161]. Given that visceral fat is an important risk factor for T2D and evidence indicates that some racial and ethnic groups (e.g., Hispanics[76–79]and South Asians[80,81]) have higher levels of visceral fat compared to Whites, visceral fat may explain the higher peripheral and hepatic insulin resistance in Hispanics, the higher hepatic and peripheral insulin resistance and lower β-cell function in South Asians, and the higher T2D risk in these minority groups.

2.3. Data source and methods

Data source

MESA cohort: The proposed study, MESA, is a longitudinal study of 6814 adults aged 45–84 years and free of CVD. Study participants were recruited in 2000–2002 (exam 1, baseline) from 6 field centers in the US (Baltimore, Maryland; Chicago, Illinois; St. Paul, Minnesota; Los Angeles, California; New York, New York; and Forsyth County, North Carolina)[162]. Among all enrolled participants, 38.5% (n=2622) are White; 11.8% (804) are Chinese; 27.8% (n=1892) are Black; 22.0% (n=1496) are Hispanic. Following examinations occurred at 2002–2004 (exam 2), 2004–2005 (exam 3), 2005–2007 (exam 4), 2010–2013 (exam 5), and 2016–2018 (exam 6)[162]. MESA also has 21 follow-up telephone interviews from 2001 to 2020 to inquire about new disease diagnoses. We used this dataset in the objective 1 and 2.

We also used the other MESA ancillary study measuring abdominal aortic calcification including a subset of participants (n=1947) who obtained abdominal computed tomography (CT) scans of visceral fat at either exam 2 or exam 3 (randomly assigned)[163–166]. Among participants in this ancillary study, 40.3% (n=785) are White; 12.9% (n=252) are Chinese; 20.9% (n=406) are Black; 25.9% (n=504) are Hispanic[163]. We used this dataset in the objective 3.

We compared the participants of MESA ancillary study in objective 3 with the participants not included in the ancillary study in MESA main dataset in objective 2 and found they had similar baseline characteristics (**Table 2.1**). It supported that the MESA ancillary data could be a random subsample of the overall MESA cohort. The findings from objective 3 MESA ancillary data could be reasonably generalized to the entire MESA cohort.

Table 2.1. Baseline characteristics comparison between MESA and MESA ancillary data

Characteristics	**Participants of MESA data not recruited in MESA ancillary study in objective 2 (n=4316)**		**Participants of MESA ancillary study in objective 3 (n=1457)**		**P**
Age (years)	61.70	(10.43)	61.97	(9.85)	0.39
Female, % (N)	54.2	(2340)	51.2	(746)	0.05
Family history of diabetes, % (N)	34.8	(1328)	33.1	(474)	0.23
Married/living with a partner, % (N)	62.0	(3544)	64.9	(936)	
Education, % (N)					0.27
High school or less	34.3	(1479)	32.2	(468)	
Associates	28.7	(1238)	28.9	(420)	
Bachelor's or higher	37.0	(1595)	39.0	(567)	
Annual household income, % (N)					0.17
<$25,000	29.8	(1238)	27.5	(389)	
$25,000–$49,999	28.8	(1198)	28.6	(404)	
≥$50,000	41.4	(1723)	44.0	(622)	
Stress, % (N)					0.05
Low	39.0	(1679)	42.1	(613)	
Medium	32.1	(1383)	29.0	(422)	
High	29.0	(1249)	28.9	(421)	
Hypertension medication use, % (N)	33.6	(1449)	32.1	(468)	0.31
Lipid-lowering medication use, % (N)	14.5	(624)	14.9	(217)	0.66
Antidepressant use, % (N)	7.8	(337)	6.5	(94)	0.09
Cigarettes smoking, % (N)					0.78
Never	50.5	(2179)	50.4	(733)	
Former	36.4	(1568)	37.1	(540)	
Current	13.1	(566)	12.5	(182)	
Alternative healthy eating index (AHEI)-2010	53.73	(9.65)	53.40	(9.64)	0.26
Sedentary behavior (MET-hours/day)	4.06	(2.74)	3.96	(2.62)	0.21
Systolic blood pressure (SBP, mmHg)	125.50	(21.24)	125.87	(21.33)	0.53
Diastolic blood pressure (DBP, mmHg)	71.80	(10.35)	72.25	(10.04)	0.15
Total cholesterol (mg/dl)	194.60	(34.99)	196.22	(34.14)	0.14
High-density lipoprotein (HDL) cholesterol (mg/dl)	51.53	(14.98)	52.15	(15.09)	0.17
Low-density lipoprotein (LDL) cholesterol (mg/dl)	117.80	(31.38)	118.79	(29.99)	0.29
Triglycerides (mg/dl)	127.10	(78.89)	126.48	(72.14)	0.81

Data were presented as mean (standard deviation, SD) for continuous variables, and percentage, % (frequency, N) for categorical variables.
P-values were compared using t-test for continuous variables and $\chi 2$-tests for categorical variables.

Variables

Table 2.2. Available variables

Measure	Exam 1	Exam 2	Exam 3	Exam 4	Exam 5	Exam 6	21 Follow-up interviews
Sociodemographic variables							
Age	X	X	X	X	X	X	
Sex	X						
Family history of diabetes		X					
Race and ethnicity	X						
Marital status	X	X	X	X	X	X	
Education	X						
Annual household income, employment status, insurance	X	X	X	X	X	X	
Language spoken	X						
Residence	X	X	X	X	X	X	
Neighborhood and social cohesion	X	X	X	X	X	X	
Stress	X		X				
Medications	X	X	X	X	X	X	
Behaviors							
Exercise	X	X	X		X	X	
Sedentary behavior	X	X	X		X	X	
Diet	X				X		
Cigarette smoking	X	X	X	X	X	X	
Anthropometrics: weight, body mass	X	X	X	X	X	X	

index, waist circumference							
Body composition: total fat mass	X	X	X	X	X	X	
Body composition: Abdominal muscle area and density		X	X				
Blood pressure, lipids	X	X	X	X	X	X	
Visceral fat		X	X				
Type 2 Diabetes	X	X	X	X	X	X	X

Social determinants of health

SDOH was defined as the conditions in which people live, work, and play and the wider set of social structures and economic systems that shape the conditions of daily living by WHO[110]. Previous studies using data from the National Health Interview Survey (NHIS) and REasons for Geographic and Racial Differences in Stroke (REGARDS) assessed SDOH comprehensively and found positive associations of an comprehensive SDOH measure, including multiple factors in economic stability; education; neighborhood and physical environment; community and social context; health and system; and food security domain, with obesity and CVD[32,33,111,112]. We used the SDOH framework from a widely applied method in the NHIS studies[111,112,167]. We included nine variables across four domains: economic stability (employment status, annual household income), education (education, language spoken), neighborhood, physical environment and social cohesion (residence, neighborhood trusted, neighborhood help, close-knit neighborhood), and health and system domain (health insurance). We classified each SDOH variable as high-risk or low-risk according to **Table 2.3**. For each of the nine SDOH variables, we assigned a score of 1 if individuals' SDOH variable level was the high-risk level, and 0 otherwise. We calculated

SDOH score by taking the sum of all 9 SDOH scores, ranging from 0 to 9 and higher score indicating higher levels of SDOH.

Table 2.3. Classification of social determinants of health variables

Primary analysis	**Classification of SDOH variables changed in sensitivity analysis**
Domain: Economic stability	
Employment status (high risk: unemployed, homemaker vs. low risk: employed or retired)	Employment status (high risk: unemployed vs. low risk: employed, retired or homemaker)
Annual household income (high risk: <$35,000 vs. low risk: ≥$35,000)	
Domain: Education	
Education (high risk: less than or equal to vs. low risk: higher than high school)	
Language spoken in exam 1 (high risk: Spanish, Chinese vs. low risk: English)	
Domain: Neighborhood, physical environment, and social cohesion	
Residence (high risk: rent or pay a mortgage or other vs. low risk: own fee and clear)	
Neighborhood can be trusted (high risk: disagree, neither agree nor disagree vs. low risk: agree)	Neighborhood can be trusted (high risk: disagree vs. low risk: agree, neither agree nor disagree)
Neighborhood help each other (high risk: disagree, neither agree nor disagree vs. low risk: agree)	Neighborhood help each other (high risk: disagree vs. low risk: agree, neither agree nor disagree)
A close-knit neighborhood (high risk: disagree, neither agree nor disagree vs. low risk: agree)	A close-knit neighborhood (high risk: disagree vs. low risk: agree, neither agree nor disagree)
Domain: Health and system	
Health insurance (high risk: yes vs. low risk: no)	

Mediation analysis

We used mediation analysis to examine causes of racial and ethnic differences in T2D. Mediation analysis could be used to examine etiology and pathways, and assess how the exposure influence the outcome through mediators[168–171].

There are two traditional approaches for mediation analysis, the product approach: (X-M effect)*(M-Y effect) and the difference approach: (total effect of X-Y)-(direct effect of X-Y)[168]. However, if there are interactions between exposure and mediator, between mediator and mediator; uncontrolled confounders; or non-linear models, the traditional approaches could not be used.

A more flexible modern approach, natural mediation effects, decomposing total effects (TE) to natural direct effect (NDE) and natural indirect effect (NIE) using g-computation allows for mediation analysis through multiple causally related mediators and accommodates exposure–mediator and mediator-mediator interactions and models in nonlinearities[169]. The NDE and NIE require four assumptions[170]: (i) the effect of exposure X on outcome Y is unconfounded given covariates (confounders) C; (ii) the effect of mediator M on Y is unconfounded given X, C; (iii) the effect of X on M is unconfounded given C; and (iv) there is no exposure-induced mediator-outcome confounder L. However, in our study, SES, stress, other behaviors (e.g., smoking), and obesity (BMI, total fat) could be confounders for the association of exercise with T2D and for the association of visceral fat with T2D induced by race. Thus, due to potentially exposure-induced mediator-outcome confounders, we may not meet the assumption (iv) of NDE and NIE[170].

There are three methods proposed by VanderWeele to overcome the assumption exposure-induced mediator-outcome confounding[170]. First is to treat the exposure induced confounder (L) and mediators (M) jointly, then decompose TE to NDE and NIE. However, we do not want to examine that joint mediator. Second is to use path-specific effects (PSEs) (note: PSEs

do not have natural or control effect classification), however, in this method, the X→L→M→Y and X→L→Y could not be separated. Thus, to separate the indirect effect through M, we could only use the intervention path-specific effect (iPSE), which is the third method proposed by VanderWeele[170,171].

Thus, we applied the iPSEs for sequential mediators[170,172]. We used g-computation for iPSEs and bootstrapping 200 times for 95% confidence intervals (CIs)[170,172,173].

2.4. Research gaps

SES is an upstream factor that influences behaviors and obesity, which are key contributors to the development of T2D and its disparities among different racial and ethnic groups[13,22,174]. Meanwhile, associations of personal and neighborhood SES with T2D are deeply intertwined[13,22]. A comprehensive measure that includes personal, neighborhood, and social conditions, collectively known as SDOH[13,22], is essential for a thorough understanding of how these interconnected social conditions relate to T2D. Meanwhile, racial and ethnic minorities may have worse SDOH[13,22,34,35] due to systemic racism and higher T2D risk[1,2,7] than Whites. However, up to now, there has been no investigation into the association between a multidomain SDOH measure and T2D. Thus, we examined the association between a comprehensive SDOH measure and T2D in a cohort study, and if these associations varied among racial and ethnic subgroups in **objective 1**.

Previous evidence has shown that racial and ethnic minorities tend to have lower level of exercise compared to White individuals[63,65–67,175]. Given that exercise is a modifiable risk factor for T2D[10,11], it is important to understand how much of the racial and ethnic disparities in T2D can be attributed to differences in exercise levels. However, no studies have yet quantified the extent to which exercise mediates the relationship between race and ethnicity and T2D.

Therefore, we examined whether, and to what extent, the association of race and ethnicity (Hispanic, Black, Asian vs. White) with T2D was explained by exercise in a cohort study with longitudinal measures of exercise in **objective 2**.

In addition to exercise, visceral fat is a critical risk factor for T2D[133–137], and studies have shown that some racial and ethnic groups, such as Hispanics[76–79] and South Asians[80,81], tend to have higher levels of visceral fat compared to Whites. Despite this, no studies have examined the extent to which visceral fat mediates the relationship between race and ethnicity and T2D[75]. Furthermore, there are known sex differences in visceral fat distribution[82–84] and potential interactions between sex and race in visceral fat accumulation[79,85–87]. Thus, we examined whether and to what degree the association of race and ethnicity (Hispanic, Black, Asian vs. White) with T2D was explained by visceral fat in sex subgroups using data from a cohort study in **objective 3**.

2.5. Study goals and specific objectives

To gain a better understanding of why racial and ethnic minorities have excess risk of developing T2D by examining modifiable pathways and to give implications for public health interventions.

Objective 1: To examine the association between a comprehensive measure of SDOH and T2D, and the associations in racial and ethnic subgroups.

Objective 2: To investigate whether and to what degree racial and ethnic differences in T2D were mediated by exercise.

Objective 3: To evaluate whether and to what degree racial and ethnic differences in T2D were mediated by visceral fat in sex subgroups.

3. Chapter three: Social determinants of health and type 2 diabetes in the United States: the Multi-Ethnic Study of Atherosclerosis

3.1. Abstract

Importance

Low personal socioeconomic status (SES) is a risk factor for type 2 diabetes (T2D) and contributes to racial and ethnic minorities' higher T2D risk. However, personal SES clusters with social factors and there may be integrated effects on T2D development. Meanwhile, no study has examined associations of comprehensive social determinants of health (SDOH) with T2D.

Objective

To examine associations of comprehensive SDOH with T2D, and these in racial subgroups.

Design, Setting, and Participants

This cohort study included 5,557 participants aged 45–84 years from the Multi-Ethnic Study of Atherosclerosis and free of T2D at 2000–2002 and followed until 2020. Data was analyzed between June and October, 2023.

Exposure

SDOH score was calculated using 9 variables of four domains with a range of 0–9, and categorized as low, medium, and high SDOH.

Main Outcomes and Measures

T2D was diagnosed by fasting serum glucose or medications use, or diabetes diagnosis. We examined associations between SDOH and T2D using Cox proportional hazards regression models.

Results

In 5,557 participants [mean (SD) of age: 61.59 (10.25) years; 2970 females (53.5%)], SDOH score was associated with increased T2D risk in a dose-response manner [HR (95% CI): 1.11 (0.95–1.31) and 1.51 (1.24–1.83) for medium and high SDOH compared to low SDOH burden group, respectively; P-for-trend<0.001], after controlling for confounders. Stratifying by race, associations existed in Whites [medium, 1.30 (1.02–1.65); and high, 2.01 (1.35–3.01); P-for-trend=0.001] and Hispanics [medium, 1.13 (0.72–1.76); and high, 1.67 (1.07–2.61); P-for-trend<0.001], but not in Chinese [medium, 0.81 (0.44–1.48, P=0.49); and high, 1.01 (0.55–1.85, P=0.98); P-for-trend=0.39] or Blacks [medium, 0.93 (0.71–1.23, P=0.61); and high, 1.06 (0.74–1.53, P=0.75); P-for-trend=0.70].

Conclusions and Relevance

Social disadvantages were associated with increased T2D risk in all participants, and Whites and Hispanics in stratified analyses. Findings suggest prioritizing resources for populations with social disadvantages to reduce T2D burden, specifically for at-risk Hispanics to decrease T2D disparities.

3.2. Introduction

Diabetes is a major chronic disease, affecting 38.4 million people in the United States (US) in 2021, with high rates of disability and premature mortality[2]. Among people having diabetes, 95% have type 2 diabetes (T2D)[2]. In addition, racial and ethnic minorities persistently have higher T2D risk than Whites in the US[1,2,7]. Thus, it is crucial to identify determinants of T2D for targeted interventions to prevent T2D and reduce racial disparities.

Although undesired behaviors (e.g., unhealthy diet) and obesity are well-established risk factors for T2D[176], upstream factors socioeconomic status (SES) may impact downstream behaviors and obesity, then influence T2D development and disparities among racial and ethnic

groups[13,22,174]. Evidence showed personal SES (e.g., education and income)[23–27] and neighborhood environmental and social factors (e.g., physical activity resources, neighborhood adults with primary education and living in rented housing)[28–31] were risk factors for T2D. In addition, personal SES or neighborhood factors are intertwined[13,22]. Therefore, it is critical to employ a composite measurement including personal and neighborhood, social and environmental conditions, which is social determinants of health (SDOH)[13,22], to present a comprehensive picture of the interconnected social conditions related to T2D risk.

SDOH was defined as the conditions in which people live, work, and play and the wider set of social structures and economic systems that shape the conditions of daily living by World Health Organization (WHO)[110]. Studies found positive associations of an comprehensive measure of SDOH using a score with multiple factors in economic stability; education; neighborhood and physical environment; community and social context; health and system; and food security domain with obesity and cardiovascular disease (CVD)[32,33,111,112]. They also found exposure to a higher SDOH score associated with elevated CVD risk[32,33]. We are not aware of studies examining associations between SDOH and incident T2D. Thus, this study aimed to examine prospective associations of the SDOH score, a comprehensive measurement of social profile, with T2D in a cohort study including multiple racial and ethnic groups in the US. Because there are racial and ethnic differences in T2D risk[1,2,7], we additionally examined if above associations varied by racial and ethnic groups.

3.3. Methods

Study design and population

The population-based prospective cohort Multi-Ethnic Study of Atherosclerosis (MESA) recruited 6,814 participants aged 45 to 85 between years 2000 and 2002 (exam 1, baseline),

followed by exam 2, 2002-2004; exam 3, 2004-2005; exam 4, 2005-2007; exam 5, 2010-2013; and exam 6, 2016-2018[162]. MESA also included 21 follow-up telephone interviews from 2001 to 2020 to collect new disease information[162].

We excluded individuals with missing data on SDOH score (n=298), or having T2D (n=879), or missing T2D status (n=61) at baseline (exam 1), or participants not having any follow-up visits after baseline (n=19), resulting in 5,557 participants included in the study (**Figure S3.1**). We conducted analyses between June and October, 2023. The study was approved by the institutional review boards of each MESA site. All participants provided written informed consent. We wrote the manuscript based on the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Assessment of social determinants of health

We used the framework from a widely applied method in the National Health Interview Survey (NHIS) studies[111,112,167] to develop the SDOH score. We included 9 variables across four domains: 1) economic stability domain (i.e., employment status, annual household income), 2) education domain (i.e., education, language spoken), 3) neighborhood, physical environment and social cohesion domain (i.e., residence, neighborhood trust, neighborhood help, close-knit neighborhood), and 4) health and system domain (i.e., health insurance). We classified each SDOH variable as high- or low-risk level [i.e., employment (high-risk: unemployed, homemaker vs. low-risk: employed or retired), income (high-risk: <$35,000 vs. low-risk: ≥$35,000), education (high-risk: less than or equal to vs. low-risk: higher than high school), language spoken (high-risk: Spanish, Chinese vs. low-risk: English), residence (high-risk: rent or pay a mortgage or other vs. low-risk: own fee and clear), neighborhood trust (high-risk: disagree, neither agree nor disagree vs. low-risk: agree), neighborhood help (high-risk: disagree, neither

agree nor disagree vs. low-risk: agree), close-knit neighborhood (high-risk: disagree, neither agree nor disagree vs. low-risk: agree), and health insurance (high-risk: no vs. low-risk: yes)]. For each of 9 SDOH variables, we assigned a score of 1 if individuals' SDOH variable level was the high-risk level, and 0 otherwise. We calculated SDOH score by summing up all 9 variable scores, with the total score ranging from 0 to 9 and higher score meaning higher SDOH levels[111,112,167].

Assessment of type 2 diabetes

Participants were classified as having T2D if they either had a fasting serum glucose (FPG) ≥126 mg/dL according to American Diabetes Association (ADA) criteria[177] or self-reported use of glucose-lowering medications at each exam, or self-reported diabetes diagnosis by physicians at exam 1, 5, 6 and at 21 telephone interviews.

Covariates

The sociodemographic information (i.e., age, gender, race and ethnicity, marital status), chronic stress, mediation use, and cigarette smoking were assessed at exam 1 from questionnaires[162,178]. Family history of diabetes was measured at exam 2 from the family history questionnaire. Sedentary behavior [metabolic equivalent of task (MET)-minutes/week] and exercise (MET- minutes/week) were assessed from the Typical Week Physical Activity Survey (TWPAS) at exam 1[162]. Dietary intake in the last year was measured using the 120-item food frequency questionnaire at exam 1. Alternative Healthy Eating Index (AHEI)-2010 was calculated to indicate the dietary quality[60]. Body mass index (BMI) (kg/m^2) was calculated as [weight (kg)]/[height (cm)/100]^2 at exam 1. Total fat mass percentage (%) was estimated using equations validated by dual-energy X-ray absorptiometry (DXA)-estimated body fat percentage with correlation coefficients ranging from 0.80 to 0.86 at exam 1: 76−(20×(height /waist)) for

females and 64−(20×(height/waist)) for males[179]. Total fat mass (kg) was calculated by weight (kg) × (total fat mass percentage/100). Resting blood pressure (BP) was measured three times using an automated oscillometric sphygmomanometer (model Pro 100, Critikon, Tampa, Florida, US) at exam 1, and calculated based on the average of the last two of three measurements. Lipid profiles were measured at exam 1 from plasma samples after a 12-hour fast[180].

Statistical analysis

We described baseline characteristics of participants and presented the distribution of SDOH and T2D incidence rate. We used SAS version 9.4 (SAS Institute, Cary, NC, USA) and R version 4.2.1 and considered the statistically significant level as a two-sided α level <0.05.

For the primary analysis, we categorized the SDOH into three groups: low (0-1, reference group), medium (2-4), and high (5-9), based on the plot of SDOH and T2D (**Figure 3.1**). This was done as first, groups of SDOH values at 0, 6, 7, 8, 9 had small sample sizes, we subsequently combined SDOH=0 and SDOH=1 together, and combined SDOH=6, 7, 8, 9 together. Second, we chose $0 \leq SDOH \leq 1$ as the reference group as it had the lowest T2D rate. Third, the T2D rate was similar when $2 \leq SDOH \leq 4$, and T2D rate increased rapidly when $SDOH \geq 5$.

We examined associations of SDOH with T2D using Cox proportional hazards regression models. The proportional hazards assumption was verified using Schoenfeld residuals. Following unadjusted models, we controlled for confounders age (years), gender (male or female), race and ethnicity (White, Chinese, Black, Hispanic), family history of diabetes (yes or no), and marital status (married/living as married, widowed/divorced/separated, never married) (**Figure 3.2**). We also explored to additionally adjust for potential mediators for associations between SDOH and T2D: stress (low, medium, or high), hypertension mediation use (yes or no), lipid-lowering

medication use (yes or no), antidepressant use (yes or no), smoking (never, former, or current), sedentary behavior (MET-minutes/week), exercise (MET- minutes/week), AHEI-2010 (continuous), BMI (kg/m^2), total fat (kg), systolic BP (SBP) (mmHg), diastolic BP (DBP) (mmHg), total cholesterol (mg/dl), high-density lipoprotein (HDL) cholesterol (mg/dl), low-density lipoprotein (LDL) cholesterol (mg/dl), and triglycerides (mg/dl). We performed above analyses first in overall participants and then in stratified racial and ethnic groups. The P for interaction between SDOH and race on T2D was calculated using the Wald χ2-test. The missing values of each adjusted covariate were < 10%, thus we applied completed data analyses as the primary approach.

We also conducted several sensitivity analyses. First, we calculated the SDOH score in which we categorized employment status as high risk (unemployed) and low risk (employed, retired or homemaker) level. Second, we calculated SDOH score in which we categorized the neighborhood relations as high risk (disagree) and low risk (agree, neither agree nor disagree) level. Third, we used continuous SDOH score as the exposure. Fourth, participants were diagnosed as having T2D using FPG and glucose-lowering medications, not using self-reported diabetes diagnosis. Fifth, we treated the missing values as a separate category for adjusted models. Sixth, we applied multiple imputation for the missing data.

3.4. Results

Characteristics of study participants

Among 5,557 MESA participants, 20.8% (n=1157), 57.2% (n=3178), and 22.0% (n=1222) had low, medium and high SDOH, respectively. Participants with high SDOH had the highest percentages of females (62.1%), Hispanics (43.1%), current smokers (15.3%), the lowest percentage of Whites (13.5%), and married/living as married (53.5%) (**Table 3.1**).

Associations of social determinants of health with type 2 diabetes

During a median follow-up time of 15.79 years, 1253 developed T2D (17.30 per 1000 person-years). The T2D incidence rates in participants with low, medium and high SDOH were 13.87, 16.24, and 24.06 per 1000 person-years, respectively. In unadjusted models, compared to persons having low SDOH, those with medium and high SDOH had higher risk of T2D in overall participants and Whites. The test for interaction between race and SDOH on T2D using Wald χ2-test was insignificant (P for interaction=0.78). After adjustment for confounders of age, gender, family history of diabetes, race and ethnicity, and marital status, we found positive associations between SDOH and T2D in a dose-response manner in the overall cohort of MESA participants [HR (95% CI): 1.11 (0.95–1.31), P=0.20 and 1.51 (1.24–1.83) , P<0.001 for medium and high SDOH compared to low SDOH burden groups; P-for-trend < 0.001]. When stratified by race and ethnicity, associations existed in Whites [medium, 1.30 (1.02–1.65), P=0.03; and high, 2.01 (1.35–3.01), P=0.001; P-for-trend=0.001], and Hispanics [medium, 1.13 (0.72–1.76), P=0.60; and high, 1.67 (1.07–2.61), P=0.02; P-for-trend<0.001]. SDOH was not associated with T2D in Chinese [medium, 0.81 (0.44–1.48, P=0.49); and high, 1.01 (0.55–1.85, P=0.98); P-for-trend=0.39] or Blacks [medium, 0.93 (0.71–1.23, P=0.61); and high, 1.06 (0.74–1.53, P=0.75); P-for-trend=0.70]. The test for interaction between race and SDOH on T2D was insignificant, either (P for interaction=0.59) (**Table 3.2**).

After further adjusting for potential mediators of stress, medications, behaviors, BMI, body fat, BP and lipids, the associations decreased in overall participants [medium, 1.07 (0.91–1.27), P=0.42; and high, 1.46 (1.19–1.79), P<0.001; P-for-trend<0.001]. When stratified by race and ethnicity, the associations decreased and were insignificant in Whites [medium, 1.21 (0.94–1.56), P=0.13; and high, 1.35 (0.87–2.10), P=0.18; P-for-trend=0.11], but increased in Hispanics

[medium, 1.29 (0.78–2.15), P=0.32; and high, 1.88 (1.13–3.11), P=0.01; P-for-trend=0.001]. SDOH was not associated with T2D in Chinese [medium, 0.67 (0.36–1.25), P=0.21; and high, 0.93 (0.49–1.76), P=0.83; P-for-trend=0.28] or Blacks [medium, 0.92 (0.69–1.24), P=0.60; and high, 1.08 (0.72–1.62), P=0.73; P-for-trend=0.69], either. The test for interaction between race and SDOH on T2D was insignificant (P for interaction=0.34) (**Table 3.2**).

In sensitivity analysis, after examining associations using SDOH categorized employment with homemakers/employed/retried participants as the low-risk level (**Table S3.1**), or using SDOH categorized neighborhood relations with neutral/positive relations as the low-risk level (**Table S3.2**), or using continuous SDOH (**Table S3.3**), or using T2D diagnosed by FPG or glucose-lowering medications (**Table S3.4**), or creating a category for covariates missing (**Table S3.5**), or using multiple imputation for the missing data (**Table S3.6**), results remained unchanged, although some estimates were statistically insignificant.

3.5. Discussion

In the large multiracial and ethnic cohort of MESA, SDOH score was associated with increased T2D risk in a dose-response manner after controlling for confounders. When stratified by race and ethnicity, the associations existed in Whites and Hispanics, but were insignificant in Blacks and Chinese. We found no significant interactions between SDOH score and race on T2D, which may be due to insufficient sample size or no heterogeneity in associations between SDOH and T2D across racial and ethnic groups. Further studies with larger sample sizes are needed. Our study is the first cohort study investigating the comprehensive SDOH with T2D in the US.

We are not aware previous studies examining associations of cumulative SODH score integrating several domains with T2D. In the same vein, two studies, one in the US and one in

Finland, reported positive association of cumulative personal sociodemographic variables (i.e., low family income, low education level, minority racial and ethnic group, and single-living status)[27] or cumulative neighborhood factors (sum of neighborhood socioeconomic disadvantage using the proportion of adults with primary education only, unemployment, and living in rented housing)[31] with T2D, which corroborated our findings. However, these two studies examined personal sociodemographic factors or neighborhood SES with T2D, without acknowledging the interplay between personal and neighborhood factors[27,31]. Our study found aggregated SDOH integrating personal and neighborhood factors positively associated with T2D in a dose-response manner. Similar to our study, work using the NHIS and Reasons for Geographic and Racial Differences in Stroke (REGARDS) studies assessed SDOH by calculating the SODH scores using numbers of factors in several domains, including economic stability; education; neighborhood and physical environment; community and social context; health and system and food security[32,33,111,112]. These studies found progressively increased associations of SDOH score with obesity and CVD[32,33,111,112]. We expanded such work by prospectively examining SDOH integrating several domains with T2D, and investigating the racial and ethnic specific associations.

Our findings of associations between SDOH and increased T2D risks after adjusting for confounders in Whites and Hispanics are novel, but supported by the results from studies examining associations between individual personal SES and T2D[24,26]. One cohort study from Multiethnic Cohort in the US found lower education associated with higher T2D risk in Whites[24]. The other cohort study from the Hispanic Community Health Study/Study of Latinos in the US found lower education and household income associated with higher T2D prevalence in Hispanics[26]. As Hispanics had the higher percentage of undesired SDOH[13,22,34,35] (**Table S3.7**)

and higher T2D risk[1,2,7] than Whites, our findings suggested resources and interventions may be needed for Hispanics to narrow T2D disparities. Our results in Blacks were similar to those reported in the Atherosclerosis Risk in Communities study in the US which found positive associations between area SES and progressive chronic kidney disease in Whites but not in Blacks[181]. However, our results were inconsistent with a cross-sectional study using national data from NHANES which showed lower income associated with higher T2D risk in Black females[25]. Our study is the first examining associations between SDOH and T2D in Chinese, and we are not aware of previous studies examining SES or SDOH with T2D in Chinese.

The mechanisms underlying positive trends between SDOH and T2D are multifactorial. Undesired SDOH may be associated with poor diet and low exercise levels, which may increase T2D risk[36,37]. In addition, people with undesirable SDOH perceive more stress which may increase T2D risk through both undesired behaviors (e.g., unhealthy diet) and activated hypothalamic-pituitary-adrenal (HPA) axis, leading to dysregulation of cortisol and metabolic system[36,37]. These explanations were supported by decreased associations between SDOH and T2D after adjusting for potential mediators stress, behaviors, and biomarkers in metabolic system (e.g., BMI, total fat, BP and lipids) in overall participants and Whites (**Table 3.2**, **Table S3.8**). The increased associations between SDOH and T2D in Hispanics may be due to adjusting for AHEI-2010 and BMI (**Table S3.8**). When looking at individual SDOH variables with T2D, we found associations between language spoken (speaking Spanish vs. English) and T2D significantly increased in Hispanics following adjustment for AHEI-2010 and BMI (**Table S3.9**). It may be because in our study, Hispanics with high SDOH scores had the highest percentage of speaking Spanish (78.8%), compared to those with low (1.1%) or medium (36.2%) SDOH scores, then those people may be less acculturated. Meanwhile, research showed that Hispanics

who were less acculturated may maintain traditional dietary habits, leading to better diet quality and lower BMI[182], which was also found in our study [AHEI: 52.14 vs. 51.98; BMI (kg/m^2): 28.34 vs. 29.20 in Hispanics speaking Spanish vs. speaking English]. Thus, Hispanics with high SDOH scores may have better diet and lower BMI, which may confer a reduced risk of T2D, and controlling for diet and BMI may remove protective effects on T2D attributed to these two variables, resulting in increased T2D risk in Hispanics.

The explanation for lack of associations observed in Blacks may be that Blacks in our study were from urban who may not be representative of national Blacks, and may have better SES than Blacks elsewhere in the US. This may also be the reason why we found inconsistent results compared to previous research using national data from NHANES[25]. Compared to national statistics, Blacks in MESA had lower percentages of having high school or less education (MESA Blacks: 27.7% vs. national Blacks: 36.0%)[183] and no insurance (MESA Blacks: 6.2% vs. national Blacks: 17.5%)[184] (**Table S3.7**). In addition, previous evidence showed that Blacks had the highest resilience to stress compared to other racial and ethnic groups[185], and they may be better at managing stress, which can include maintaining healthier lifestyles and avoiding stress-induced behaviors that increase T2D risk. More national studies on Blacks are needed. No associations of SDOH with T2D in Chinese may be because that they had the lowest percentage of not close-knit neighborhoods and the second lowest percentage of not trusted neighborhoods (**Table S3.7**), which may help them buffer the stress from SDOH[186]. In addition, Chinese had small sample size resulting in not enough power to find associations. For example, we found the borderline significant associations between education and T2D in Chinese [HR (95%CI): 1.36 (0.96, 1.92), P=0.08] when adjusting for confounders (**Table S3.9**). More studies with larger sample sizes of Chinese are warranted. In addition, we did not find that individual

SDOH variables significantly associated with T2D in Blacks or Chinese (**Table S3.9**). Our SDOH score may not capture social disadvantage of Blacks and Chinese. Future studies assessing SDOH including more racial specific variables are needed.

Strengths and limitations

This is the first study examining SDOH employing a score which included multiple domains of personal and neighborhood risk factors with T2D, using a large multi-ethnic sample in a longitudinal cohort study in the US. Nonetheless, limitations of our study should be mentioned. First, we used the SDOH framework from NHIS studies[111,112,167], but did not include food security and community and social context domains as we did not have relevant variables. Second, we assumed equal weight of each SDOH variable when calculating SDOH score, which may simplify the complex interactions between SDOH variables. However, this metric has been used and positively associated with other negative health outcomes, including stroke, obesity, and less healthcare[111,112,167]. More studies may be needed to investigate whether a weighted or unweighted model is better for calculating SDOH score.

3.6. Conclusions

In this large prospective cohort study with multiple racial and ethnic groups, we found a positive trend between SDOH and T2D. When stratified by race and ethnicity, associations existed in Whites and Hispanics. Our findings implicate aggregated SDOH is a risk factor for T2D and resources may be needed for vulnerable groups who experienced social disadvantages comprehensively to reduce the T2D burden. It is critical for the Hispanics at heightened risk, as targeted interventions may narrow T2D disparities and promote health equity.

Table 3.1. Baseline characteristics of participants by social determinants of health in the Multi-Ethnic Study of Atherosclerosis

Characteristics	Overall (n=5557)		SDOH						P-values
			Low [20.8% (1157)]		Medium [57.2% (3178)]		High [22.0% (1222)]		
Age (years)	61.59	(10.25)	62.30	(9.94)	61.24	(10.25)	61.84	(10.48)	0.01
Female, % (N)	53.5	(2970)	43.5	(503)	53.7	(1708)	62.1	(759)	<0.001
Race and ethnicity									<0.001
White	42.3	(2348)	61.8	(715)	46.2	(1468)	13.5	(165)	
Chinese	12.3	(684)	5.3	(61)	10.2	(325)	24.4	(298)	
Black	24.8	(1377)	25.2	(291)	26.9	(854)	19.0	(232)	
Hispanic	20.7	(1148)	7.8	(90)	16.7	(531)	43.1	(527)	
Family history of diabetes, % (N)	34.3	(1739)	31.5	(342)	35.8	(1048)	32.9	(349)	0.02
Marital status									<0.001
Married/living as married	62.2	(3427)	74.5	(858)	61.0	(1922)	53.5	(647)	
Widowed/divorced/separated	29.4	(1618)	19.0	(219)	29.5	(930)	38.8	(469)	
Never married	8.5	(468)	6.5	(75)	9.5	(300)	7.7	(93)	
Stress									0.001
Low	39.5	(2161)	42.6	(485)	38.2	(1195)	39.8	(481)	
Medium	31.3	(1716)	33.3	(379)	31.1	(973)	30.1	(364)	
High	29.2	(1600)	24.1	(274)	30.7	(962)	30.1	(364)	

Hypertension medication use, % (N)	32.8	(1820)	34.2	(396)	32.6	(1037)	31.7	(387)	0.40
Lipid-lowering medication use, % (N)	14.6	(808)	15.9	(184)	15.1	(479)	11.9	(145)	0.01
Antidepressant use, % (N)	7.6	(421)	7.7	(89)	8.3	(262)	5.7	(70)	0.02
Cigarette smoking, % (N)									<0.001
Never	50.7	(2815)	49.2	(569)	49.1	(1559)	56.2	(687)	
Former	36.5	(2029)	41.5	(480)	37.8	(1201)	28.5	(348)	
Current	12.8	(713)	9.3	(108)	13.2	(418)	15.3	(187)	
Alternative healthy eating index (AHEI)-2010	53.73	(9.69)	55.13	(9.87)	53.67	(9.81)	52.53	(8.98)	<0.001
Sedentary behavior (MET-minutes/week)	1683.74	(1133.53)	1669.87	(1062.90)	1711.42	(1148.94)	1624.92	(1156.15)	0.07
Exercise (MET-minutes/week)	1595.36	(2374.67)	1881.36	(2480.53)	1665.75	(2501.68)	1141.59	(1803.94)	<0.001
Body mass index (kg/m2)	27.73	(5.27)	27.47	(4.96)	27.94	(5.36)	27.41	(5.30)	0.002
Total fat mass (kg)	27.51	(9.72)	26.82	(9.11)	27.97	(9.94)	26.97	(9.63)	<0.001
Systolic blood pressure (SBP, mmHg)	125.20	(21.09)	123.96	(19.66)	125.06	(21.27)	126.75	(21.86)	0.005
Diastolic blood pressure (DBP, mmHg)	71.86	(10.25)	72.08	(9.98)	71.79	(10.22)	71.82	(10.57)	0.70
Total cholesterol (mg/dl)	195.05	(35.05)	191.77	(34.10)	195.24	(34.67)	197.68	(36.64)	<0.001
High-density lipoprotein (HDL) cholesterol (mg/dl)	51.66	(14.92)	51.85	(15.69)	51.96	(15.03)	50.72	(13.82)	0.04

Low-density lipoprotein (LDL) cholesterol (mg/dl)	118.01	(31.08)	116.54	(30.18)	118.11	(31.31)	119.17	(31.28)	0.12
Triglycerides (mg/dl)	127.38	(77.40)	118.42	(73.34)	126.26	(73.41)	138.79	(89.10)	<0.001

Data were presented as mean (standard deviation, SD) for continuous variables, and percentage, % (frequency, N) for categorical variables.

P-values were compared between three SDOH groups using $\chi 2$-tests and one-way ANOVA for categorical and continuous variables, respectively.

SDOH was calculated from 9 variables of four domains: economic stability, education, neighborhood, physical environment and social cohesion, and health and system domain. For each of the 9 variables, an individual received a score of 1 if individuals' SDOH variable level was the high-risk level, and 0 otherwise. The SDOH sum-score was calculated by taking the sum of all 9 variable scores. SDOH was categorized as low (0-1, reference group), medium (2-4), and high (5-9).

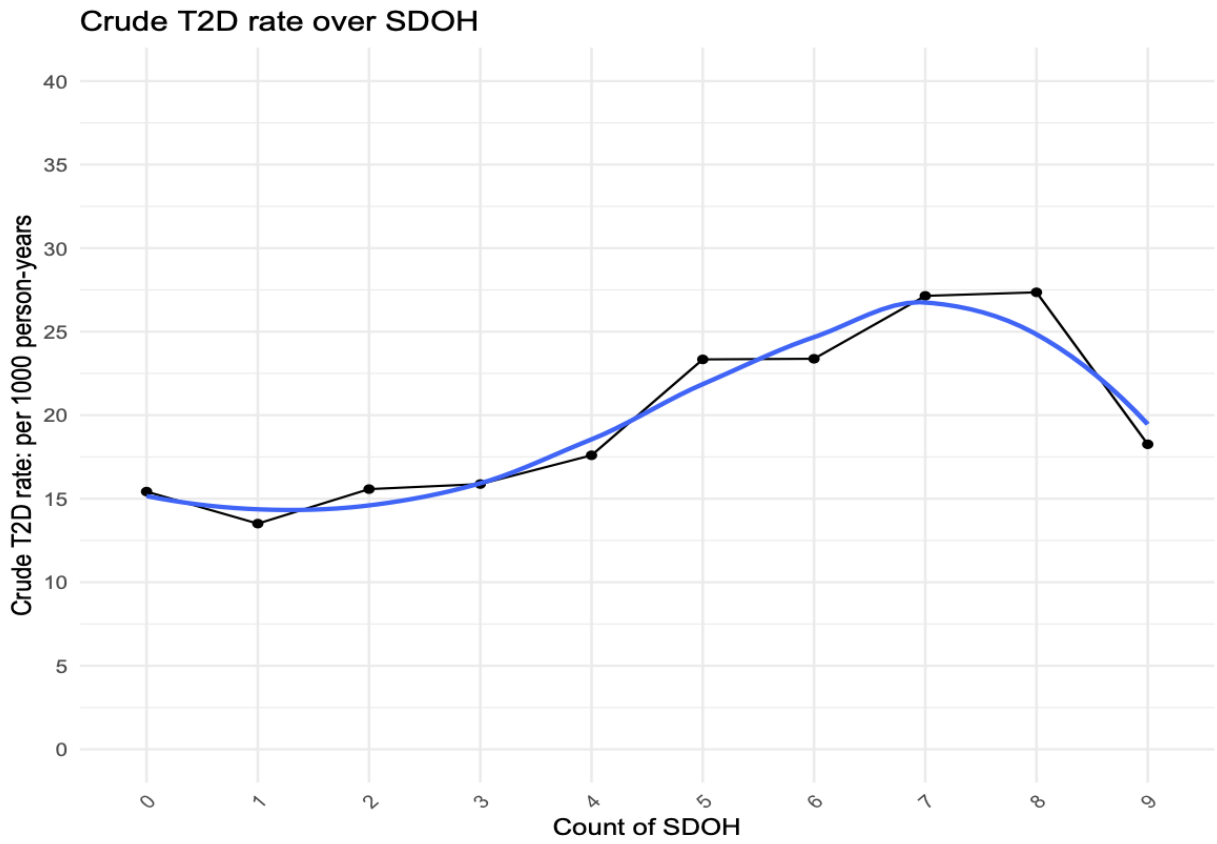
Table 3.2. Associations of social determinants of health with type 2 diabetes in the Multi-Ethnic Study of Atherosclerosis

	Overall				White				Chinese			
	HR	**95%CI**	***P***	**P-for-trend**	**HR**	**95%CI**	***P***	**P-for-trend**	**HR**	**95%CI**	***P***	**P-for-trend**
Model 1				**<0.001**				**0.01**				0.19
Low	1.00				1.00				1.00			
Medium	1.17	(1.00, 1.36)	0.05		1.24	(0.98, 1.56)	0.07		0.93	(0.51, 1.69)	0.81	
High	**1.74**	**(1.47, 2.07)**	**<0.001**		**1.59**	**(1.08, 2.34)**	**0.02**		1.19	(0.66, 2.17)	0.56	
Model 2				**<0.001**				**0.001**				0.39
Low	1.00				1.00				1.00			
Medium	1.11	(0.95, 1.31)	0.20		1.30	(1.02, 1.65)	0.03		0.81	(0.44, 1.48)	0.49	
High	**1.51**	**(1.24, 1.83)**	**<0.001**		**2.01**	**(1.35, 3.01)**	**0.001**		1.01	(0.55, 1.85)	0.98	
Model 3				**<0.001**				0.11				0.28
Low	1.00				1.00				1.00			
Medium	1.07	(0.91, 1.27)	0.42		1.21	(0.94, 1.56)	0.13		0.67	(0.36, 1.25)	0.21	
High	**1.46**	**(1.19, 1.79)**	**<0.001**		1.35	(0.87, 2.10)	0.18		0.93	(0.49, 1.76)	0.83	

	Black				Hispanic			
	HR	**95%CI**	***P***	**P-for-trend**	**HR**	**95%CI**	***P***	**P-for-trend**
Model 1				0.40				**0.01**
Low	1.00				1.00			
Medium	0.94	(0.72, 1.21)	0.61		1.01	(0.67, 1.54)	0.95	
High	1.13	(0.81, 1.58)	0.46		1.37	(0.91, 2.07)	0.14	
Model 2				0.70				**<0.001**
Low	1.00				1.00			
Medium	0.93	(0.71, 1.23)	0.61		1.13	(0.72, 1.76)	0.60	
High	1.06	(0.74, 1.53)	0.75		**1.67**	**(1.07, 2.61)**	**0.02**	
Model 3				0.69				**0.001**
Low	1.00				1.00			
Medium	0.92	(0.69, 1.24)	0.60		1.29	(0.78, 2.15)	0.32	
High	1.08	(0.72, 1.62)	0.73		**1.88**	**(1.13, 3.11)**	**0.01**	

Cox proportional hazard regression was used. Hazard ratio, 95% CI and P-value were reported. Boldface indicated statistical significance (P<0.05).

SDOH was calculated from 9 variables of four domains: economic stability, education, neighborhood, physical environment and social cohesion, and health and system domain. For each of the 9 variables, an individual received a score of 1 if individuals' SDOH variable level was the high-risk level, and 0 otherwise. The SDOH sum-score was calculated by taking the sum of all 9 variable scores. SDOH was categorized as low (0-1, reference group), medium (2-4), and high (5-9).
Model 1: Crude model
Model 2: Adjusted for age, gender, family history of diabetes, race and ethnicity, and marital status.
Model 3: Adjusted for age, gender, family history of diabetes, race and ethnicity, marital status, stress, hypertension mediation use, lipid-lowering medication use, antidepressant use , smoking, alternative healthy eating index (AHEI)-2010, sedentary behavior, exercise, body mass index (BMI), total fat mass, systolic blood pressure (SBP), diastolic blood pressure (DBP), total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides.
When stratified by race and ethnicity, the variable was not controlled.



N	230	927	1183	1079	916	620	349	175	68	10
Cases	46	173	248	229	207	175	96	54	23	2
Incidence	0.20	0.19	0.21	0.21	0.23	0.28	0.28	0.31	0.34	0.20
Rate	15.4	13.5	15.6	15.9	17.6	23.3	23.4	27.1	27.4	18.3

Figure 3.1. Plot of crude type 2 diabetes rate with social determinants of health score. The black line is drawn through the actual data points to show the relationship between the SDOH count and the crude T2D rate. The blue line represents a locally estimated scatterplot smoothing (LOESS) smoothed line.

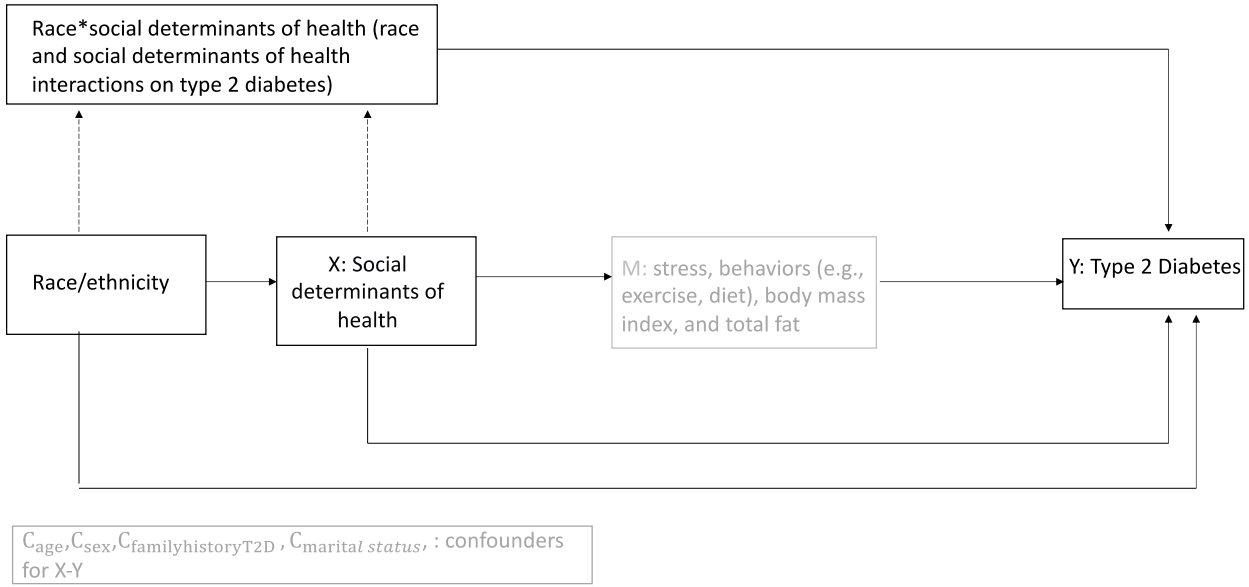


Figure 3.2. Directed acyclic graph (DAG) for social determinants of health and type 2 diabetes. Here the exposure is social determinants of health (SDOH), outcome is type 2 diabetes (T2D). The potential mediators were in gray color, as these mediators were not our main aim in the dissertation. The race*SDOH interaction term on T2D was drawn in the DAG as we examined whether associations between SDOH and T2D varied across racial and ethnic groups and we tested interactions between race and SDOH on T2D.

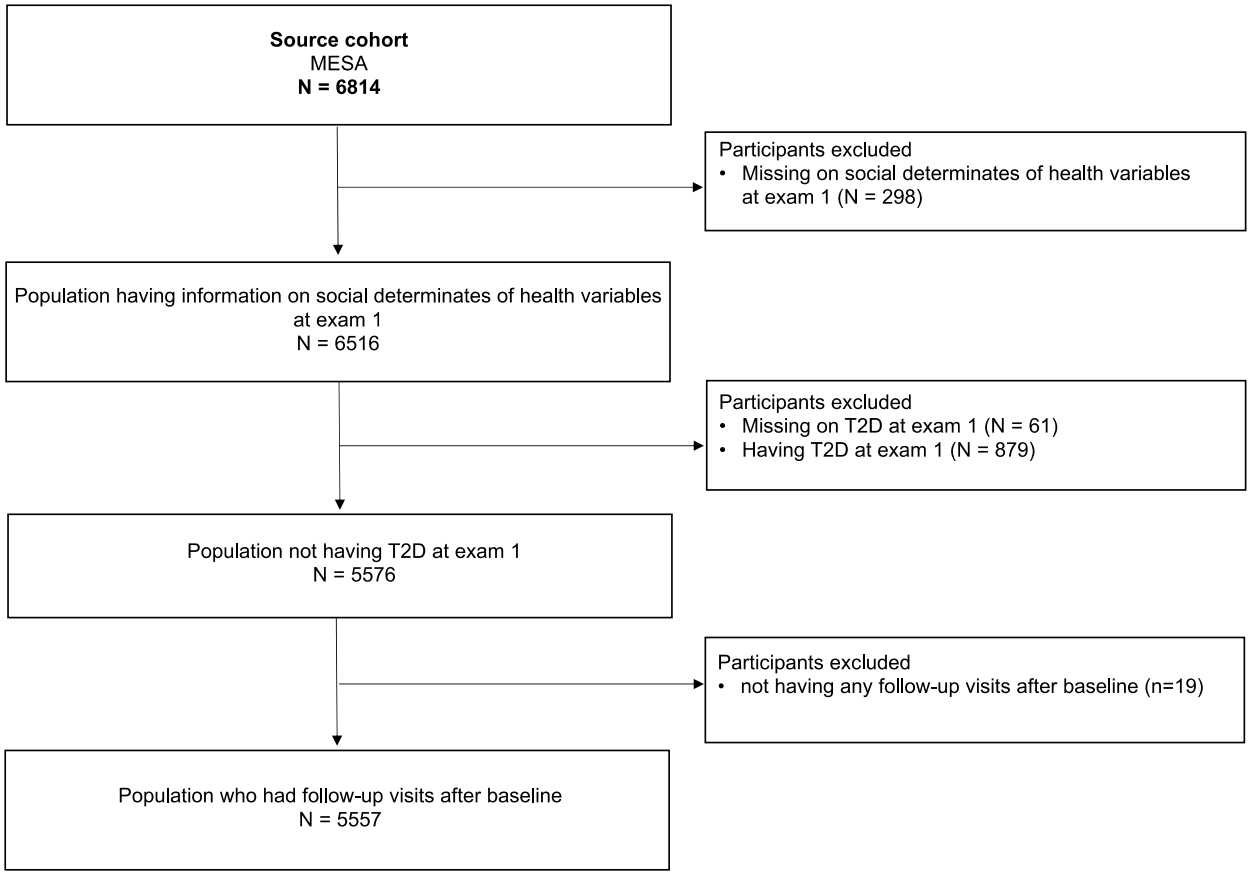


Figure S3.1. Participants flow chart

Table S3.1. Associations of social determinants of health with type 2 diabetes in the Multi-Ethnic Study of Atherosclerosis, reclassifying employment status

	Overall					White					Chinese				
	HR	**95%CI**		***P***	**P-for-trend**	**HR**	**95%CI**		***P***	**P-for-trend**	**HR**	**95%CI**		***P***	**P-for-trend**
Model 1					**<0.001**					**<0.001**					0.67
Low	1.00					1.00					1.00				
Medium	1.07	0.92	1.25	0.40		1.15	0.92	1.45	0.22		0.79	0.45	1.39	0.42	
High	**1.45**	**1.19**	**1.76**	**<0.001**		**2.33**	**1.56**	**3.48**	**<0.001**		0.92	0.52	1.66	0.79	
Model 2					**0.001**					0.08					0.67
Low	1.00					1.00					1.00				
Medium	1.02	0.86	1.20	0.86		1.03	0.81	1.31	0.79		0.68	0.38	1.23	0.20	
High	**1.37**	**1.12**	**1.68**	**0.003**		**1.62**	**1.04**	**2.52**	**0.03**		0.85	0.46	1.55	0.58	

	Black					Hispanic				
	HR	**95%CI**		***P***	**P-for-trend**	**HR**	**95%CI**		***P***	**P-for-trend**
Model 1					0.62					**0.003**
Low	1.00					1.00				
Medium	0.92	0.70	1.21	0.55		1.21	0.78	1.88	0.40	
High	1.09	0.75	1.58	0.65		**1.63**	**1.05**	**2.55**	**0.03**	
Model 2					0.80					**0.003**
Low	1.00					1.00				
Medium	0.91	0.68	1.23	0.55		1.38	0.83	2.29	0.21	
High	1.05	0.69	1.58	0.83		**1.84**	**1.11**	**3.06**	**0.02**	

Cox proportional hazard regression was used. Hazard ratio, 95% CI and P-value were reported. Boldface indicated statistical significance (P<0.05).
SDOH was calculated from 9 variables of four domains: economic stability, education, neighborhood, physical environment and social cohesion, and health and system domain. For each of the 9 variables, an individual received a score of 1 if individuals' SDOH variable level was the high-risk level, and 0 otherwise. **Employment status was classified as high risk (unemployed) vs. low risk (employed, retired or homemaker).** The SDOH sum-score was calculated by taking the sum of all 9 variable scores. SDOH was categorized as low (0-1, reference group), medium (2-4), and high (5-9).
Model 1: Adjusted for age, gender, family history of diabetes, race and ethnicity, and marital status.
Model 2: Adjusted for age, gender, family history of diabetes, race and ethnicity, marital status, stress, hypertension mediation use, lipid-lowering medication use, antidepressant use , smoking, alternative healthy eating index (AHEI)-2010, sedentary behavior, exercise, body mass index (BMI), total fat mass, systolic blood pressure (SBP), diastolic blood pressure (DBP), total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides.
When stratified by race and ethnicity, the variable was not controlled.

Table S3.2. Associations of social determinants of health with type 2 diabetes in the Multi-Ethnic Study of Atherosclerosis, reclassifying neighborhood relations

	Overall					White					Chinese				
	HR	**95%CI**		***P***	**P-for-trend**	**HR**	**95%CI**		***P***	**P-for-trend**	**HR**	**95%CI**		***P***	**P-for-trend**
Model 1					**<0.001**					**0.001**					0.96
Low	1.00					1.00					1.00				
Medium	1.10	0.96	1.27	0.18		1.28	1.03	1.59	0.02		0.62	0.39,	1.00	0.05	
High	**1.60**	**1.34**	**1.90**	**<0.001**		**1.96**	**1.24**	**3.10**	**0.004**		0.80	0.50,	1.29	0.36	
Model 2					**<0.001**					0.43					0.58
Low	1.00					1.00					1.00				
Medium	1.10	0.96	1.27	0.18		1.12	0.90	1.40	0.32		0.66	0.41	1.06	0.08	
High	**1.67**	**1.34**	**2.09**	**<0.001**		0.94	0.33	2.65	0.90		0.95	0.55	1.65	0.85	

	Black					Hispanic				
	HR	**95%CI**		***P***	**P-for-trend**	**HR**	**95%CI**		***P***	**P-for-trend**
Model 1					0.41					**<0.001**
Low	1.00					1.00				
Medium	1.06	0.84	1.34	0.63		1.13	0.79	1.63	0.50	
High	1.17	0.80	1.71	0.43		**1.91**	**1.36**	**2.69**	**<0.001**	
Model 2					0.35					**<0.001**
Low	1.00					1.00				
Medium	0.99	0.77	1.28	0.95		**1.65**	**1.14**	**2.39**	**0.01**	
High	1.56	0.88	2.76	0.13		**2.28**	**1.50**	**3.45**	**<0.001**	

Cox proportional hazard regression was used. Hazard ratio, 95% CI and P-value were reported. Boldface indicated statistical significance (P<0.05). SDOH was calculated from 9 variables of four domains: economic stability, education, neighborhood, physical environment and social cohesion, and health and system domain. For each of the 9 variables, an individual received a score of 1 if individuals' SDOH variable level was the high-risk level, and 0 otherwise. **Neighborhood trust, neighborhood help, and close-knit neighborhood were classified as high risk (disagree) vs. low risk (agree, neither agree nor disagree).** The SDOH sum-score was calculated by taking the sum of all 9 variable scores. SDOH was categorized as low (0-1, reference group), medium (2-4), and high (5-9). Model 1: Adjusted for age, gender, family history of diabetes, race and ethnicity, and marital status. Model 2: Adjusted for age, gender, family history of diabetes, race and ethnicity, marital status, stress, hypertension mediation use, lipid-lowering medication use, antidepressant use , smoking, alternative healthy eating index (AHEI)-2010, sedentary behavior, exercise, body mass index (BMI), total fat mass, systolic blood pressure (SBP), diastolic blood pressure (DBP), total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides. When stratified by race and ethnicity, the variable was not controlled.

Table S3.3. Associations of social determinants of health with type 2 diabetes in the Multi-Ethnic Study of Atherosclerosis, using continuous social determinants of health

	Overall				White				Chinese			
	HR	**95%CI**		***P***	**HR**	**95%CI**		***P***	**HR**	**95%CI**		***P***
Model 1	**1.08**	**1.04**	**1.12**	**<0.001**	**1.14**	**1.06**	**1.23**	**0.001**	1.03	0.94	1.13	0.50
Model 2	**1.07**	**1.03**	**1.11**	**0.001**	1.05	0.97	1.14	0.25	1.04	0.94	1.15	0.43
					Black				**Hispanic**			
					HR	**95%CI**		***P***	**HR**	**95%CI**		***P***
Model 1					1.02	0.94	1.09	0.69	**1.09**	**1.03**	**1.16**	**0.003**
Model 2					1.00	0.92	1.09	0.97	**1.10**	**1.03**	**1.17**	**0.004**

Cox proportional hazard regression was used. Hazard ratio, 95% CI and P-value were reported. Boldface indicated statistical significance (P<0.05).

SDOH was calculated from 9 variables of four domains: economic stability, education, neighborhood, physical environment and social cohesion, and health and system domain. For each of the 9 variables, an individual received a score of 1 if individuals' SDOH variable level was the high-risk level, and 0 otherwise. The SDOH sum-score was calculated by taking the sum of all 9 variable scores. **Continuous SDOH score was used.**

Model 1: Adjusted for age, gender, family history of diabetes, race and ethnicity, and marital status.

Model 2: Adjusted for age, gender, family history of diabetes, race and ethnicity, marital status, stress, hypertension mediation use, lipid-lowering medication use, antidepressant use , smoking, alternative healthy eating index (AHEI)-2010, sedentary behavior, exercise, body mass index (BMI), total fat mass, systolic blood pressure (SBP), diastolic blood pressure (DBP), total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides.

When stratified by race and ethnicity, the variable was not controlled.

Table S3.4. Associations of social determinants of health with type 2 diabetes in the Multi-Ethnic Study of Atherosclerosis, type 2 diabetes diagnosed by fasting serum glucose and use of glucose-lowering medications

	Overall					White					Chinese				
	HR	**95%CI**		***P***	**P-for-trend**	**HR**	**95%CI**		***P***	**P-for-trend**	**HR**	**95%CI**		***P***	**P-for-trend**
Model 1					**<0.001**					**0.002**					0.62
Low	1.00					1.00					1.00				
Medium	1.20	0.97	1.48	0.09		**1.44**	**1.04**	**1.99**	**0.03**		0.68	0.35	1.33	0.26	
High	**1.56**	**1.21**	**2.01**	**0.001**		**2.43**	**1.47**	**4.01**	**0.001**		0.79	0.41	1.52	0.48	
Model 2					**<0.001**					0.51					0.40
Low	1.00					1.00					1.00				
Medium	1.12	0.90	1.40	0.32		1.20	0.85	1.69	0.30		0.71	0.36	1.41	0.33	
High	**1.45**	**1.11**	**1.88**	**0.01**		1.62	0.93	2.81	0.09		0.78	0.39	1.58	0.49	

	Black					Hispanic				
	HR	**95%CI**		***P***	**P-for-trend**	**HR**	**95%CI**		***P***	**P-for-trend**
Model 1					0.43					**0.001**
Low	1.00					1.00				
Medium	1.08	0.75	1.55	0.69		1.27	0.73	2.23	0.40	
High	0.96	0.57	1.61	0.87		**2.00**	**1.18**	**3.39**	**0.01**	
Model 2					0.53					**0.001**
Low	1.00					1.00				
Medium	1.03	0.68	1.54	0.90		1.40	0.76	2.55	0.28	
High	1.01	0.56	1.80	0.98		**2.05**	**1.15**	**3.63**	**0.01**	

Cox proportional hazard regression was used. Hazard ratio, 95% CI and P-value were reported. Boldface indicated statistical significance (P<0.05).
SDOH was calculated from 9 variables of four domains: economic stability, education, neighborhood, physical environment and social cohesion, and health and system domain. For each of the 9 variables, an individual received a score of 1 if individuals' SDOH variable level was the high-risk level, and 0 otherwise. The SDOH sum-score was calculated by taking the sum of all 9 variable scores. SDOH was categorized as low (0-2, reference group), medium (3-4), and high (5-9), based on plot of SDOH and objectively defined T2D.
Participants were diagnosed as having T2D using fasting plasma glucose and glucose-lowering medications, not using self-reported diabetes diagnosis in the sensitivity analyses.
Model 1: Adjusted for age, gender, family history of diabetes, race and ethnicity, and marital status.
Model 2: Adjusted for age, gender, family history of diabetes, race and ethnicity, marital status, stress, hypertension mediation use, lipid-lowering medication use, antidepressant use , smoking, alternative healthy eating index (AHEI)-2010, sedentary behavior, exercise, body mass index (BMI), total fat mass, systolic blood pressure (SBP), diastolic blood pressure (DBP), total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides.
When stratified by race and ethnicity, the variable was not controlled.

Table S3.5. Associations of social determinants of health with type 2 diabetes in the Multi-Ethnic Study of Atherosclerosis, addressing missing of covariates

	Overall					White					Chinese				
	HR	**95%CI**		***P***	**P-for-trend**	**HR**	**95%CI**		***P***	**P-for-trend**	**HR**	**95%CI**		***P***	**P-for-trend**
Model 1					**<0.001**					**0.004**					0.32
Low	1.00					1.00					1.00				
Medium	1.09	0.93	1.27	0.30		1.27	1.01	1.60	0.04		0.85	0.47	1.56	0.61	
High	**1.45**	**1.20**	**1.74**	**<0.001**		**1.73**	**1.16**	**2.57**	**0.01**		1.07	0.58	1.96	0.83	
Model 2					**<0.001**					0.27					0.19
Low	1.00					1.00					1.00				
Medium	1.04	0.88	1.22	0.68		1.17	0.92	1.49	0.20		0.72	0.39	1.34	0.30	
High	**1.40**	**1.15**	**1.71**	**0.001**		1.21	0.78	1.87	0.39		1.02	0.54	1.90	0.96	

	Black					Hispanic				
	HR	**95%CI**		***P***	**P-for-trend**	**HR**	**95%CI**		***P***	**P-for-trend**
Model 1					0.50					**0.001**
Low	1.00					1.00				
Medium	0.90	0.69	1.18	0.46		1.07	0.70	1.62	0.77	
High	1.10	0.78	1.55	0.58		1.53	1.00	2.32	0.05	
Model 2					0.73					**0.001**
Low	1.00					1.00				
Medium	0.87	0.65	1.16	0.34		1.22	0.75	1.97	0.43	
High	1.05	0.71	1.54	0.81		**1.74**	**1.08**	**2.82**	**0.02**	

Cox proportional hazard regression was used. Hazard ratio, 95% CI and P-value were reported. Boldface indicated statistical significance (P<0.05).

As the percentage of family history of diabetes were higher than 5%, a separated category for family history of diabetes missing was created.

SDOH was calculated from 9 variables of four domains: economic stability, education, neighborhood, physical environment and social cohesion, and health and system domain. For each of the 9 variables, an individual received a score of 1 if individuals' SDOH variable level was the high-risk level, and 0 otherwise. The SDOH sum-score was calculated by taking the sum of all 9 variable scores. SDOH was categorized as low (0-1, reference group), medium (2-4), and high (5-9).

Model 1: Adjusted for age, gender, family history of diabetes, race and ethnicity, and marital status.

Model 2: Adjusted for age, gender, family history of diabetes, race and ethnicity, marital status, stress, hypertension mediation use, lipid-lowering medication use, antidepressant use , smoking, alternative healthy eating index (AHEI)-2010, sedentary behavior, exercise, body mass index (BMI), total fat mass, systolic blood pressure (SBP), diastolic blood pressure (DBP), total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides.

When stratified by race and ethnicity, the variable was not controlled.

Table S3.6. Associations of social determinants of health with type 2 diabetes in the Multi-Ethnic Study of Atherosclerosis, using multiple imputation for missing

	Overall					White					Chinese				
	HR	**95%CI**		***P***	**P-for-trend**	**HR**	**95%CI**		***P***	**P-for-trend**	**HR**	**95%CI**		***P***	**P-for-trend**
Model 1					**<0.001**					**0.004**					0.37
Low															
Medium	1.09	0.93	1.27	0.28		**1.28**	**1.02**	**1.62**	**0.04**		0.87	0.48	1.59	0.66	
High	**1.45**	**1.20**	**1.74**	**<0.001**		**1.72**	**1.15**	**2.56**	**0.01**		1.06	0.58	1.96	0.84	
Model 2					**<0.001**					0.39					0.24
Low															
Medium	1.02	0.87	1.19	0.81		1.16	0.91	1.46	0.23		0.74	0.40	1.37	0.34	
High	**1.34**	**1.11**	**1.62**	**0.002**		1.13	0.75	1.72	0.55		1.01	0.54	1.89	0.98	

	Black					Hispanic				
	HR	**95%CI**		***P***	**P-for-trend**	**HR**	**95%CI**		***P***	**P-for-trend**
Model 1					0.54					**0.001**
Low										
Medium	0.90	0.69	1.17	0.44		1.08	0.71	1.64	0.72	
High	1.08	0.77	1.52	0.64		**1.56**	**1.03**	**2.37**	**0.04**	
Model 2					0.62					**0.001**
Low										
Medium	0.86	0.65	1.12	0.26		1.12	0.72	1.72	0.62	
High	1.05	0.74	1.50	0.77		**1.61**	**1.04**	**2.49**	**0.03**	

Cox proportional hazard regression was used. Hazard ratio, 95% CI and P-value were reported. Boldface indicated statistical significance (P<0.05).

Multiple imputation was used for the missing data.

SDOH was calculated from 9 variables of four domains: economic stability, education, neighborhood, physical environment and social cohesion, and health and system domain. For each of the 9 variables, an individual received a score of 1 if individuals' SDOH variable level was the high-risk level, and 0 otherwise. The SDOH sum-score was calculated by taking the sum of all 9 variable scores. SDOH was categorized as low (0-1, reference group), medium (2-4), and high (5-9).

Model 1: Adjusted for age, gender, family history of diabetes, race and ethnicity, and marital status.

Model 2: Adjusted for age, gender, family history of diabetes, race and ethnicity, marital status, stress, hypertension mediation use, lipid-lowering medication use, antidepressant use , smoking, alternative healthy eating index (AHEI)-2010, sedentary behavior, exercise, body mass index (BMI), total fat mass, systolic blood pressure (SBP), diastolic blood pressure (DBP), total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides.

When stratified by race and ethnicity, the variable was not controlled.

Table S3.7. Distribution of individual and cumulative social determinants of health variables in the Multi-Ethnic Study of Atherosclerosis

	Overall		White		Chinese		Black		Hispanic		P
Individual SDOH variables and cumulative SDOH score	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	
Employment status (unemployed, homemaker)	12.8	(712)	11.9	(279)	18.9	(129)	7.8	(108)	17.1	(196)	<0.001
Annual household income (<$35,000)	42.0	(2334)	25.3	(593)	61.3	(419)	42.6	(586)	64.1	(736)	<0.001
Education (less than or equal to high school)											
Language spoken in exam 1 (Spanish, Chinese)	33.3	(1849)	20.6	(483)	39.5	(270)	27.7	(381)	62.3	(715)	<0.001
Residence (rent or pay a mortgage or other)	20.8	(1157)	0.0	(1)	80.1	(548)	0.0	(0)	53.0	(608)	<0.001
Neighborhood can be trusted (disagree, neither agree nor disagree)											
Neighborhood help each other out (disagree, neither agree nor disagree)	72.1	(4008)	59.0	(1386)	74.3	(508)	81.0	(1115)	87.0	(999)	<0.001
A close-knit neighborhood (disagree, neither agree nor disagree)	39.0	(2166)	31.4	(738)	41.8	(286)	46.0	(634)	44.3	(508)	<0.001
Health insurance (no)	27.2	(1511)	23.3	(547)	32.3	(221)	27.5	(379)	31.7	(364)	<0.001
Cumulative SDOH score											<0.001
Low	20.8	(1157)	30.5	(715)	8.9	(61)	21.1	(291)	7.8	(90)	
Medium	57.2	(3178)	62.5	(1468)	47.5	(325)	62.0	(854)	46.3	(531)	
High	22.0	(1222)	7.0	(165)	43.6	(298)	16.9	(232)	45.9	(527)	

Data were presented as percentage, % (frequency, N) for categorical variables.P-values were compared between four racial/ethnic groups using $\chi 2$-tests or Fisher's exact test when frequency less than 5.

Table S3.8. Associations of social determinants of health with type 2 diabetes in the Multi-Ethnic Study of Atherosclerosis, adjusting for mediators stepwise

	Overall				White				Chinese				Black				Hispanic			
	HR	**95%CI**		***P***	**HR**	**95%CI**		***P***	**HR**	**95%CI**		***P***	**HR**	**95%CI**		***P***	**HR**	**95%CI**		***P***
Model 1																				
Low	1.00				1.00				1.00				1.00				1.00			
Medium	1.10	0.93	1.29	0.26	**1.28**	**1.01**	**1.63**	**0.04**	0.81	0.44	1.49	0.50	0.91	0.69	1.20	0.51	1.10	0.70	1.72	0.68
High	**1.51**	**1.24**	**1.83**	**<0.001**	**2.00**	**1.33**	**3.00**	**0.001**	1.02	0.55	1.88	0.95	1.07	0.74	1.55	0.73	**1.64**	**1.05**	**2.56**	**0.03**
Model 2																				
Low	1.00				1.00				1.00				1.00				1.00			
Medium	1.09	0.93	1.29	0.28	1.26	0.99	1.61	0.06	0.81	0.44	1.48	0.49	0.91	0.69	1.21	0.52	1.10	0.70	1.72	0.68
High	1.50	**1.23**	**1.82**	**<0.001**	**1.97**	1.32	2.96	**0.001**	1.03	0.56	1.90	0.92	1.06	0.74	1.54	0.74	**1.62**	**1.04**	**2.52**	**0.03**
Model 3																				
Low	1.00				1.00				1.00				1.00				1.00			
Medium	1.09	0.92	1.28	0.28	1.25	0.98	1.59	0.07	0.80	0.44	1.47	0.48	0.92	0.69	1.21	0.55	1.09	0.69	1.70	0.72
High	1.50	**1.23**	**1.82**	**<0.001**	**1.92**	1.28	2.89	**0.002**	1.06	0.57	1.95	0.86	1.06	0.73	1.54	0.74	**1.62**	**1.04**	**2.52**	**0.03**
Model 4																				
Low	1.00				1.00				1.00				1.00				1.00			
Medium	1.09	0.92	1.28	0.32	1.25	0.98	1.59	0.07	0.81	0.44	1.48	0.49	0.92	0.70	1.22	0.55	1.07	0.69	1.68	0.76
High	**1.50**	**1.23**	**1.82**	**<0.001**	**1.92**	**1.28**	**2.89**	**0.002**	1.06	0.57	1.95	0.86	1.07	0.74	1.56	0.72	**1.62**	**1.04**	**2.53**	**0.03**
Model 5																				
Low	1.00				1.00				1.00				1.00				1.00			
Medium	1.08	0.92	1.27	0.35	1.25	0.98	1.59	0.07	0.77	0.42	1.42	0.41	0.91	0.69	1.20	0.49	1.06	0.68	1.66	0.80
High	**1.49**	**1.22**	**1.80**	**<0.001**	**1.88**	**1.25**	**2.83**	**0.003**	1.01	0.54	1.87	0.99	1.05	0.72	1.52	0.82	**1.61**	**1.04**	**2.52**	**0.03**
Model 6																				
Low	1.00				1.00				1.00				1.00				1.00			
Medium	1.08	0.92	1.27	0.37	1.22	0.96	1.56	0.10	0.77	0.42	1.42	0.40	0.90	0.68	1.19	0.47	1.06	0.68	1.67	0.79
High	**1.47**	**1.21**	**1.79**	**<0.001**	**1.72**	**1.14**	**2.61**	**0.01**	1.01	0.54	1.87	0.99	1.04	0.71	1.51	0.84	**1.61**	**1.03**	**2.52**	**0.04**
Model 7																				
Low	1.00				1.00				1.00				1.00				1.00			
Medium	1.07	0.91	1.26	0.40	1.22	0.96	1.55	0.11	0.77	0.42	1.43	0.41	0.91	0.69	1.21	0.51	1.04	0.66	1.64	0.85
High	**1.46**	**1.20**	**1.78**	**<0.001**	**1.69**	**1.12**	**2.56**	**0.01**	1.01	0.54	1.89	0.97	1.06	0.72	1.54	0.78	1.56	0.99	2.44	0.05
Model 8																				

	Low	1.00				1.00				1.00				1.00				1.00			
	Medium	1.10	0.93	1.30	0.27	1.22	0.96	1.56	0.11	0.77	0.42	1.42	0.40	0.91	0.68	1.22	0.52	1.23	0.76	2.02	0.40
	High	**1.52**	**1.24**	**1.86**	**<0.001**	**1.64**	**1.07**	**2.51**	**0.02**	1.01	0.54	1.89	0.98	1.07	0.72	1.60	0.74	**1.84**	**1.13**	**3.00**	**0.01**
Model 9																				
	Low	1.00				1.00				1.00				1.00				1.00			
	Medium	1.08	0.91	1.27	0.39	1.22	0.96	1.56	0.11	0.70	0.38	1.29	0.25	0.88	0.66	1.18	0.39	1.23	0.75	2.02	0.41
	High	**1.52**	**1.24**	**1.86**	**<0.001**	1.50	0.98	2.30	0.06	0.95	0.50	1.78	0.86	1.07	0.72	1.59	0.75	**1.89**	**1.16**	**3.09**	**0.01**
Model 10																				
	Low	1.00				1.00				1.00				1.00				1.00			
	Medium	1.09	0.92	1.29	0.30	1.24	0.97	1.58	0.09	0.70	0.38	1.29	0.25	0.92	0.68	1.23	0.56	1.23	0.75	2.02	0.41
	High	**1.54**	**1.26**	**1.88**	**<0.001**	1.49	0.97	2.29	0.07	0.95	0.51	1.79	0.88	1.12	0.75	1.67	0.59	**1.89**	**1.16**	**3.09**	**0.01**
Model 11																				
	Low	1.00				1.00				1.00				1.00				1.00			
	Medium	1.08	0.92	1.28	0.35	1.23	0.96	1.57	0.10	0.70	0.38	1.30	0.26	0.91	0.68	1.23	0.56	1.22	0.75	2.00	0.43
	High	**1.53**	**1.25**	**1.87**	**<0.001**	1.52	0.99	2.32	0.06	0.95	0.51	1.79	0.88	1.09	0.73	1.63	0.67	**1.88**	**1.15**	**3.08**	**0.01**
Model 12																				
	Low	1.00				1.00				1.00				1.00				1.00			
	Medium	1.09	0.92	1.28	0.34	1.22	0.96	1.57	0.11	0.70	0.38	1.30	0.26	0.91	0.68	1.23	0.55	1.24	0.76	2.04	0.39
	High	**1.53**	**1.25**	**1.87**	**<0.001**	1.51	0.99	2.32	0.06	0.96	0.51	1.80	0.89	1.08	0.72	1.62	0.70	**1.91**	**1.16**	**3.12**	**0.01**
Model 13																				
	Low	1.00				1.00				1.00				1.00				1.00			
	Medium	1.08	0.92	1.28	0.34	1.22	0.95	1.56	0.12	0.70	0.38	1.30	0.26	0.91	0.68	1.23	0.54	1.25	0.76	2.05	0.38
	High	**1.52**	**1.24**	**1.87**	**<0.001**	1.50	0.98	2.30	0.06	0.98	0.52	1.84	0.95	1.10	0.73	1.64	0.66	**1.91**	**1.17**	**3.12**	**0.01**
Model 14																				
	Low	1.00				1.00				1.00				1.00				1.00			
	Medium	1.07	0.90	1.27	0.43	1.21	0.94	1.54	0.14	0.68	0.36	1.26	0.22	0.92	0.68	1.23	0.57	1.23	0.75	2.01	0.42
	High	**1.47**	**1.20**	**1.80**	**<0.001**	1.40	0.91	2.14	0.13	0.92	0.49	1.74	0.81	1.10	0.73	1.65	0.65	**1.83**	**1.12**	**2.99**	**0.02**
Model 15																				
	Low	1.00				1.00				1.00				1.00				1.00			
	Medium	1.07	0.91	1.27	0.42	1.21	0.94	1.56	0.13	0.67	0.36	1.26	0.21	0.92	0.69	1.24	0.60	1.26	0.76	2.09	0.37
	High	**1.46**	**1.19**	**1.79**	**<0.001**	1.37	0.88	2.13	0.16	0.93	0.49	1.76	0.82	1.08	0.72	1.62	0.73	**1.85**	**1.11**	**3.06**	**0.02**
Model 16																				
	Low	1.00				1.00				1.00				1.00				1.00			

Medium	1.07	0.91	1.27	0.42	1.21	0.94	1.56	0.13	0.67	0.36	1.25	0.21	0.92	0.69	1.24	0.60	1.29	0.78	2.15	0.32
High	**1.46**	**1.19**	**1.79**	**<0.001**	1.35	0.87	2.10	0.18	0.93	0.49	1.76	0.83	1.08	0.72	1.62	0.73	**1.88**	**1.13**	**3.11**	**0.01**

Cox proportional hazard regression was used. Hazard ratio, 95% CI and P-value were reported. Boldface indicated statistical significance (P<0.05).
SDOH was calculated from 9 variables of four domains: economic stability, education, neighborhood, physical environment and social cohesion, and health and system domain. For each of the 9 variables, an individual received a score of 1 if individuals' SDOH variable level was the high-risk level, and 0 otherwise. The SDOH sum-score was calculated by taking the sum of all 9 variable scores. SDOH was categorized as low (0-1, reference group), medium (2-4), and high (5-9).
Model 1: Adjusted for age, gender, family history of diabetes, race and ethnicity, marital status, and stress
Model 2: Adjusted for age, gender, family history of diabetes, race and ethnicity, marital status, stress, and hypertension mediation use
Model 3: Adjusted for age, gender, family history of diabetes, race and ethnicity, marital status, stress, hypertension mediation use, and lipid-lowering medication use
Model 4: Adjusted for age, gender, family history of diabetes, race and ethnicity, marital status, stress, hypertension mediation use, lipid-lowering medication use, and antidepressant use
Model 5: Adjusted for age, gender, family history of diabetes, race and ethnicity, marital status, stress, hypertension mediation use, lipid-lowering medication use, antidepressant use, and smoking
Model 6: Adjusted for age, gender, family history of diabetes, race and ethnicity, marital status, stress, hypertension mediation use, lipid-lowering medication use, antidepressant use, smoking, and sedentary behavior
Model 7: Adjusted for age, gender, family history of diabetes, race and ethnicity, marital status, stress, hypertension mediation use, lipid-lowering medication use, antidepressant use, smoking, sedentary behavior, and exercise
Model 8: Adjusted for age, gender, family history of diabetes, race and ethnicity, marital status, stress, hypertension mediation use, lipid-lowering medication use, antidepressant use, smoking, sedentary behavior, and exercise, and alternative healthy eating index (AHEI)-2010
Model 9: Adjusted for age, gender, family history of diabetes, race and ethnicity, marital status, stress, hypertension mediation use, lipid-lowering medication use, antidepressant use, smoking, sedentary behavior, and exercise, AHEI-2010, and body mass index (BMI)
Model 10: Adjusted for age, gender, family history of diabetes, race and ethnicity, marital status, stress, hypertension mediation use, lipid-lowering medication use, antidepressant use, smoking, sedentary behavior, and exercise, AHEI-2010, BMI, and total fat mass
Model 11: Adjusted for age, gender, family history of diabetes, race and ethnicity, marital status, stress, hypertension mediation use, lipid-lowering medication use, antidepressant use, smoking, sedentary behavior, and exercise, AHEI-2010, BMI, total fat mass, and systolic blood pressure (SBP)
Model 12: Adjusted for age, gender, family history of diabetes, race and ethnicity, marital status, stress, hypertension mediation use, lipid-lowering medication use, antidepressant use, smoking, sedentary behavior, and exercise, AHEI-2010, BMI, total fat mass, systolic blood pressure (SBP), and diastolic blood pressure (DBP)
Model 13: Adjusted for age, gender, family history of diabetes, race and ethnicity, marital status, stress, hypertension mediation use, lipid-lowering medication use, antidepressant use, smoking, sedentary behavior, and exercise, AHEI-2010, BMI, total fat mass, systolic blood pressure (SBP), diastolic blood pressure (DBP), and total cholesterol
Model 14: Adjusted for age, gender, family history of diabetes, race and ethnicity, marital status, stress, hypertension mediation use, lipid-lowering medication use, antidepressant use, smoking, sedentary behavior, and exercise, AHEI-2010, BMI, total fat mass, systolic blood pressure (SBP), diastolic blood pressure (DBP), total cholesterol, and high-density lipoprotein (HDL) cholesterol
Model 15: Adjusted for age, gender, family history of diabetes, race and ethnicity, marital status, stress, hypertension mediation use, lipid-lowering medication use, antidepressant use, smoking, sedentary behavior, and exercise, AHEI-2010, BMI, total fat mass, systolic blood pressure (SBP), diastolic blood pressure (DBP), total cholesterol, high-density lipoprotein (HDL) cholesterol, and low-density lipoprotein (LDL) cholesterol
Model 16: Adjusted for age, gender, family history of diabetes, race and ethnicity, marital status, stress, hypertension mediation use, lipid-lowering medication use, antidepressant use, smoking, sedentary behavior, and exercise, AHEI-2010, BMI, total fat mass, systolic blood pressure (SBP), diastolic blood pressure (DBP), total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides.
When stratified by race and ethnicity, the variable was not controlled**.**

Table S3.9. Associations of individual social determinants of health variables with type 2 diabetes in the Multi-Ethnic Study of Atherosclerosis, adjusting for confounders and mediators stepwise

	Overall				**White**				**Chinese**				**Black**				**Hispanic**			
	HR	**95%CI**		***P***	**HR**	**95%CI**		***P***	**HR**	**95%CI**		***P***	**HR**	**95%CI**		***P***	**HR**	**95%CI**		***P***
Model 1																				
Employment status (high vs. low risk)	**1.20**	**1.01**	**1.43**	**0.04**	1.16	0.83	1.63	0.38	1.19	0.78	1.81	0.42	0.83	0.52	1.32	0.42	**1.48**	**1.10**	**1.99**	**0.01**
Annual household income (high vs. low risk)	**1.32**	**1.16**	**1.51**	**<0.001**	**1.46**	**1.13**	**1.89**	**0.004**	0.87	0.61	1.24	0.44	1.19	0.93	1.52	0.16	**1.68**	**1.31**	**2.15**	**<0.001**
Education (high vs. low risk)	**1.31**	**1.15**	**1.49**	**<0.001**	**1.51**	**1.18**	**1.93**	**0.001**	1.36	0.96	1.92	0.08	0.96	0.74	1.25	0.76	**1.38**	**1.10**	**1.75**	**0.01**
Language spoken in exam 1 (high vs. low risk)	**1.41**	**1.15**	**1.72**	**0.001**					0.89	0.58	1.36	0.59					**1.53**	**1.22**	**1.92**	**<0.001**
Residence (high vs. low risk)	**1.22**	**1.05**	**1.42**	**0.01**	1.10	0.87	1.39	0.42	1.09	0.74	1.58	0.67	1.11	0.80	1.52	0.53	**1.96**	**1.31**	**2.95**	**0.001**
Neighborhood can be trusted (high vs. low risk)	1.01	0.89	1.13	0.94	1.05	0.84	1.30	0.70	0.98	0.70	1.37	0.91	1.05	0.84	1.32	0.65	0.91	0.72	1.13	0.39
Neighborhood help each other out (high vs. low risk)	1.05	0.93	1.20	0.43	1.23	0.97	1.55	0.08	1.09	0.77	1.54	0.62	1.01	0.79	1.30	0.93	0.91	0.72	1.16	0.45
A close-knit neighborhood (high vs. low risk)	0.98	0.87	1.10	0.67	1.01	0.82	1.24	0.93	1.13	0.82	1.57	0.46	1.05	0.84	1.31	0.65	0.81	0.65	1.01	0.06
Health insurance (high vs. low risk)	1.08	0.88	1.33	0.44	**2.31**	**1.44**	**3.71**	**0.001**	0.96	0.63	1.46	0.84	0.65	0.38	1.10	0.11	1.12	0.83	1.53	0.46
Model 2																				
Employment status (high vs. low risk)	1.20	1.01	1.43	0.04	1.18	0.84	1.65	0.35	1.19	0.78	1.81	0.42	0.82	0.51	1.30	0.40	1.47	1.09	1.98	0.01
Annual household	**1.32**	**1.16**	**1.51**	**<0.001**	**1.45**	**1.11**	**1.88**	**0.01**	0.86	0.61	1.23	0.41	1.20	0.94	1.53	0.15	**1.68**	**1.31**	**2.15**	**<0.001**

income (high vs. low risk)																				
Education (high vs. low risk)	**1.34**	**1.18**	**1.53**	**<0.001**	**1.55**	**1.21**	**1.99**	**0.001**	1.35	0.96	1.91	0.09	1.00	0.76	1.30	0.98	**1.43**	**1.13**	**1.82**	**0.003**
Language spoken in exam 1 (high vs. low risk)	**1.42**	**1.17**	**1.74**	**0.001**					0.88	0.58	1.35	0.56					**1.54**	**1.23**	**1.94**	**<0.001**
Residence (high vs. low risk)	1.22	1.04	1.42	0.01	1.07	0.85	1.36	0.56	1.09	0.75	1.59	0.65	1.09	0.79	1.50	0.61	**1.99**	**1.32**	**2.99**	**0.001**
Neighborhood can be trusted (high vs. low risk)	0.99	0.87	1.11	0.82	1.01	0.81	1.27	0.91	0.99	0.71	1.38	0.95	1.03	0.82	1.29	0.83	0.90	0.71	1.13	0.35
Neighborhood help each other out (high vs. low risk)	1.05	0.93	1.20	0.43	1.23	0.97	1.55	0.09	1.10	0.78	1.55	0.59	1.03	0.80	1.33	0.81	0.90	0.71	1.15	0.41
A close-knit neighborhood (high vs. low risk)	0.97	0.86	1.08	0.55	1.00	0.81	1.24	0.99	1.14	0.82	1.58	0.44	1.03	0.83	1.29	0.77	0.80	0.64	0.99	0.04
Health insurance (high vs. low risk)	1.08	0.88	1.33	0.45	**2.31**	**1.44**	**3.71**	**0.001**	0.97	0.63	1.48	0.87	0.60	0.35	1.04	0.07	1.14	0.83	1.55	0.42
Model 3																				
Employment status (high vs. low risk)	1.23	1.03	1.47	0.02	1.23	0.87	1.72	0.24	1.30	0.86	1.98	0.22	0.81	0.50	1.29	0.36	1.51	1.12	2.04	0.01
Annual household income (high vs. low risk)	**1.32**	**1.16**	**1.51**	**<0.001**	**1.47**	**1.13**	**1.91**	**0.005**	0.88	0.61	1.26	0.47	1.19	0.93	1.52	0.17	**1.68**	**1.31**	**2.16**	**<0.001**
Education (high vs. low risk)	**1.34**	**1.18**	**1.53**	**<0.001**	**1.50**	**1.17**	**1.92**	**0.001**	1.42	1.00	2.01	0.05	1.01	0.77	1.32	0.95	1.40	1.10	1.78	0.01
Language spoken in exam 1 (high vs. low risk)	**1.39**	**1.14**	**1.70**	**0.001**					0.93	0.60	1.42	0.72					**1.48**	**1.18**	**1.87**	**0.001**
Residence (high vs. low risk)	1.22	1.04	1.42	0.01	1.04	0.82	1.32	0.76	1.16	0.79	1.69	0.46	1.16	0.84	1.61	0.36	**1.90**	**1.26**	**2.86**	**0.002**

Neighborhood can be trusted (high vs. low risk)	0.98	0.87	1.10	0.72	1.02	0.81	1.27	0.89	1.00	0.71	1.39	0.98	1.02	0.81	1.28	0.86	0.90	0.71	1.12	0.34
Neighborhood help each other out (high vs. low risk)	1.06	0.93	1.21	0.38	1.23	0.97	1.56	0.08	1.06	0.75	1.50	0.74	1.02	0.79	1.32	0.86	0.95	0.75	1.21	0.68
A close-knit neighborhood (high vs. low risk)	0.96	0.85	1.08	0.48	0.99	0.80	1.22	0.90	1.11	0.80	1.54	0.55	1.02	0.81	1.27	0.87	0.81	0.65	1.01	0.06
Health insurance (high vs. low risk)	1.14	0.93	1.40	0.22	**2.46**	**1.53**	**3.97**	**<0.001**	1.05	0.68	1.62	0.82	0.60	0.34	1.06	0.08	1.18	0.86	1.61	0.30
Model 4																				
Employment status (high vs. low risk)	1.20	1.01	1.43	0.04	1.13	0.80	1.60	0.48	1.28	0.84	1.95	0.25	0.80	0.50	1.27	0.34	1.52	1.13	2.06	0.01
Annual household income (high vs. low risk)	**1.30**	**1.14**	**1.49**	**<0.001**	1.38	1.06	1.81	0.02	0.86	0.60	1.24	0.41	1.18	0.92	1.50	0.20	**1.67**	**1.30**	**2.15**	**<0.001**
Education (high vs. low risk)	**1.34**	**1.17**	**1.52**	**<0.001**	1.39	1.08	1.79	0.01	1.40	0.98	2.00	0.06	1.03	0.79	1.34	0.85	1.38	1.08	1.76	0.01
Language spoken in exam 1 (high vs. low risk)	**1.41**	**1.15**	**1.73**	**0.001**					0.91	0.59	1.40	0.66					**1.48**	**1.16**	**1.88**	**0.001**
Residence (high vs. low risk)	1.22	1.04	1.42	0.01	1.03	0.81	1.31	0.82	1.15	0.78	1.69	0.47	1.16	0.84	1.61	0.37	**1.89**	**1.26**	**2.86**	**0.002**
Neighborhood can be trusted (high vs. low risk)	0.97	0.86	1.09	0.57	0.99	0.79	1.24	0.94	0.98	0.70	1.38	0.93	1.00	0.80	1.26	0.98	0.91	0.72	1.14	0.39
Neighborhood help each other out (high vs. low risk)	1.05	0.92	1.20	0.46	1.21	0.96	1.54	0.11	1.05	0.74	1.49	0.77	1.02	0.79	1.32	0.85	0.95	0.74	1.20	0.64
A close-knit neighborhood	0.95	0.85	1.07	0.41	0.96	0.78	1.19	0.72	1.11	0.80	1.55	0.53	1.02	0.81	1.28	0.87	0.81	0.65	1.01	0.06

(high vs. low risk)																			
Health insurance (high vs. low risk)	1.13	0.92	1.39	0.25	**2.45**	**1.51**	**3.97**	**<0.001**	1.04	0.68	1.61	0.85	0.60	0.34	1.05	0.07	1.12	0.81	1.54	0.49
Model 5																				
Employment status (high vs. low risk)	1.24	1.04	1.49	0.02	1.11	0.78	1.58	0.56	1.29	0.85	1.96	0.24	0.88	0.54	1.43	0.61	1.58	1.17	2.14	0.003
Annual household income (high vs. low risk)	**1.30**	**1.14**	**1.50**	**<0.001**	1.34	1.02	1.76	0.03	0.86	0.60	1.24	0.41	1.14	0.88	1.48	0.34	**1.71**	**1.32**	**2.22**	**<0.001**
Education (high vs. low risk)	**1.33**	**1.16**	**1.52**	**<0.001**	1.30	1.00	1.69	0.05	1.40	0.98	2.00	0.07	0.97	0.73	1.30	0.85	**1.44**	**1.12**	**1.85**	**0.004**
Language spoken in exam 1 (high vs. low risk)	**1.53**	**1.24**	**1.88**	**<0.001**					0.91	0.59	1.41	0.68					**1.62**	**1.26**	**2.07**	**<0.001**
Residence (high vs. low risk)	1.21	1.03	1.41	0.02	1.02	0.80	1.30	0.87	1.15	0.78	1.69	0.47	1.12	0.80	1.58	0.50	**2.00**	**1.30**	**3.06**	**0.002**
Neighborhood can be trusted (high vs. low risk)	0.98	0.86	1.11	0.71	1.00	0.79	1.25	0.99	0.98	0.70	1.38	0.91	1.04	0.82	1.32	0.77	0.91	0.72	1.15	0.44
Neighborhood help each other out (high vs. low risk)	1.06	0.93	1.21	0.39	1.21	0.95	1.54	0.12	1.05	0.74	1.49	0.79	1.05	0.81	1.37	0.70	0.95	0.74	1.21	0.67
A close-knit neighborhood (high vs. low risk)	0.96	0.85	1.08	0.46	0.97	0.78	1.19	0.74	1.11	0.80	1.55	0.53	0.99	0.78	1.25	0.91	0.84	0.67	1.06	0.14
Health insurance (high vs. low risk)	1.17	0.95	1.45	0.13	**2.67**	**1.64**	**4.33**	**<0.001**	1.04	0.68	1.61	0.85	0.70	0.40	1.24	0.22	1.11	0.81	1.54	0.51
Model 6																				
Employment status (high vs. low risk)	1.25	1.05	1.50	0.01	1.21	0.85	1.73	0.29	1.32	0.87	2.01	0.20	0.86	0.53	1.39	0.52	1.57	1.16	2.12	0.003
Annual household	**1.29**	**1.12**	**1.48**	**<0.001**	1.24	0.94	1.63	0.13	0.90	0.62	1.29	0.55	1.13	0.87	1.47	0.36	**1.69**	**1.30**	**2.20**	**<0.001**

income (high vs. low risk)																				
Education (high vs. low risk)	**1.34**	**1.17**	**1.53**	**<0.001**	1.24	0.95	1.60	0.11	1.36	0.95	1.96	0.10	0.99	0.74	1.32	0.95	**1.47**	**1.14**	**1.89**	**0.003**
Language spoken in exam 1 (high vs. low risk)	**1.67**	**1.35**	**2.06**	**<0.001**					0.95	0.62	1.48	0.83					**1.81**	**1.40**	**2.33**	**<0.001**
Residence (high vs. low risk)	1.19	1.01	1.39	0.03	0.97	0.76	1.24	0.82	1.24	0.84	1.83	0.29	1.10	0.79	1.55	0.57	**2.01**	**1.31**	**3.08**	**0.001**
Neighborhood can be trusted (high vs. low risk)	0.97	0.85	1.10	0.60	1.03	0.82	1.29	0.83	0.91	0.65	1.28	0.60	1.00	0.78	1.27	0.97	0.92	0.73	1.16	0.46
Neighborhood help each other out (high vs. low risk)	1.04	0.92	1.19	0.52	1.20	0.95	1.53	0.13	1.04	0.73	1.47	0.85	1.04	0.79	1.35	0.80	0.93	0.73	1.19	0.58
A close-knit neighborhood (high vs. low risk)	0.94	0.83	1.06	0.29	0.92	0.74	1.14	0.44	1.06	0.76	1.48	0.75	0.99	0.78	1.25	0.93	0.83	0.66	1.04	0.10
Health insurance (high vs. low risk)	1.22	0.99	1.51	0.06	1.88	1.15	3.07	0.01	1.05	0.68	1.62	0.83	0.72	0.40	1.27	0.25	1.26	0.91	1.74	0.17
Model 7																				
Employment status (high vs. low risk)	1.19	0.99	1.44	0.06	1.16	0.81	1.67	0.42	1.33	0.87	2.04	0.19	0.84	0.51	1.36	0.47	1.40	1.02	1.91	0.04
Annual household income (high vs. low risk)	**1.24**	**1.08**	**1.43**	**0.003**	1.18	0.89	1.57	0.26	0.90	0.62	1.30	0.56	1.11	0.85	1.45	0.43	**1.61**	**1.23**	**2.11**	**0.001**
Education (high vs. low risk)	**1.29**	**1.13**	**1.48**	**<0.001**	1.17	0.90	1.52	0.24	1.41	0.98	2.04	0.07	0.99	0.74	1.32	0.94	1.38	1.06	1.78	0.02
Language spoken in exam 1 (high vs. low risk)	**1.65**	**1.33**	**2.04**	**<0.001**					0.96	0.61	1.52	0.87					**1.81**	**1.39**	**2.34**	**<0.001**
Residence (high vs. low risk)	1.19	1.01	1.39	0.04	0.96	0.75	1.23	0.75	1.26	0.84	1.88	0.26	1.08	0.76	1.52	0.68	**2.13**	**1.37**	**3.32**	**0.001**

Neighborhood can be trusted (high vs. low risk)	0.97	0.85	1.10	0.59	1.00	0.79	1.26	0.98	0.92	0.66	1.31	0.66	1.03	0.80	1.32	0.82	0.92	0.72	1.16	0.47
Neighborhood help each other out (high vs. low risk)	1.03	0.90	1.17	0.67	1.16	0.91	1.48	0.23	1.05	0.74	1.50	0.79	1.05	0.80	1.37	0.75	0.91	0.71	1.18	0.48
A close-knit neighborhood (high vs. low risk)	0.94	0.83	1.06	0.29	0.93	0.75	1.15	0.50	1.02	0.72	1.42	0.93	0.99	0.78	1.25	0.90	0.82	0.65	1.04	0.10
Health insurance (high vs. low risk)	1.12	0.90	1.38	0.31	1.80	1.09	2.98	0.02	0.96	0.61	1.51	0.85	0.62	0.35	1.10	0.10	1.12	0.80	1.57	0.53

Cox proportional hazard regression was used. Hazard ratio, 95% CI and P-value were reported. Boldface indicated statistical significance (Bonferroni-corrected P<0.05/9).
Model 1: Adjusted for age, gender, family history of diabetes, race/ethnicity, and marital status.
From model 2, mediators were adjusted.
Model 2: Adjusted for age, gender, family history of diabetes, race and ethnicity, marital status, and stress
Model 3: Adjusted for age, gender, family history of diabetes, race and ethnicity, marital status, stress, hypertension mediation use, lipid-lowering medication use, and antidepressant use
Model 4: Adjusted for age, gender, family history of diabetes, race and ethnicity, marital status, stress, hypertension mediation use, lipid-lowering medication use, antidepressant use, smoking, sedentary behavior, and exercise
Model 5: Adjusted for age, gender, family history of diabetes, race and ethnicity, marital status, stress, hypertension mediation use, lipid-lowering medication use, antidepressant use, smoking, sedentary behavior, and exercise, and alternative healthy eating index (AHEI)-2010
Model 6: Adjusted for age, gender, family history of diabetes, race and ethnicity, marital status, stress, hypertension mediation use, lipid-lowering medication use, antidepressant use, smoking, sedentary behavior, and exercise, AHEI-2010, and body mass index (BMI)
Model 7: Adjusted for age, gender, family history of diabetes, race and ethnicity, marital status, stress, hypertension mediation use, lipid-lowering medication use, antidepressant use, smoking, sedentary behavior, and exercise, AHEI-2010, BMI, total fat mass, systolic blood pressure (SBP), diastolic blood pressure (DBP), total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides.
When stratified by race and ethnicity, the variable was not controlled.

4. Chapter four: Racial and ethnic disparities of type 2 diabetes in the United States: the pathways through exercise in the Multi-Ethnic Study of Atherosclerosis

4.1. Abstract

Objective

To examine whether and to what degree racial and ethnic differences in type 2 diabetes (T2D) were explained by different exercise levels in the United States.

Methods

We included 5,772 adults (45–84 years) free of T2D at 2000–2002 and followed until 2020 from the Multi-Ethnic Study of Atherosclerosis (MESA) cohort. We examined associations of race and T2D risk using multivariable Cox proportional hazard regressions and assessed effects explained by exercise using natural mediation effects.

Results

Controlling for confounders, Hispanic [HR (95% CI): 2.02 (1.74–2.34)], Chinese [1.50 (1.24–1.82)], and Black participants [1.66 (1.44–1.93)] had higher T2D risks than White participants. Compared to White participants, Hispanic [β (SE): -0.29 (0.04) square root of MET-hour/day] and Chinese [-0.25 (0.04)] participants had lower exercise, but not for Black participants [-0.01 (0.03)]. Exercise explained T2D relative risk by 9.7% for Hispanic and 11.7% for Chinese, but not for Black participants compared to White participants.

Conclusions

Promoting exercise is crucial to decrease T2D risk for all racial groups but may additionally narrow disparities in T2D among Hispanic and Chinese populations.

4.2. Introduction

Diabetes is one of the most common chronic diseases, posing huge healthcare costs and increasing risks of cardiovascular disease (CVD) and premature mortality.[2] In the United States (US) in 2021, 38.4 million people had diabetes, representing 11.6% of the population, with 95% having type 2 diabetes (T2D).[2] Moreover, racial and ethnic disparities of T2D in the US have been well documented and they are worsening over time.[1,2,7] According to the National Diabetes Statistics Report in 2017–2018, the age-adjusted incidence of diagnosed T2D was the highest among Hispanic (9.7 per 1000 persons), followed by Black (8.2 per 1000 persons), Asian (7.4 per 1000 persons) and White (5.0 per 1000 persons) populations.[1]

To potentially reduce the higher risk of T2D in racial and ethnic minority groups, it is critical to identify modifiable factors contributing to such disparities. In this regard, previous studies in the US have identified multiple factors [e.g., education, dietary quality, and body mass index (BMI)] that may explain the racial and ethnic disparities of T2D.[7,34,56,63,64,108,187–189] However, most studies were cross-sectional by design (not establishing the time sequence),[7,187,188] conducted in special populations (e.g., postmenopausal women)[56,63] or single geographic location (e.g., San Antonio, Texas)[189]. In addition, most studies only provided qualitative estimations[34,108] or controlled for multiple factors together and could not find one factor explaining how much racial differences in T2D[63,64].

Exercise is a well-established modifiable factor for T2D.[116] Increasing the level of exercise by 5 hours per week may reduce T2D risk by 25%.[61] Previous studies found that Hispanic, Black and Asian populations engaged in less exercise compared to White populations.[64,66,67] However, studies investigating whether exercise level could explain the racial differences of T2D are sparse. The Women's Health Initiative (WHI) Study found the combined

exercise and household activities explained approximately 6% racial difference of T2D for Black and Hispanic populations, compared to White populations.[56] However, this study did not differentiate between exercise and household activities, only assessed baseline activities, and only included postmenopausal women.[56] Thus, we aimed to examine whether exercise potentially explained racial and ethnic differences (Hispanic, Black, Asian vs. White) in T2D in a multi-racial and ethnic cohort study having longitudinal measures of exercise. We also estimated the degree to which exercise accounted for these disparities.

4.3. Methods

Study design and population

Study participants were from the Multi-Ethnic Study of Atherosclerosis (MESA), a population-based, prospective cohort study of 6,814 adults aged 45–84 years who were free of known CVD in 2000–2002 (study exam 1, baseline).[162] Following exams were administered in 2002–2004 (exam 2), 2004–2005 (exam 3), 2005–2007 (exam 4), 2010–2013 (exam 5), and 2016–2018 (exam 6).[162]

MESA also conducted 21 follow-up telephone interviews from 2001 to 2020 to inquire about new disease diagnoses.[162] For the current study, we excluded participants who had T2D (n=938) or missing T2D status (n=66) at baseline, or those without exercise information at any of the exams (n=17), or participants not having any follow-up visits after baseline (n=21). Finally, we included 5,772 participants in the study sample (**Figure S4.1**). We conducted the analysis between February 2023 and June 2023. The institutional review boards of each site approved the study, and all participants provided written informed consent. This manuscript was written according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Assessment of race and ethnicity

Race and ethnicity, a primarily social construct, was self-reported at baseline (exam 1) as non-Hispanic White (White thereafter), Hispanic, non-Hispanic Black (Black thereafter), or non-Hispanic Chinese American (Chinese thereafter).

Assessment of exercise

Physical activity was measured longitudinally via the self-administrated Typical Week Physical Activity Survey (TWPAS) at exam 1, 2, 3, 5, and 6. The TWPAS was validated for measuring PA in the Cross Cultural Activity Participation Study.[190,191] Participants reported the frequency and duration of various activities during a typical week in the past month, including household chores, lawn/yard/garden/farm, care of children/adults, transportation, walking for exercise (not at work), sports/dancing, conditioning activities (e.g., aerobics, cycling, and swimming), leisure activities (e.g., watching TV, read, knit, sew, visit, do nothing, non-work recreational computer use), occupational and volunteer activities.

We calculated the amount of exercise [i.e., metabolic equivalent of task (MET)-minutes/week] by multiplying the MET value of walking for exercise, sports/dancing, and conditioning activities with the time spent on these activities and then summed them. We used habitual exercise (i.e., a cumulative average method, the average of exercise from baseline to develop T2D, or until last contact if not developing T2D), as it could decrease within-subject variation and reflect long-term exercise.[192]

Ascertainment of type 2 diabetes

Individuals were diagnosed as having T2D if they either had a fasting serum glucose (FPG) ≥126 mg/dL according to American Diabetes Association criteria[193] or self-reported use of

glucose-lowering medications at each exam or self-reported diabetes diagnosis by physicians at exam 1, 5, 6 and at 21 telephone interviews.

Assessment of covariates

The sociodemographic information (i.e., age, gender, marital status, education, employment, annual household income, health insurance), medication use (i.e., hypertension medication use, lipid-lowering medication use, antidepressant use), and cigarettes smoking were measured at exam 1 from detailed questionnaires.[162,178] Family history of diabetes was measured at exam 2 from the family history questionnaire. Dietary intake over the past year was assessed using the 120-item food frequency questionnaire (FFQ) at exam 1. We calculated the Alternative Healthy Eating Index (AHEI)-2010 using a common method developed in previous studies as an indicator of the dietary quality.[60] Chronic stress was assessed using the Chronic Burden Scale (CBS) at exam 1, including job difficulties, financial strain, relationship problems, or health problems (self), health problems (someone close to participants)], ranging from 0 to 5) and categorized as low (score of 0), medium (score of 1) and high (score ≥2) levels.[194] Sedentary behavior (MET-minutes/week) was assessed including reading, sitting, recreational computer, and watching television from the TWPAS at exam 1.

Weight (pound) and height (cm) were assessed at exam 1 using a balance-beam scale and stadiometer, respectively. BMI (kg/m^2) was calculated as [weight (pound) × 0.45]/[height (cm)/100]. Total fat mass percentage (%) was estimated using equations validated by dual-energy X-ray absorptiometry (DXA)-estimated body fat percentage with correlation coefficients ranging from 0.80 to 0.86: 76−(20×(height/waist)) for women and 64−(20×(height/waist)) for men.[179] We calculated total fat mass (kg) by weight × (total fat mass percentage/100). Resting blood pressure (BP) was measured three times in a seated position using an automated oscillometric

sphygmomanometer (model Pro 100, Critikon, Tampa, Florida, US), and calculated based on the average of the last two of three measurements. Lipid profiles [i.e., total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides] were measured at exam 1 from plasma samples. Low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald equation.[180]

Statistical analysis

We presented baseline characteristics and described the distribution of exercise. We reported the percentage and frequency [% (N)] for categorical variables and mean and standard deviation (SD) for continuous variables. We used SAS version 9.4 (SAS Institute, Cary, NC, USA) and R version 4.2.1. for analyses and considered the statistically significant level as α level <0.05.

We first examined associations of race and ethnicity with incident T2D using Cox proportional hazard regression models. The proportional hazards assumption was verified using Schoenfeld residuals. The adjusted models controlled for confounders of age (years), gender (male or female), and family history of diabetes (yes or no). We also additionally adjusted for potential mediators that might influence racial and ethnic differences in T2D: marital status (married/living with a partner or not), education (high school or less, associates, bachelor's or higher degree), employment (employed or unemployed/homemaker), annual household income (<$25,000, $25,000-$49,999, ≥$50,000), health insurance (with or without insurance), stress (low, medium ,or high), hypertension medication use (yes or no), lipid-lowering medication use (yes or no), antidepressant use (yes or no), smoking (never, former, or current), AHEI-2010, sedentary behavior (MET-minutes/week), BMI (kg/m^2), total fat (kg), systolic BP (SBP) (mmHg), diastolic BP (DBP) (mmHg), total cholesterol (mg/dl), HDL cholesterol (mg/dl), LDL cholesterol (mg/dl), triglycerides (mg/dl), and habitual exercise (MET-minutes/week). Age as the

time scale with left truncation of age at study entry was used in Cox regressions, to minimize immortal time survival bias.[195] Second, we explored associations of race and ethnicity with habitual exercise using linear regression models adjusting for confounders of age, gender, and family history of diabetes. We transformed the habitual exercise to the square root of exercise to ensure its normality. Third, we assessed associations between habitual exercise and T2D using Cox proportional hazard regression models, adjusting for confounders of age, gender, family history of diabetes marital status, education, employment, annual household income, health insurance, stress, hypertension medication use, lipid-lowering medication use, antidepressant use, smoking, AHEI-2010, sedentary behavior, BMI, total fat, SBP, DBP, total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides in each racial and ethnic group.

We assessed the potential mediating role of exercise using interventional path-specific effects (iPSEs)[170,172] (**Figure S4.2**), with bootstrapping 200 times for 95% confidence intervals (CIs). The iPSEs was estimated by the hazard ratio (HR) using the Cox proportional hazard regressions. For the interventional effects, we decomposed the interventional total effect (iTE) into two iPSEs,: (1) the indirect pathway: iPSE (Exercise) ($HR_{ipseExercise}$, red color in **Figure S4.2**) for the path through exercise; (2) the direct pathway: iPSE (NotExercise) ($HR_{ipseNotExercise}$, yellow color in **Figure S4.2**) for the path not through exercise. The mediated proportion explained by exercise was calculated from $\ln(HR_{ipseExercise})/\ln(HR_{iTE})$ in iPSEs.[196]

As missing percentages of each adjusted covariate were < 9.5%, we used the completed data analyses in the primary analysis and treated the missing value as a separate category for adjusted models in sensitivity analyses. In addition, individuals were diagnosed as having T2D using FPG and glucose-lowering medications, not using self-reported receiving diabetes diagnosis by physicians in the sensitivity analyses.

4.4. Results

Characteristics of study participants

Among 5772 participants, 41.7% were White; 26.0% were Black; 20.4% were Hispanic; and 11.9% were Chinese. Hispanic and Black participants were younger (Hispanic: 60.66 years, Black: 61.69 years, White: 62.38 years), had higher percentages of current smokers (Hispanic: 13.8%, Black: 18.1%, White: 11.6%), had lower AHEI-2010 (Hispanic: 52.02, Black: 52.71, White: 54.66) and higher BMI (kg/m^2) (Hispanic: 28.75, Black: 29.61, White: 27.28) than White participants. Hispanic, Black, and Chinese participants were less likely to have bachelor's or higher degree (Hispanic: 11.4%, Black: 35.6%, Chinese: 39.7%, White: 50.8%) and annual household income ≥$50,000 (Hispanic: 20.2%, Black: 39.4%, Chinese: 29.7%, White: 57.9%), and were more likely to have no insurance (Hispanic: 17.5%, Black: 6.2%, Chinese: 19.6%, White: 2.7%) than White participants (**Table 4.1**).

Risk of type 2 diabetes by race and ethnicity

During a median follow-up time of 15.7 years, 1305 participants developed T2D (incidence rate 17.4 per 1000 person-years). Hispanic participants had the highest crude incidence rate of T2D (25.6 per 1000 person-years), followed by Black (21.4 per 1000 person-years), Chinese (17.0 per 1000 person-years), and White participants (12.0 per 1000 person-years). After adjusting for confounders of age, gender, and family history of diabetes, Hispanic (HR = 2.02, 95% CI: 1.74–2.34, $P < 0.001$), Black (HR = 1.66, 95% CI: 1.44–1.93, $P < 0.001$), and Chinese (HR = 1.50, 95% CI: 1.24–1.82, $P < 0.001$) participants still had higher risk of T2D than White participants. After further adjusting for potential mediators including socioeconomic status (SES), marital status, stress, medications, smoking, AHEI-2010, sedentary behavior, BMI, total fat, BP, lipids, and habitual exercise, both Hispanic (HR = 1.55, 95% CI: 1.27–1.88, P <

0.001) and Black (HR = 1.39, 95% CI: 1.15–1.68, P = 0.001) participants continued to exhibit a higher risk of T2D than White participants, although this risk was reduced. Chinese participants' T2D risk (HR = 2.01, 95% CI: 1.55–2.60, P < 0.001) not only remained higher but also increased than White participants (**Table 4.2**).

Level of exercise by race and ethnicity

During the following up, White participants had the highest habitual exercise (MET-hours/day)] [White: median (quartile 1, quartile 3), 3.15 (1.44, 5.99); Black: 2.99 (1.12, 5.83); Chinese: 2.33 (1.18, 4.29); Hispanic: 2.04 (0.81, 4.61)] (**Figure 4.1**). In the linear regressions adjusted for confounders of age, gender, and family history of diabetes, Hispanic [β = -0.29 (standard error, SE = 0.04), P < 0.001] and Chinese [β = -0.25 (SE = 0.04), P < 0.001] participants still had lower habitual exercise (square root of MET-hours/day) than White participants, while Black participants had similar habitual exercise [β = -0.01 (SE = 0.03), P = 0.85] as White participants (**Table 4.2**).

Associations of exercise with type 2 diabetes

In unadjusted models, habitual exercise (MET-hours/day) was inversely associated with T2D risk in White (HR = 0.93, 95% CI: 0.90–0.96, P < 0.001), Hispanic (HR = 0.94, 95% CI: 0.90–0.97, P < 0.001), Black (HR = 0.99, 95% CI: 0.97–1.01, P = 0.27), and Chinese participants (HR = 0.98, 95% CI: 0.93–1.03, P = 0.40), although results were only statistically significant among White and Hispanic participants. After adjusting for confounders of age, gender, family history of diabetes, marital status, SES, stress, medication use, smoking, AHEI-2010, sedentary behavior, BMI, total fat, BP, lipids, habitual exercise (MET-hours/day) was still inversely associated with T2D risk in White (HR = 0.96, 95% CI: 0.93–0.99, P = 0.02) and Hispanic participants (HR = 0.95, 95% CI: 0.92–0.99, P = 0.02), but not in Black (HR = 1.01, 95% CI:

0.98–1.03, P = 0.67) and Chinese participants (HR = 1.00, 95% CI: 0.94–1.06, P = 0.91) (**Table 4.2).**

Mediation analyses of race and ethnicity and type 2 diabetes explained by exercise

Black participants had a similar level of habitual exercise as White participants (**Figure 4.1, Table 4.2**) and we did not find exercise explained racial differences in T2D when comparing Black to White participants (**Table S4.1**). The estimated risk of T2D mediated by exercise was 1.08 [(1.04–1.13), P <0.001] for Hispanic and 1.06 [(1.02–1.10), P <0.001] for Chinese participants. Exercise may account for 9.7% and 11.7% of racial and ethnic differences in T2D when comparing Hispanic and Chinese to White participants (**Table 4.2**). In sensitivity analysis, results were unchanged after creating a missing category for the missing covariate (**Table S4.2**), or using FPG and glucose-lowering medications to diagnose T2D (**Table S4.3**).

4.5. Discussion

In this large multi-race and ethnicity study with longitudinal measurements of exercise in the US, we confirmed that all Hispanic, Black and Chinese participants had higher risks of T2D, and found only Hispanic and Chinese participants had lower levels of exercise than White participants. In addition, we discovered that exercise may be a mediator of the T2D risk differences for Hispanic and Chinese, but not for Black participants, when compared to White participants. Overall, exercise contributed to about one-tenth of racial differences in T2D when comparing Hispanic and Chinese to White participants, respectively. To our knowledge, the present study is the first longitudinal study examining to what degree the racial and ethnic differences in T2D are mediated by exercise in the US.

Evidence suggested that the higher risk of T2D observed in racial and ethnic minorities may be attributed to a range of factors, including low SES, high stress levels, undesired

lifestyles, and obesity.[7,34,56,63,64,108,187–189] Our analysis also revealed that, comparing Hispanic and Black with White participants, the disparity in T2D risk decreased after adjusting for potential mediators such as SES, stress, behavioral factors, obesity, BP, and lipid levels, based on the age-, gender-, and family history of diabetes- adjusted model (**Table 4.2**). We also detailed the stepwise adjustments for mediators in **Table S4.4,** which preliminarily suggested that the aforementioned mediators may explain part of the racial and ethnic disparities in T2D risk, comparing Hispanic and Black to White participants. Conversely, the risk of T2D in Chinese relative to White participants was found to increase after including these mediators based on the confounders- adjusted model (**Table 4.2**). Notably, this increase was largely attributed to adjustments for BMI (**Table S4.4**). Given that Chinese exhibited lower BMI compared to White participants[197] (**Table 4.1**), controlling for BMI in the model likely diminished the protective effect associated with lower levels of obesity. Future studies quantify the mediation proportion by each mediator are needed.

Although exercise is an established modifiable risk reduction factor for T2D, limited research has been done to understand whether and to what degree exercise may explain the racial differences in T2D. In the Nurses' Health Study, further adjusting for exercise, family history of diabetes, smoking and alcohol drinking based on the age- and BMI-controlled model, Hispanic and Asian participants' T2D risk decreased compared to White participants.[63] In the Atherosclerosis Risk in Communities Study, further adjusting or exercise, smoking, alcohol drinking, and dietary energy based on the age- and family history- adjusted model, Black participants' T2D risk decreased compared to White participants.[64] However, in both studies, as exercise and other factors (e.g., smoking and alcohol drinking) were adjusted simultaneously, it was unclear whether the reduced T2D risk was due to exercise or other factors.[63,64] Furthermore,

WHI study among 158,833 postmenopausal women examined baseline mixed activities as a mediator for racial and ethnic differences in T2D.[56] It found that Hispanic [10.46 (13.73)] and Black [9.60 (12.35)], but not Asian participants [13.05 (14.18)], had lower combined exercise and household activities (MET-hours/week) than White participants [12.83 (13.76)], which explained 6% of racial differences (Hispanic or Black vs. White) in T2D.[56] Although promising, the major limitation of the WHI study was that the exercise was combined with household activities, thus, it was unable to differentiate the effect of exercise and household activities.[56] In addition, the study had an average of 10.4 years of follow-up but only assessed baseline activities which were likely to change over time. Moreover, the WHI study did not have data for Asian subpopulations.[56] Our findings were in the same line with the WHI study regarding the role of exercise in explaining the risk difference between Hispanic and White participants.[56] More importantly, our study provided new evidence that habitual exercise also explained about one-tenth of higher T2D risk in Chinese as compared to White participants.

We did not find that exercise was a mediator for Black participants' higher T2D risk, which could be explained by the fact that Black participants in MESA had similar levels of habitual exercise as White participants (**Table 4.2**).[198] Compared to national samples, Black participants in MESA tended to have better SES, including a higher proportion of above high school degree (MESA Black: 71.0% vs. national Black: 64.0%)[183] and a higher proportion of having health insurance (MESA Black: 93.8% vs. national Black: 82.5%)[184]. Indeed, we found positive correlations between higher education (r=0.21) and having insurance (r=0.10) and exercise levels in our studies, which indicated that SES was likely to be the upstream factors related to similar exercise levels between Black and White populations. Future studies are

needed to investigate the role of exercise in Black populations' higher T2D risk, either using nationally representative samples or stratifying the analyses by SES levels.[199]

Strengths and limitations

This study included four racial and ethnic groups in the US and had longitudinal measures of exercise which was unique to address our research questions. The time sequence of exercise and T2D ensured the temporality of associations and the use of cumulative exercise captured not only the habitual levels of exercises over time but also reduced measurement errors. Some limitations of our study are worthy of discussion. First, this study was observational in design. Although we tried to control for multiple confounders, the residual confounding could not be completely ruled out. Second, exercise in our study was self-reported using TWPAS. However, the TWPAS has been validated by accelerometers (r=0.54) in the Cross-Cultural Activity Participation Study.[190,191] In addition, given the prospective cohort design, exercise was measured before the onset of T2D. Thus, the measurement errors were likely to be non-differential. Lastly, we only had Chinese in MESA, future studies including more Asian subgroups are needed.

4.6. Conclusions

In this prospective study with longitudinal measurements, we found that exercise may explain approximately 10% of racial differences in T2D when comparing Hispanic and Chinese to White populations. Promoting regular exercise remains essential for reducing T2D risk across all racial and ethnic groups, but may additionally narrow the T2D risk disparities among Hispanic and Chinese populations. Future studies are warranted to confirm these findings and develop culture-appropriated exercise interventions.

Table 4.1. Baseline characteristics of participants by racial and ethnic groups in the Multi-Ethnic Study of Atherosclerosis study

Characteristics	Overall (n=5772)		White [41.7% (n=2409)]		Hispanic [20.4% (n=1175)]			Black [26.0% (1499)]			Chinese [11.9% (689)]		
							P-values			P-values			P-values
Age (years)	61.77	(10.29)	62.38	(10.26)	60.66	(10.34)	<0.001	61.69	(10.17)	0.04	61.71	(10.40)	0.14
Female, % (N)	53.5	(3085)	52.9	(1274)	52.0	(611)	0.62	56.1	(841)	0.05	52.1	(359)	0.72
Family history of diabetes, % (N)	34.3	(1802)	28.8	(646)	40.5	(429)	<0.001	42.6	(566)	<0.001	26.2	(161)	0.21
Married/living with a partner, % (N)	62.0	(3544)	66.6	(1596)	60.3	(700)	<0.001	46.3	(681)	<0.001	82.4	(567)	<0.001
Education, % (N)							<0.001			<0.001			<0.001
High school or less	33.8	(1947)	20.9	(504)	62.7	(737)		29.0	(434)		39.5	(272)	
Associates	28.8	(1658)	28.3	(682)	25.9	(304)		35.4	(529)		20.8	(143)	
Bachelor's or higher	37.5	(2162)	50.8	(1222)	11.4	(134)		35.6	(533)		39.7	(273)	
Unemployed/homemaker, % (N)	13.2	(763)	12.3	(295)	18.1	(213)	<0.001	8.2	(123)	<0.001	19.2	(132)	<0.001
Annual household income, % (N)							<0.001			<0.001			<0.001
<$25,000	29.2	(1627)	15.6	(367)	46.4	(533)		28.5	(394)		48.7	(333)	
$25,000–$49,999	28.7	(1602)	26.6	(626)	33.4	(384)		32.1	(444)		21.6	(148)	
≥$50,000	42.1	(2345)	57.9	(1365)	20.2	(232)		39.4	(545)		29.7	(203)	
No insurance, % (N)	8.6	(496)	2.7	(64)	17.5	(205)	<0.001	6.2	(92)	<0.001	19.6	(135)	<0.001
Stress, % (N)							0.27			0.09			<0.001
Low	39.7	(2292)	36.6	(881)	39.2	(461)		36.6	(547)		58.5	(403)	
Medium	31.3	(1805)	33.2	(799)	32.6	(383)		30.4	(454)		24.5	(169)	
High	29.0	(1670)	30.2	(727)	28.2	(331)		33.1	(495)		17.0	(117)	
Hypertension medication use, % (N)	33.2	(1917)	31.1	(748)	25.1	(173)	0.003	44.9	(673)	<0.001	27.5	(323)	0.03

Lipid-lowering medication use, % (N)	14.6	(841)	17.6	(423)	11.6	(80)	<0.001	13.6	(203)	0.001	11.5	(135)	<0.001
Antidepressant use, % (N)	7.5	(431)	12.4	(299)	5.5	(65)	<0.001	3.4	(51)	<0.001	2.3	(16)	<0.001
Cigarettes smoking, % (N)							<0.001			<0.001			<0.001
Never	50.5	(2912)	44.4	(1070)	54.7	(643)		45.1	(675)		76.2	(524)	
Former	36.6	(2108)	44.0	(1060)	31.5	(370)		36.8	(550)		18.6	(128)	
Current	13.0	(748)	11.6	(279)	13.8	(162)		18.1	(271)		5.2	(36)	
Alternative healthy eating index (AHEI)-2010	53.69	(9.64)	54.66	(10.26)	52.02	(8.83)	<0.001	52.71	(9.67)	<0.001	55.09	(7.96)	0.25
Sedentary behavior (MET-minutes/week)	1694.19	(1138.81)	1742.90	(1153.60)	1417.90	(980.30)	<0.001	1951.60	(1247.00)	<0.001	1435.10	(918.90)	<0.001
Body mass index (BMI, kg/m^2)	27.75	(5.27)	27.28	(4.91)	28.75	(4.72)	<0.001	29.61	(5.81)	<0.001	23.64	(3.27)	<0.001
Total fat mass (kg)	27.54	(9.71)	27.37	(9.05)	28.07	(8.45)	0.02	30.85	(11.02)	<0.001	19.99	(6.03)	<0.001
Systolic blood pressure (SBP, mmHg)	125.56	(21.26)	123.00	(20.27)	123.60	(21.66)	0.54	130.70	(21.50)	<0.001	125.40	(21.55)	0.002
Diastolic blood pressure (DBP, mmHg)	71.91	(10.27)	70.24	(9.97)	71.94	(10.34)	<0.001	74.65	(10.21)	<0.001	71.84	(10.20)	<0.001
Total cholesterol (mg/dl)	195.04	(34.99)	196.30	(34.51)	193.50	(32.02)	0.05	190.80	(36.12)	<0.001	198.80	(35.59)	0.04
High-density lipoprotein (HDL) cholesterol (mg/dl)	51.69	(14.98)	52.74	(15.74)	50.34	(12.74)	<0.001	53.28	(15.50)	0.29	48.29	(13.24)	<0.001
Low-density lipoprotein (LDL) cholesterol (mg/dl)	118.07	(31.04)	117.70	(30.12)	116.10	(29.18)	0.22	117.40	(32.85)	0.84	120.90	(31.42)	0.003
Triglycerides (mg/dl)	126.91	(77.24)	129.40	(76.73)	136.70	(75.44)	0.03	99.81	(54.85)	<0.001	150.70	(92.20)	<0.001

Data were presented as mean (standard deviation, SD) for continuous variables, and percentage, % (frequency, N) for categorical variables.
When comparing each racial and ethnic minority group to White group, P-values were compared using t-test for continuous variables and $\chi 2$-tests for categorical variables.

Table 4.2. Associations of race and ethnicity with type 2 diabetes and exercise, and associations of exercise and type 2 diabetes

	Race and ethnicity and T2D§											
	Hispanic vs. White				**Black vs. White**				**Chinese vs. White**			
	HR	**95%CI**		**P**	**HR**	**95%CI**		**P**	**HR**	**95%CI**		**P**
Model 1	**2.15**	**(1.87,**	**2.48)**	**<0.001**	**1.76**	**(1.53,**	**2.03)**	**<0.001**	**1.42**	**(1.18,**	**1.71)**	**0.001**
Model 2	**2.02**	**(1.74,**	**2.34)**	**<0.001**	**1.66**	**(1.44,**	**1.93)**	**<0.001**	**1.50**	**(1.24,**	**1.82)**	**<0.001**
Model 3	**1.55**	**(1.27,**	**1.88)**	**<0.001**	**1.39**	**(1.15,**	**1.68)**	**0.001**	**2.01**	**(1.55,**	**2.60)**	**<0.001**

	Race and ethnicity and exercise (Square root of MET-hours/day)ǂ									
	Hispanic vs. White			**Black vs. White**			**Chinese vs. White**			
	β	**SE**	***P***	***β***	**SE**	***P***	***β***	**SE**	***P***	
Model 1	**-0.30**	**(0.03)**	**<0.001**	-0.03	(0.03)	0.36	**-0.24**	**(0.04)**	**<0.001**	
Model 2	**-0.29**	**(0.04)**	**<0.001**	-0.01	(0.03)	0.85	**-0.25**	**(0.04)**	**<0.001**	

	Exercise (MET-hours/day) and T2D§																
	White				**Hispanic**				**Black**				**Chinese**				
	HR	**95%CI**		***P***	**HR**	**95%CI**		***P***	**HR**	**95%CI**		***P***	**HR**	**95%CI**		***P***	
Model 1	**0.93**	**(0.90,**	**0.96)**	**<0.001**	**0.94**	**(0.90,**	**0.97)**	**<0.001**	0.99	(0.97,	1.01)	0.27	0.98	(0.93,	1.03)	0.40	
Model 2	**0.96**	**(0.93,**	**0.99)**	**0.02**	**0.95**	**(0.92,**	**0.99)**	**0.02**	1.01	(0.98,	1.03)	0.67	1.00	(0.94,	1.06)	0.91	

§For race and T2D, exercise and T2D, cox proportional hazard regression models were used. Hazard ratio (HR), 95% confidence interval (CI) and P-value were reported.

ǂFor race and exercise, linear regression models were used. β (SE) and P-value were reported.

Boldface indicated statistical significance (P<0.05).

Model 1: Crude model.

Model 2: Model 2 adjust for confounders. For race and T2D, race and exercise, model 2 adjusted for age, gender, and family history of diabetes. For exercise and T2D, model 2 adjusted for age, gender, family history of diabetes, marital status, education, employment, annual household income, health insurance, stress, hypertension medication use, lipid-lowering medication use, antidepressant use, smoking, alternative healthy eating index (AHEI)-2010, sedentary behavior, body mass index (BMI), total fat, systolic blood pressure (SBP), diastolic blood pressure (DBP), total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides.

Model 3: Adjust for potential mediators for race and T2D, including marital status, education, employment, annual household income, health insurance, stress, hypertension mediation use, lipid-lowering medication use, antidepressant use, smoking, AHEI-2010, sedentary behavior, BMI, total fat, SBP, DBP, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, and habitual exercise.

Table 4.3. Decomposition of associations of race and ethnicity with type 2 diabetes by exercise

	Outcome: T2D									
	Hispanic vs. White					**Chinese vs. White**				
	HR	**95%CI**		***P***	***Proportion explained (%)***	**HR**	**95%CI**		***P***	***Proportion explained (%)***
iPSE (Exercise)	**1.08**	**(1.04,**	**1.13)**	**<0.001**	9.7%	**1.06**	**(1.02,**	**1.10)**	**<0.001**	11.7%
iPSE (NotExercise)	**2.01**	**(1.69,**	**2.43)**	**<0.001**		**1.53**	**(1.27,**	**1.87)**	**<0.001**	
iTE	**2.17**	**(1.83,**	**2.60)**	**<0.001**		**1.62**	**(1.31,**	**1.97)**	**<0.001**	

Interventional path specific effects (iPSEs) were used to assessed racial and ethnic differences in T2D explained by exercise. Hazard ratio (HR), 95% confidence interval (CI) and P-value were reported. Boldface indicated statistical significance (P<0.05). Bootstrap was used to get 95% CI and P-values. Continuous square root of exercise (square root of MET-hours/day) was used as the mediator.
Type 2 diabetes (T2D) was regressed on age, gender, family history of diabetes, race/ethnicity, marital status, education, employment status, annual household income, health insurance, stress, hypertension medication use, lipid-lowering medication use, antidepressant use, smoking, alternative healthy eating index (AHEI)-2010, sedentary behavior, body mass index (BMI), total fat, systolic blood pressure (SBP), diastolic blood pressure (DBP), total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, and habitual exercise.
iPSE, interventional path specific effects.

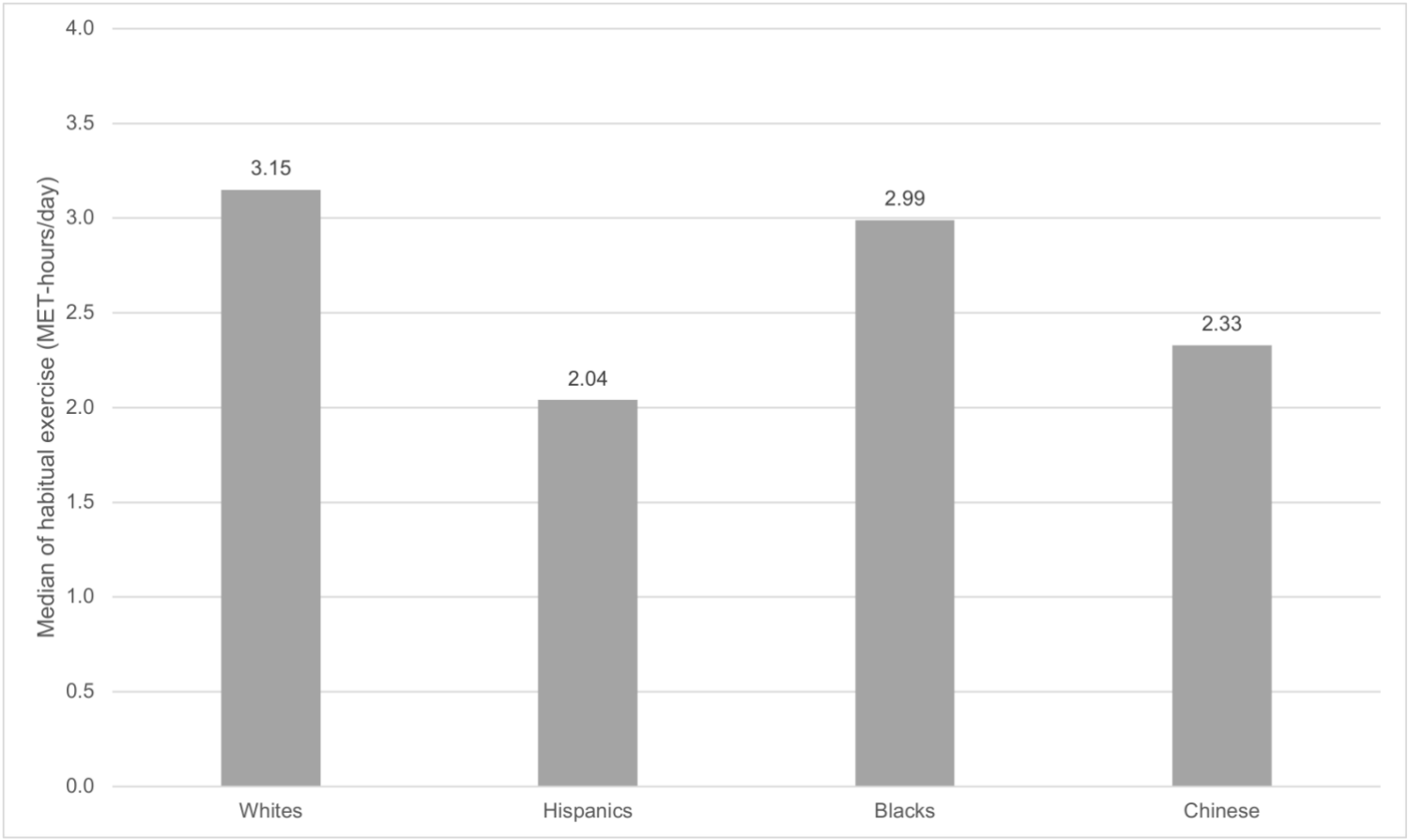


Figure 4.1. Habitual exercise by racial and ethnic groups in the Multi-Ethnic Study of Atherosclerosis study. Median (quartile 1, quartile 3) of habitual exercise (MET-hours/day) in four racial and ethnic groups: White: 3.15 (1.44, 5.99); Hispanic: 2.04 (0.81, 4.61); Black: 2.99 (1.12, 5.83); Chinese: 2.33 (1.18, 4.29). MESA, Multi-Ethnic Study of Atherosclerosis; MET, metabolic equivalent of task.

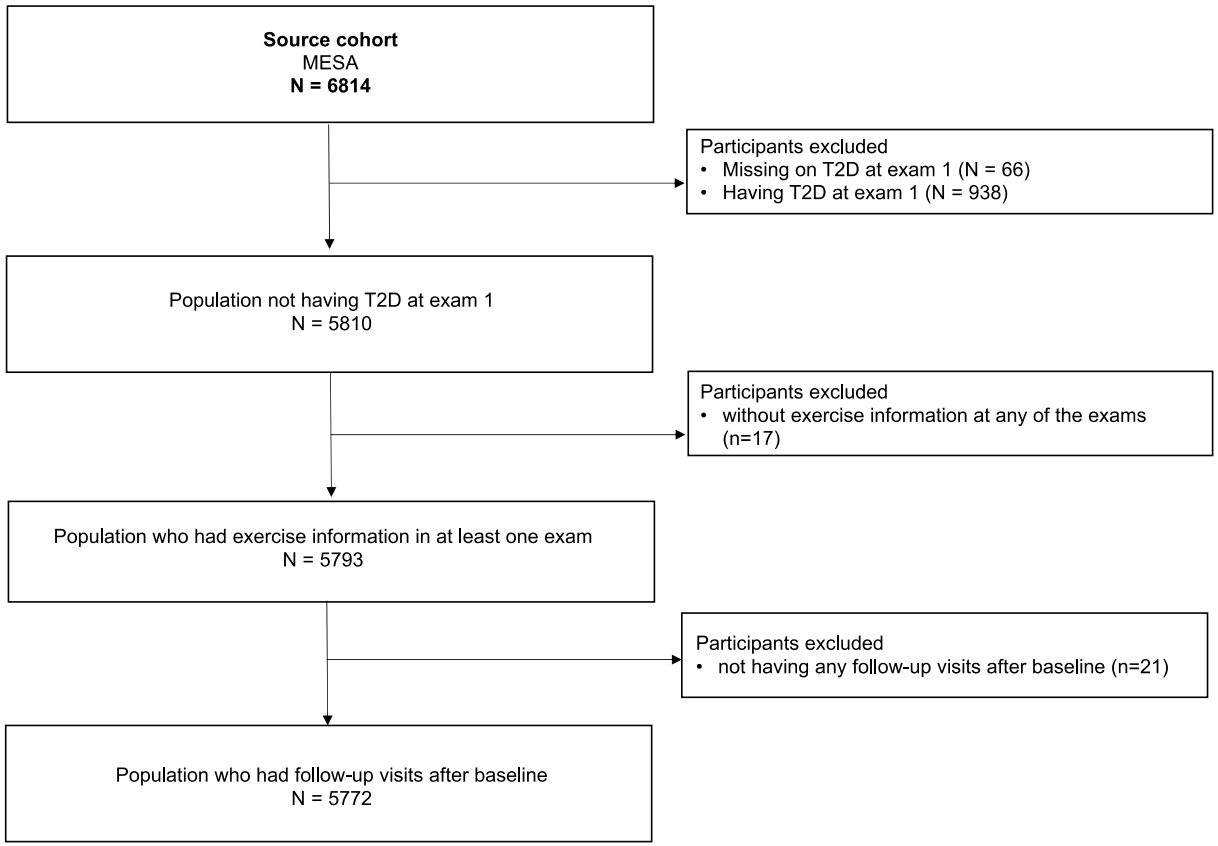


Figure S4.1. Participants flow chart

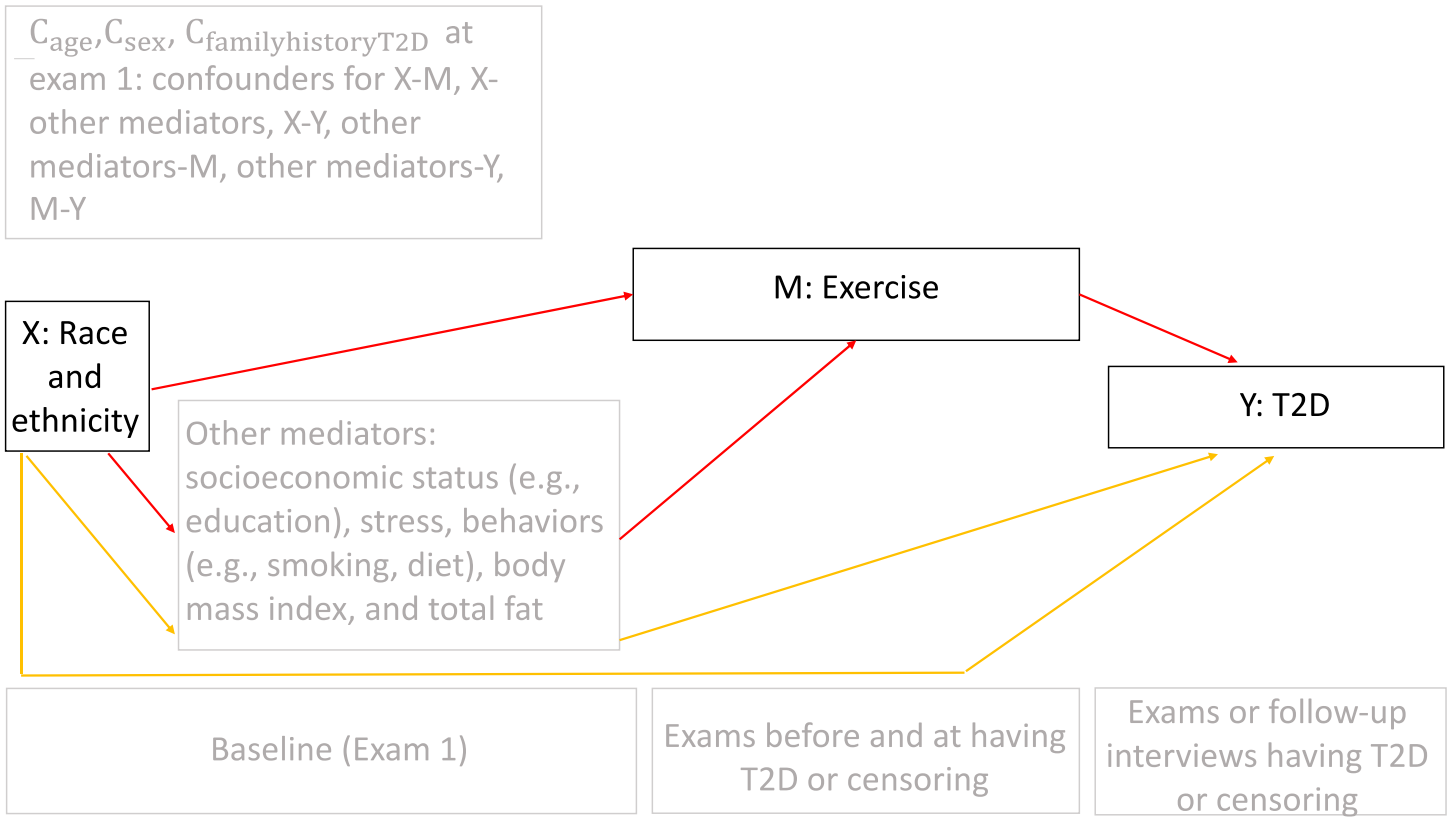


Figure S4.2. Directed acyclic graph (DAG) for racial and ethnic differences in type 2 diabetes through exercise

Notes: Two intervention path specific effects (iPSEs) decomposed from the intervention total effect (iTE): the path through exercise (M) (red color) and the path not through exercise (M) (yellow color). X is exposure (race and ethnicity); M is the mediator (exercise) we aimed to examine; Y is outcome (T2D); C_{age} , C_{sex} and $C_{familyhistoryT2D}$ are confounders for X-M (exercise), X-other mediators, X-Y, other mediators-M (exercise), other mediators-Y, M (exercise)-Y; other mediators including several variables [i.e., socioeconomic status (e.g., education), stress, hypertension medication use, lipid-lowering medication use, antidepressant use, smoking, alternative healthy eating index (AHEI)-2010, sedentary behavior, body mass index (BMI), total fat, systolic blood pressure (SBP), diastolic blood pressure (DBP), total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides]

Table S4.1. Decomposition of associations of race and ethnicity with type 2 diabetes by exercise, among Black and White participants

	Outcome: T2D Black vs. White		
	HR	**95%CI**	***P***
iPSE (Exercise)	1.00	(0.99, 1.01)	0.61
iPSE (NotExercise)	**1.60**	**(1.31, 1.91)**	**<0.001**
iTE	**1.60**	**(1.32, 1.91)**	**<0.001**

Interventional path specific effects (iPSEs) were used to assessed racial and ethnic differences in T2D explained by exercise. Hazard ratio (HR), 95% confidence interval (CI) and P-value were reported. Boldface indicated statistical significance (P<0.05). Bootstrap was used to get 95% CI and P-values.
Continuous square root of exercise (square root of MET-hours/day) was used as the mediator.
Type 2 diabetes (T2D) was regressed on age, gender, family history of diabetes, race/ethnicity, marital status, education, employment status, annual household income, health insurance, stress, hypertension medication use, lipid-lowering medication use, antidepressant use, smoking, alternative healthy eating index (AHEI)-2010, sedentary behavior, body mass index (BMI), total fat, systolic blood pressure (SBP), diastolic blood pressure (DBP), total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, and habitual exercise.
iPSE, interventional path specific effects.

Table S4.2. Decomposition of associations of race and ethnicity with type 2 diabetes by exercise, addressing missing of covariates

	Outcome: T2D								
	Hispanic vs. White					**Chinese vs. White**			
	HR	**95%CI**		***P***	***Proportion explained (%)***	**HR**	**95%CI**	***P***	***Proportion explained (%)***
iPSE (Exercise)	**1.08**	**(1.04,**	**1.13)**	**<0.001**	9.7%	**1.06**	**(1.02,** **1.10)**	**<0.001**	11.7%
iPSE (NotExercise)	**2.01**	**(1.69,**	**2.43)**	**<0.001**		**1.53**	**(1.27,** **1.87)**	**<0.001**	
iTE	**2.17**	**(1.83,**	**2.60)**	**<0.001**		**1.62**	**(1.31,** **1.97)**	**<0.001**	

Interventional path specific effects (iPSEs) were used to assessed racial and ethnic differences in T2D explained by exercise. Hazard ratio (HR), 95% confidence interval (CI) and P-value were reported. Boldface indicated statistical significance (P<0.05). Bootstrap was used to get 95% CI and P-values.
As the percentage of family history of diabetes were higher than 5%, a separated category for family history of diabetes missing was created.
Continuous square root of exercise (square root of MET-hours/day) was used as the mediator.
Type 2 diabetes (T2D) was regressed on age, gender, family history of diabetes, race/ethnicity, marital status, education, employment status, annual household income, health insurance, stress, hypertension medication use, lipid-lowering medication use, antidepressant use, smoking, alternative healthy eating index (AHEI)-2010, sedentary behavior, body mass index (BMI), total fat, systolic blood pressure (SBP), diastolic blood pressure (DBP), total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, and habitual exercise.
iPSE, interventional path specific effects.

Table S4.3. Decomposition of associations of race and ethnicity with type 2 diabetes by exercise, type 2 diabetes diagnosed by fasting serum glucose and use of glucose-lowering medications

	Outcome: T2D									
	Hispanic vs. White					**Chinese vs. White**				
	HR	**95%CI**		***P***	***Proportion explained (%)***	**HR**	**95%CI**		***P***	***Proportion explained (%)***
iPSE (Exercise)	**1.06**	**(1.01,**	**1.13)**	**<0.001**	11.1%	**1.05**	**(1.00,**	**1.12)**	**0.03**	12.1%
iPSE (NotExercise)	**1.63**	**(1.26,**	**2.18)**	**<0.001**		1.43	(1.00,	1.96)	0.05	
iTE	**1.73**	**(1.33,**	**2.32)**	**<0.001**		**1.51**	**(1.06,**	**2.09)**	**<0.001**	

Interventional path specific effects (iPSEs) were used to assessed racial and ethnic differences in T2D explained by exercise. Hazard ratio (HR), 95% confidence interval (CI) and P-value were reported. Boldface indicated statistical significance (P<0.05). Bootstrap was used to get 95% CI and P-values.
Individuals were diagnosed as having T2D if they either had a fasting serum glucose (FPG) ≥126 mg/dL) or self-reported use of glucose-lowering medications (e.g., oral hypoglycemic or insulin).
Continuous square root of exercise (square root of MET-hours/day) was used as the mediator.
Type 2 diabetes (T2D) was regressed on age, gender, family history of diabetes, race/ethnicity, marital status, education, employment status, annual household income, health insurance, stress, hypertension medication use, lipid-lowering medication use, antidepressant use, smoking, alternative healthy eating index (AHEI)-2010, sedentary behavior, body mass index (BMI), total fat, systolic blood pressure (SBP), diastolic blood pressure (DBP), total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, and habitual exercise.
iPSE, interventional path specific effects.

Table S4.4. Associations of race and ethnicity with type 2 diabetes adjusting for mediators stepwise

	Race/ethnicity and T2D											
	Hispanic vs. White				Black vs. White				Chinese vs. White			
	HR	95%CI		P	HR	95%CI		P	HR	95%CI		P
Model 1	**2.15**	**1.87**	**2.48**	**<0.001**	**1.76**	**1.53**	**2.03**	**<0.001**	**1.42**	**1.18**	**1.71**	**0.001**
Model 2	**2.02**	**1.74**	**2.34**	**<0.001**	**1.66**	**1.44**	**1.93**	**<0.001**	**1.50**	**1.24**	**1.82**	**<0.001**
Model 3	**1.45**	**1.21**	**1.73**	**<0.001**	**1.49**	**1.27**	**1.74**	**<0.001**	**1.25**	**1.01**	**1.55**	**0.04**
Model 4	**1.46**	**1.22**	**1.74**	**<0.001**	**1.49**	**1.27**	**1.75**	**<0.001**	**1.27**	**1.02**	**1.59**	**0.03**
Model 5	**1.46**	**1.22**	**1.75**	**<0.001**	**1.49**	**1.27**	**1.74**	**<0.001**	**1.29**	**1.03**	**1.61**	**0.03**
Model 6	**1.52**	**1.27**	**1.82**	**<0.001**	**1.40**	**1.19**	**1.65**	**<0.001**	**1.37**	**1.09**	**1.73**	**0.01**
Model 7	**1.58**	**1.31**	**1.90**	**<0.001**	**1.31**	**1.11**	**1.55**	**0.002**	**1.41**	**1.11**	**1.79**	**0.005**
Model 8	**1.45**	**1.20**	**1.74**	**<0.001**	**1.16**	**0.98**	**1.37**	**0.09**	**2.09**	**1.63**	**2.68**	**<0.001**
Model 9	**1.54**	**1.27**	**1.86**	**<0.001**	**1.21**	**1.02**	**1.44**	**0.03**	**2.24**	**1.74**	**2.89**	**<0.001**
Model 10	**1.55**	**1.27**	**1.88**	**<0.001**	**1.39**	**1.15**	**1.68**	**0.001**	**2.01**	**1.55**	**2.60**	**<0.001**

Cox proportional hazard regression models were used. Hazard ratio (HR), 95% confidence interval (CI) and P-value were reported. Boldface indicated statistical significance (P<0.05).
Model 1: Crude model.
Model 2: Adjust for confounders, age, gender, and family history of diabetes.
From model 3, mediators were additionally adjusted.
Model 3: Adjust for age, gender, family history of diabetes, education, employment, annual household income, and health insurance.
Model 4: Adjust for age, gender, family history of diabetes, education, employment, annual household income, health insurance, and marital status.
Model 5: Adjust for age, gender, family history of diabetes, education, employment, annual household income, health insurance, marital status, and stress.
Model 6: Adjust for age, gender, family history of diabetes, education, employment, annual household income, health insurance, marital status, stress, hypertension medication use, lipid-lowering medication use, and antidepressant use.
Model 7: Adjust for age, gender, family history of diabetes, education, employment, annual household income, health insurance, marital status, stress, hypertension medication use, lipid-lowering medication use, antidepressant use, smoking, AHEI-2010, and sedentary behavior.
Model 8: Adjust for age, gender, family history of diabetes, education, employment, annual household income, health insurance, marital status, stress, hypertension medication use, lipid-lowering medication use, antidepressant use, smoking, AHEI-2010, sedentary behavior, and BMI.
Model 9: Adjust for age, gender, family history of diabetes, education, employment, annual household income, health insurance, marital status, stress, hypertension medication use, lipid-lowering medication use, antidepressant use, smoking, AHEI-2010, sedentary behavior, BMI, and total fat.

Model 10: Adjust for age, gender, family history of diabetes, education, employment, annual household income, health insurance, marital status, stress, hypertension medication use, lipid-lowering medication use, antidepressant use, smoking, AHEI-2010, sedentary behavior, BMI, total fat, SBP, DBP, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, and habitual exercise.
AHEI-2010, alternative healthy eating index-2010; BMI, body mass index; DBP, diastolic blood pressure; HDL cholesterol, high-density lipoprotein cholesterol; LDL cholesterol, low-density lipoprotein cholesterol; SBP, systolic blood pressure.

5. Chapter five: Racial and ethnic disparities of type 2 diabetes in the United States: the pathways through visceral fat in the Multi-Ethnic Study of Atherosclerosis

5.1. Abstract

Objectives

In the United States, racial and ethnic minorities have higher type 2 diabetes (T2D) risk than Whites. One hypothesis is that some minorities (e.g., Hispanics and South Asians) have more visceral fat than Whites in a sex-specific manner. We aimed to test this hypothesis by examining to what degree racial differences in T2D were explained by visceral fat in males and females.

Methods

This study included 1,457 participants (51.2% females) who had visceral fat measured by computed tomography and followed from 2002–2005 to 2020 for incident T2D from the Multi-Ethnic Study of Atherosclerosis cohort. We assessed associations of race and T2D risk using Cox proportional hazard regressions and estimated associations explained by visceral fat using natural mediation effects in males and females.

Results

Controlling for confounders, racial minority females [Hispanic: HR (95%CI): 1.77 (1.17–2.69), Chinese: 1.91 (1.15–3.15), Black: 1.59 (1.02–2.49)] and males [Hispanic: 1.82 (1.20–2.76), Black: 1.48 (0.92–2.38)], but not Chinese males [0.86 (0.48–1.55)], had higher T2D risks than White counterparts. By sex, Hispanic females [mean difference (SE): 22.72 (5.68)] had higher visceral fat (cm^2) than White females, while Chinese [-77.56 (8.47)] and Black [-57.57 (8.11)] males had lower visceral fat (cm^2) than White males. Visceral fat explained 20.3% of T2D risk between Hispanic and White females, but not for other racial and sex subgroups.

Conclusion

Visceral fat explained one-fifth of racial and ethnic differences in T2D comparing Hispanic females to White females and may contribute to Hispanic females' higher T2D risk.

5.2. Introduction

In 2021, 11.6% (i.e., over 30 million) Americans are estimated to live with diabetes, with 95% having type 2 diabetes (T2D) [2]. Meanwhile, racial and ethnic disparities in T2D are persistent in the United States (US) [1,2,7]. The National Diabetes Statistics Report showed from 2017 through 2018, Hispanics had the highest age-adjusted incidence rate of diagnosed T2D at 9.7 per 1000 persons, followed by non-Hispanic Blacks at 8.2, non-Hispanic Asians at 7.4, and non-Hispanic Whites at 5.0 per 1000 persons in the US [1]. Thus, it is essential to find determinants of T2D to narrow such racial and ethnic disparities.

Visceral fat, surrounding the abdominal organs, has been hypothesized as a leading risk factor for T2D, independent of overall body adiposity [133,200], and has been considered as the more pathogenic adipose tissue compartment and more closely associated with T2D than subcutaneous fat [128]. The relationship between visceral fat and T2D may be due to the high lipolysis rate in visceral fat [72] and visceral adipocytes releasing adipocytokines [75] that link visceral fat to insulin resistance, resulting in developing T2D.

Previous studies have suggested that Hispanics may have more visceral fat, while Blacks may have less, compared to Whites [76,201]; levels vary among Asian subgroups. For instance, Chinese and Japanese may have similar visceral fat [197,202,203], whereas Filipinos and South Asians exhibit greater visceral fat compared to Whites [80,197]. However, it remains unknown to what degree visceral fat could explain the racial and ethnic differences in T2D. In the Women's Health Initiative (WHI) Study, Black females were found to have higher waist circumference (WC) than White females and the difference explained about 19% of the higher risk of T2D [56]. Although a

valuable measurement, the WC includes both visceral and subcutaneous fat around the waist, thus, it does not distinguish visceral fat from subcutaneous fat [75]. In addition, there are sex differences in visceral fat [82–84] and there may be sex and race interactions for visceral fat [79,85–87,204]. Thus, we aimed to examine whether visceral fat is a mediator and to what degree the association of race and ethnicity (Hispanic, Black, Asian vs. White) with incident T2D might be explained by visceral fat in sex subgroups based on data from a cohort study including multiple racial and ethnic groups.

5.3. Methods

Study design and study population

The Multi-Ethnic Study of Atherosclerosis (MESA) is a prospective population-based cohort study including 6,814 adults aged 45–84 years, who were free of cardiovascular disease (CVD) at baseline. Study participants were recruited in 2000–2002 (exam 1) from 6 field centers in the US [162]. Following five examinations from 2002 to 2018 [162], MESA also conducted 21 follow-up telephone interviews from 2001 to 2020 to inquire about new disease diagnoses [162]. More information on the MESA study has been published previously [162].

The current analysis included participants from an ancillary study, which included a 30% random sample (n=1,947) of the MESA cohort receiving abdominal computed tomography (CT) scans of the distal abdominal aorta at either exam 2 (2002–2004) or exam 3 (2004–2005) [164,205] that were interrogated for abdominal body composition. From these, we excluded participants who had T2D (n=326) or with missing T2D status (n=138) before or at visceral fat measurement, or those with missing visceral fat (n=26), with a total of 1457 participants included in the study sample (**Figure S5.1**).

The institutional review boards of each MESA site approved the study. All participants provided written informed consent. The analysis was conducted between June 2023 and November 2023. The manuscript followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Assessment of race and ethnicity

Race and ethnicity was self-reported as non-Hispanic White (White hereafter), Hispanic, non-Hispanic Black (Black hereafter), or non-Hispanic Chinese (Chinese hereafter) at exam 1 by participants.

Assessment of visceral fat

Electron-beam or multidetector CT scans of the abdomen were obtained at either exam 2 (n=563) or exam 3 (n=894) (randomly assigned). Two analysts separately assessed the CT scans using the Medical Imaging Processing Analysis and Visualization (MIPAV) 4.1.2 Software (National Institutes of Health, Bethesda, Maryland). Visceral fat was defined as the adipose tissue enclosed by the visceral cavity. Participants had six transverse cross sectional slices analyzed: 2 at L2/L3, 2 at L3/L4 and 2 at L4/L5 vertebral spaces. We assessed visceral fat using the average of the six slices [166,206]. Inter-rater and intra-rater reliability for abdominal CT measurements was 0.99 [166,206].

Assessment of type 2 diabetes

T2D was assessed from both clinic visits and self-reported information across exams and follow-up phone interviews. Individuals who had a fasting plasma glucose (FPG) ≥126 mg/dL at each exam according to American Diabetes Association (ADA) criteria [4], received a diagnosis of diabetes by physicians at exam 5, 6 and from each telephone interview, or used glucose-lowering medications at each exam were classified as having T2D.

Assessment of covariates

The sociodemographic information (i.e., sex, marital status, education, annual household income), chronic stress, medication use (i.e., hypertension medication use, lipid-lowering medication use), and cigarette smoking were collected at exam 1 from self-administrated questionnaires [162,178]. We used age at measurement when the visceral fat was scanned (i.e., exam 2 or 3) and we used age as the time scale in Cox proportional hazard regression models [195]. Family history of T2D was collected at exam 2 from the family history questionnaire. Chronic stress was assessed using the Chronic Burden Scale (CBS) at exam 1, which evaluates factors including job difficulties, financial strain, relationship problems, and personal or close other's health issues. Scores ranged from 0 to 5 and were categorized as follows: low (score of 0), medium (score of 1), and high (score ≥2) [194]. Dietary intake over the past year was obtained using the 120-item food frequency questionnaire (FFQ) at exam 1. Alternative Healthy Eating Index (AHEI)-2010 was calculated using a common method to indicate the dietary quality [60]. Sedentary behavior (i.e., reading, sitting, recreational computer, and watching television) [metabolic equivalent of task (MET)-hours/day] and exercise (i.e., walking for exercise, sports/dancing, and conditioning activities) (MET-hours/day) were measured from the Typical Week Physical Activity Survey (TWPAS) at exam 1 [162].

Weight (pound) and height (cm) were assessed at exam 1 using a balance-beam scale and stadiometer, respectively. Body mass index (BMI) (kg/m^2) was calculated as [weight (pound)*0.45]/[height (cm)/100]. We estimated total fat percentage at exam 1 using validated equations with correlation coefficients ranging from 0.80 to 0.86: total fat mass percentage = 76−(20×(height/waist)) for females and 64−(20×(height/waist)) for males [179]. We calculated total fat mass (kg) by weight* (total fat mass percentage/100). Abdominal muscle area (cm^2) and

density (Hounsfield units, HU) were assessed using CT scans. The analyzed muscle groups included the bilateral obliques, rectus abdominis, paraspinous, and psoas muscles. Six transverse cross-sectional slices were evaluated for each participant: two at the L2/L3 vertebral space, two at L3/L4, and two at L4/L5. The measurements of muscle area and density were based on the average values from these six slices. Resting blood pressure (BP) was assessed three times using an automated oscillometric sphygmomanometer (model Pro 100, Critikon, Tampa, Florida, US) at exam 1, and calculated by taking the average of the last two of three measurements. Lipid profiles were assessed at exam 1 from plasma samples after a 12-hour fast.

Statistical analysis

Characteristics by race and the distribution of visceral fat by race and sex were reported. The percentage and frequency [% (N)] for categorical variables and mean and standard deviation (SD) for continuous variables were presented. This study used SAS version 9.4 (SAS Institute, Cary, NC, USA) and R version 4.2.1. for analyses and considered the statistically significant level after controlling for multiple testing [i.e., false-discovery rate (FDR) <0.05 using the Benjamini-Hochberg method].

Prior to mediation analysis, this study first assessed associations between race and ethnicity and incident T2D using Cox proportional hazards regression models. The proportional hazards assumption was verified using Schoenfeld residuals. The adjusted models controlled for confounders of age (years) and family history of diabetes (yes or no) across sex groups. We also additionally adjusted for potential mediators that might influence racial and ethnic differences in T2D: marital status (married/living with a partner or not), education (high school or less, associates, bachelor's or higher degree), annual household income (<$25,000, $25,000-$49,999, ≥$50,000), stress (low, medium, or high), hypertension medication use (yes or no), lipid-

lowering medication use (yes or no), smoking (never, former, or current), AHEI-2010 (continuous), sedentary behavior (MET-hours/day), physical activity (MET-hours/day), BMI (kg/m^2), total fat (kg), abdominal muscle area (cm^2), abdominal muscle density (HU), systolic BP (SBP) (mmHg), total cholesterol (mg/dl), high-density lipoprotein (HDL) cholesterol (mg/dl), and triglycerides (mg/dl), and visceral fat (cm^2) .To minimize immortal time survival bias, age as the time scale with left truncation of age at study entry was used in Cox regressions [195]. Second, associations between race and ethnicity and visceral fat (cm^2) were examined using linear regression models adjusting for age and family history of diabetes across sex groups. Third, this study assessed associations between visceral fat (cm^2) and T2D using Cox proportional hazards regression models, adjusting for age, family history of diabetes, marital status, education, annual household income, stress, hypertension medication use, lipid-lowering medication use, smoking, AHEI-2010, sedentary behavior, exercise, BMI, total fat, abdominal muscle area, abdominal muscle density, SBP, total cholesterol, HDL cholesterol and triglycerides within each racial and sex subgroup. The P for interaction between race and visceral fat on T2D was calculated using the Wald $\chi 2$-test in each sex subgroup.

The mediation proportion of visceral fat was quantified using interventional path-specific effects (iPSEs)[170,172] (**Figure S5.2**), with bootstrapping 200 times for 95% confidence intervals (CIs). We decomposed the interventional total effect (iTE) into two iPSEs,: (1) the indirect pathway: iPSE (Visceralfat) ($HR_{ipseVAT}$, red color in **Figure S5.2**) for the path through visceral fat; (2) the direct pathway: iPSE (NotVisceralfat) ($HR_{ipseNotVAT}$, yellow color in **Figure S5.2**) for the path not through visceral fat. The mediated proportion explained by visceral fat was calculated from $\ln(HR_{ipseVAT})/\ln(HR_{iTE})$ in iPSEs [196].

Since missing percentages of each adjusted covariate were < 4.0%, completed data analyses in the primary analysis were used. In sensitivity analysis, we added the interaction between race and visceral fat on T2D in the mediation analysis.

5.4. Results

Characteristics of study participants

Among 1457 participants, 51.2% were females; 44.0% were White; 23.0% were Hispanic; 19.4% were Black; and 13.7% were Chinese. Hispanic and Black participants had higher percentages of having family history of T2D (Hispanic: 43.0%, Black: 43.0%, White: 27.3%), lower percentages of being married/living with a partner (Hispanic: 60.1%, Black: 46.1%, White: 70.1%), had lower AHEI-2010 (Hispanic: 50.85, Black: 52.61, White: 54.43) and higher BMI (kg/m^2) (Hispanic: 28.70, Black: 28.83, White: 27.07) than White participants. Hispanic, Black, and Chinese participants were less likely to have bachelor's or higher degree (Hispanic: 14.6%, Black: 38.3%, Chinese: 41.4%, White: 51.3%) and annual household income ≥$50,000 (Hispanic: 23.7%, Black: 40.7%, Chinese: 28.9%, White: 60.7%) than White participants.

Risk of type 2 diabetes by race and ethnicity

There were 294 participants developing incident T2D (incidence rate 17.0 per 1000 person-years) during a median follow-up time of 14.2 years (range 0.6–16.9 years). Among females, Hispanics had the highest crude incidence rate of T2D (22.5 per 1000 person-years), followed by Chinese (21.1 per 1000 person-years), Blacks (18.6 per 1000 person-years), and Whites (11.6 per 1000 person-years). Among males, Hispanics had the highest crude incidence rate of T2D (26.0 per 1000 person-years), followed by Blacks (23.6 per 1000 person-years), Whites (13.4 per 1000 person-years), and Chinese (11.2 per 1000 person-years). After adjusting

for confounders of age and family history of diabetes, Hispanic females (HR = 1.77, 95% CI: 1.17–2.69, P = 0.01) and Chinese females [1.91 (1.15–3.15), P = 0.01] still had higher risk of T2D than White females. The positive point estimates still existed in Blacks females [1.59 (1.02–2.49), P = 0.04]. Hispanic males [1.82 (1.20–2.76), P = 0.005] still had higher risk of T2D than White males. The positive point estimates still existed in Black males [1.48 (0.92–2.38), P = 0.10], but not in Chinese males [0.86 (0.48–1.55), P = 0.62]. After further adjusting for potential mediators including socioeconomic status (SES), marital status, stress, medications, smoking, AHEI-2010, sedentary behavior, exercise, BMI, total fat, muscle area and density, BP, and lipids, The positive point estimates existed in Hispanic females [1.29 (0.78–2.15), P = 0.32], Chinese females [2.11 (1.10–4.04), P = 0.03], and Blacks females [1.77 (1.00–3.13), P = 0.05], as well as in Hispanic males [1.53 (0.91–2.59), P = 0.11], Chinese males [1.40 (0.68–2.87), P = 0.36], and Blacks males [1.98 (1.12–3.50), P = 0.02], although these were not significant (**Table 5.2**).

Level of visceral fat by race and ethnicity

Among females, Hispanics had the highest visceral fat (cm^2) [mean (SD), 145.46 (62.60)], followed by Whites [121.34 (65.69)], Blacks [112.86 (57.02)], and Chinese [108.01 (48.58)]. Among males, Hispanics [209.15 (71.72)] and Whites [208.93 (84.06)] had similar visceral fat (cm^2), followed by Blacks [152.41 (72.33)] and Chinese [129.81 (52.71)] (**Figure 5.1**). After adjusting for confounders of age and family history of diabetes, compared to White females, Hispanic females still had higher visceral fat (cm^2) [mean difference = 22.72 (standard error, SE = 5.68), P < 0.001], but not for the Chinese females [-9.44 (7.00), P = 0.18] and Black females [-9.71 (5.86), P = 0.10]. Compared to White males, Hispanic males [1.66 (7.34), P = 0.38] had similar visceral fat (cm^2), and Chinese males [-77.56 (8.47), P < 0.001] and Black males [-57.57 (8.11), P < 0.001] had lower visceral fat (cm^2) (**Table 5.2**).

Associations of visceral fat with type 2 diabetes

In unadjusted models, a 10 cm^2 higher visceral fat level was associated with about 10% higher risks of T2D in White females (HR = 1.12, 95% CI: 1.07–1.16, P < 0.001), Chinese females [1.11 (1.02–1.20), P = 0.01], Black females [1.10 (1.05–1.16), P < 0.001], and Hispanic females [1.09 (1.04–1.14), P = 0.001]. Meanwhile, a 10 cm^2 increase in visceral fat was associated with about 5% higher risks of T2D in White males [1.06 (1.03–1.10), P < 0.001], Chinese males [1.07 (0.97–1.17), P = 0.17], Black males [1.03 (0.98–1.07), P = 0.29], and Hispanic males [1.06 (1.02–1.10), P = 0.004], although results were not statistically significant among Chinese males and Black males. After adjusting for age, family history of diabetes, marital status, education, annual household income, stress, medications, smoking, AHEI-2010, sedentary behavior, exercise, BMI, total fat, muscle area and density, BP, and lipids, visceral fat (10 cm^2) was still positively associated with T2D in White females [1.11 (1.02–1.20), P = 0.01], Black females [1.31 (1.12–1.53), P = 0.001], Hispanic females [1.19 (1.08–1.33), P = 0.001], but was not significantly associated with T2D in Chinese females [1.07 (0.88–1.29), P = 0.52]. Visceral fat (10 cm^2) was also positively associated with T2D in Hispanic males [1.10 (1.03–1.19), P = 0.01], but was not significantly associated with T2D in White males [1.01 (0.96–1.07), P = 0.62], Chinese males [1.60 (0.95–2.69), P = 0.08], or Black males [1.05 (0.95–1.16), P = 0.33]. The test for interaction between race and visceral fat on T2D was not significant in females (P for interaction = 0.97) or males (P for interaction = 0.20) (**Table 5.2).**

Mediation analyses of race and ethnicity and type 2 diabetes explained by visceral fat

Controlling for confounders, Chinese males did not have higher T2D risk compared to White males in this study. Moreover, Hispanic, Chinese and Black males, as well as Chinese and Black females, did not have higher visceral fat than Whites. We did not find visceral fat as a

mediator for racial differences in T2D when comparing those groups to White counterparts. Thus, we assessed the mediation proportions by visceral fat between Hispanic and White females. Using iPSEs, the risk of T2D mediated by visceral fat was 1.20 [(1.04–1.54), $P < 0.001$] for Hispanic females (**Table 5.3**). Visceral fat explained 20.3% of racial and ethnic differences in T2D when comparing Hispanic females to White females. In sensitivity analysis, results were unchanged when adding interactions between race and visceral fat on T2D in mediation analysis (**Table S5.1**).

5.5. Discussion

In this longitudinal cohort study including racially diverse participants in the US, we found that after controlling for confounders, Hispanic, Black and Chinese females, as well as Hispanic and Black males had higher risks of T2D than White counterparts, but Chinese males had similar T2D risk compared to White males. Only Hispanic females had significantly higher visceral fat than White females. In addition, we found that visceral fat may be a mediator of the Hispanic females' higher T2D risk, but not for Chinese and Black females' and Hispanic and Black males' higher risk of T2D. Visceral fat explained about one-fifth of racial and ethnic differences in T2D when comparing Hispanic females to White females.

Evidence suggested that racial differences in T2D may be explained by a variety of factors, such as SES, lifestyles, and BMI [7,56]. Our analysis also revealed that, when comparing Hispanic females and males with White counterparts, T2D risk disparities decreased after adjusting for potential mediators such as SES, stress, behaviors, obesity, muscle area and density, BP, and lipid levels, based on the age-, and family history of diabetes- adjusted model (**Table 5.2**). We detailed the stepwise adjustments for these mediators in **Table S5.2,** which preliminarily suggested that these mediators may partially explain the racial and ethnic disparities in T2D risk.

Conversely, the T2D risk increased in Chinese females, Black females, and Black males relative to White counterparts, and there was positive estimate of T2D risk in Chinese males compared to White males, after controlling for these mediators based on the confounders- adjusted model (**Table 5.2**). The increase in T2D risk for Chinese females was attributed to adjustments for smoking, AHEI-2010, and BMI, and the increase for Chinese males was linked to BMI, total fat and visceral fat. The rise in risk for Black females and males was due to adjustments for visceral fat (**Table S5.2**). Because Chinese females had lower percentages of current smoking, higher AHEI-2010, and lower BMI, and Chinese males had lower BMI and total fat (**Table S5.3**); and Chinese males [mean difference: -17.43 (7.37)], Black females [-31.72 (4.60)] and males [-51.60 (6.27)] had lower visceral fat (cm^2) at equivalent BMI and total fat than their White counterparts, controlling for these factors may reduce the protective effect associated with healthier lifestyles and lower obesity metrics. More studies are needed to quantify the mediation proportion attributable to each mediator.

Although visceral fat is a well-known leading risk factor for T2D, heretofore, few studies have examined to what degree visceral fat as a mediator may explain the racial disparities in T2D. One cross-sectional study among 570 women in the US found that Filipina women had higher visceral fat than White women (69.1 cm^3 vs. 62.3 cm^3), and further adjusting for education, exercise, alcohol drinking, and visceral fat based on the age- adjusted results, Filipinos' odds of T2D decreased compared to Whites [80]. However, as visceral fat and other factors (e.g., education and alcohol drinking) were adjusted simultaneously, it was unclear whether the decreased T2D risk was due to visceral fat or other factors and it was unknown to which degree racial differences in T2D were explained by visceral fat [80]. Since our data only had

Chinese, then future studies including more Asian subgroups (e.g., Filipino and South Asians) are needed, because Asian subgroups have varied visceral fat levels [80,197,202,203].

We found that Hispanic females had higher visceral fat than White females, which was also observed in an earlier published study in the US (4.4 kg vs. 3.2 kg) [79]. We did not find that visceral fat was a mediator for other minority groups who had higher T2D risks than Whites. It is likely because Black and Chinese females, as well as Hispanic males had similar level of visceral fat, but Black males had lower visceral fat compared to White counterparts in this study (**Table 5.2**), which was also observed in previous studies [79,85–87,202,204]. For example, research in the US showed that Hispanic males had similar visceral fat mass compared to White males (6.2 kg vs. 6.0 kg) [79]. Another study in the US reported that Black females had similar visceral fat volume compared to White females (1.72 liters vs. 1.69 liters), whereas Black males had lower visceral fat volume than White males (2.48 liters vs. 3.40 liters) [85]. Additionally, a study in Singapore noted that Chinese-Singaporean females had similar visceral fat volume as White females (2.13 liters vs. 2.11 liters) [202].

Visceral fat may have been a mediator for higher T2D risk among Hispanic females due to their higher level of visceral fat than White females. Visceral adipose tissue has a relative high lipolysis rate which would increase flux of free fatty acid (FFA) from visceral fat depots to the liver, leading to hepatic insulin resistance and hepatic steatosis [72]. Furthermore, visceral fat accumulation increases secretion of adipocytokines involving in inflammation [e.g., interleukin (IL)-6, IL-8, IL-10, tumour necrosis factor (TNF)-α] and the acute-phase response [e.g., plasminogen activator inhibitor (PAI)-1] and influences hormones secretion (e.g., leptin, adiponectin, resistin and visfatin), which are in regulation of insulin resistance [75]. For example, visceral fat accumulation would decrease adiponectin secretion, resulting in increased peripheral

insulin resistance [75]. Thus, visceral fat increases both hepatic insulin resistance and peripheral insulin resistance, which are the bedrocks of development of T2D.

Strengths and limitations

This study is the first cohort study including four racial and ethnic groups, examining to what degree the racial and ethnic differences in T2D are mediated by visceral fat in the US. In addition, we could ensure the temporality of associations due to the time sequence of race, visceral fat and T2D. Moreover, visceral fat was measured by CT, which allowed us to provide more precise estimates of the body fat composition than using WC. Nonetheless, some potential limitations of our study may exist. First, as it was an observational study, although we adjusted for potential confounders, there might be residual confounding effects. Second, as we only included Chinese in MESA, future studies including more Asian subgroups are suggested. Third, we excluded 25% participants having T2D, with missing T2D status before or at visceral fat measurement, or with missing visceral fat. They were more likely to be Blacks and Hispanics, have family history of diabetes, lower education attainment, lower income, take hypertension and lipid drugs, and had less exercise, higher BMI, total fat, SBP, TG levels and lower HDL cholesterol than the included study sample (**Table S5.4**). These may potentially introduce selection bias. However, we addressed this by applying inverse probability weighting to mitigate potential selection bias, which yielded similar mediation results (**Table S5.5**). Fourth, the relatively small sample size of the CT measured adiposity ancillary study may constrain detecting associations between race and T2D, race and visceral fat, visceral fat and T2D or mediation effects in sex subgroups. More studies with larger sample sizes are warranted.

5.6. Conclusions

In this prospective cohort study including racially diverse participants, we found that visceral fat could explain about one-fifth of racial and ethnic differences in T2D when comparing Hispanic females to White females. Observing the role of visceral fat in contributing to racial and ethnic disparities in T2D among Hispanic females improves understanding of the biological factor at play and may better inform planning clinical strategies for diabetes prevention. More studies are needed to confirm these findings.

Table 5.1. Characteristics of participants by racial and ethnic groups in Multi-Ethnic Study of Atherosclerosis ancillary study

Characteristics	Overall (n=1457)		Whites [44.0% (641)]		Hispanics [23.0% (335)]		P-values	Blacks [19.4% (282)]		P-values	Chinese [13.7% (199)]		P-values
Age (years)	64.58	(9.73)	65.34	(9.56)	62.93	(9.50)	<0.001	64.72	(10.01)	0.37	64.69	(10.04)	0.41
Female, % (N)	51.2	(746)	49.1	(315)	51.9	(174)	0.41	56.7	(160)	0.03	48.7	(97)	0.92
Family history of diabetes, % (N)	33.1	(474)	27.3	(174)	43.0	(142)	<0.001	43.0	(117)	<0.001	21.0	(41)	0.08
Married/living with a partner, % (N)	64.9	(936)	70.1	(448)	60.1	(196)	0.002	46.1	(129)	<0.001	82.3	(163)	0.001
Education, % (N)							<0.001			0.001			<0.001
High school or less	32.2	(468)	19.5	(125)	60.6	(203)		24.5	(69)		35.9	(71)	
Associates	28.9	(420)	29.2	(187)	24.8	(83)		37.2	(105)		22.7	(45)	
Bachelor's or higher	39.0	(567)	51.3	(328)	14.6	(49)		38.3	(108)		41.4	(82)	
Annual household income, % (N)							<0.001			<0.001			<0.001
<$25,000	27.5	(389)	13.7	(86)	42.9	(141)		25.1	(66)		48.7	(96)	
$25,000–$49,999	28.6	(404)	25.6	(160)	33.4	(110)		34.2	(90)		22.3	(44)	
≥$50,000	44.0	(622)	60.7	(380)	23.7	(78)		40.7	(107)		28.9	(57)	
Stress, % (N)							0.37			0.11			<0.001
Low	42.1	(613)	37.2	(238)	41.8	(140)		39.7	(112)		61.8	(123)	
Middle	29.0	(422)	32.7	(209)	30.2	(101)		25.9	(73)		19.6	(39)	
High	28.9	(421)	30.2	(193)	28.1	(94)		34.4	(97)		18.6	(37)	
Hypertension medication use, % (N)	32.1	(468)	31.1	(199)	28.7	(96)	0.43	44.7	(126)	<0.001	23.6	(47)	0.04
Lipid-lowering medication use, % (N)	14.9	(217)	17.7	(113)	14.0	(47)	0.14	10.4	(29)	0.01	14.1	(28)	0.23
Cigarette smoking, % (N)							0.21			0.04			<0.001
Never	50.4	(733)	44.8	(287)	50.8	(170)		45.0	(127)		75.3	(149)	
Former	37.1	(540)	42.3	(271)	37.9	(127)		36.2	(102)		20.2	(40)	
Current	12.5	(182)	12.8	(82)	11.3	(38)		18.8	(53)		4.6	(9)	
Alternative healthy eating index (AHEI)-2010	53.40	(9.64)	54.43	(9.98)	50.85	(9.06)	<0.001	52.61	(10.00)	0.01	55.43	(7.89)	0.15
Sedentary behavior (MET-hours/day)	3.96	(2.62)	4.05	(2.70)	3.49	(2.31)	0.001	4.67	(2.83)	0.002	3.42	(2.31)	0.001

Exercise (MET-hour/day)	3.61	(4.12)	3.82	(4.02)	3.09	(3.54)	0.004	4.05	(5.26)	0.53	3.17	(3.33)	0.02
Body mass index (BMI, kg/m^2)	27.34	(4.81)	27.07	(4.55)	28.70	(4.64)	<0.001	28.83	(5.24)	<0.001	23.77	(2.92)	<0.001
Total fat mass (kg)	26.83	(9.07)	26.97	(8.49)	28.17	(8.35)	0.04	29.87	(10.48)	<0.001	19.86	(5.85)	<0.001
Abdominal muscle area (cm2)	103.59	(28.89)	103.50	(28.39)	102.70	(29.10)	0.70	111.70	(30.52)	<0.001	93.93	(24.41)	<0.001
Abdominal muscle density (HU)	42.88	(5.27)	42.15	(5.24)	42.43	(5.15)	0.43	44.36	(5.46)	<0.001	43.87	(4.76)	<0.001
Systolic blood pressure (SBP, mmHg)	125.87	(21.33)	124.20	(20.22)	126.00	(22.64)	0.23	131.50	(21.47)	<0.001	123.10	(21.09)	0.51
Diastolic blood pressure (DBP, mmHg)	72.25	(10.04)	71.30	(10.02)	72.39	(9.97)	0.10	74.74	(10.32)	<0.001	71.57	(9.26)	0.74
Total cholesterol (mg/dl)	196.22	(34.14)	196.20	(34.56)	201.50	(35.38)	0.02	191.90	(33.83)	0.08	193.30	(29.90)	0.25
High-density lipoprotein (HDL) cholesterol (mg/dl)	52.15	(15.09)	52.81	(15.99)	48.80	(13.17)	<0.001	55.31	(15.98)	0.03	51.23	(12.59)	0.15
Low-density lipoprotein (LDL) cholesterol (mg/dl)	118.79	(29.99)	116.80	(29.11)	124.50	(31.95)	<0.001	118.20	(30.42)	0.50	116.60	(27.70)	0.94
Triglycerides (mg/dl)	126.48	(72.14)	133.10	(78.19)	143.40	(74.30)	0.05	90.71	(39.39)	<0.001	127.50	(67.47)	0.33

Data were presented as mean (standard deviation, SD) for continuous variables, and percentage, % (frequency, N) for categorical variables.
Comparing each racial and ethnic minority group to White group, P-values were compared using t-test for continuous variables and $\chi 2$-tests for categorical variables.

Table 5.2. Associations of race and ethnicity with type 2 diabetes and visceral fat, and associations of visceral fat with type 2 diabetes

	Race and ethnicity and T2D[§]											
	Females											
	Hispanic (n=174) vs. White (n=315)				**Chinese (n=97) vs. White (n=315)**				**Black (n=160) vs. White (n=315)**			
	HR	**95%CI**		**P**	**HR**	**95%CI**		**P**	**HR**	**95%CI**		**P**
Model 1	**1.95**	**1.29**	**2.94**	**0.002**	**1.81**	**1.10**	**2.97**	**0.02**	**1.63**	**1.04**	**2.53**	**0.03**
Model 2	**1.77**	**1.17**	**2.69**	**0.01**	**1.91**	**1.15**	**3.15**	**0.01**	1.59	1.02	2.49	0.04
Model 3	1.29	0.78	2.15	0.32	2.11	1.10	4.04	0.03	1.77	1.00	3.13	0.05
	Males											
	Hispanic (n=161) vs. White (n=326)				**Chinese (n=102) vs. White (n=326)**				**Black (n=122) vs. White (n=326)**			
	HR	**95%CI**		**P**	**HR**	**95%CI**		**P**	**HR**	**95%CI**		**P**
Model 1	**2.04**	**1.36**	**3.04**	**0.001**	0.85	0.47	1.53	0.58	**1.74**	**1.11**	**2.73**	**0.02**
Model 2	**1.82**	**1.20**	**2.76**	**0.005**	0.86	0.48	1.55	0.62	1.48	0.92	2.38	0.10
Model 3	1.53	0.91	2.59	0.11	1.40	0.68	2.87	0.36	1.98	1.12	3.50	0.02
	Race and ethnicity and visceral fat (cm^2)[‡]											
	Females											
	Hispanic (n=174) vs. White (n=315)				**Chinese (n=97) vs. White (n=315)**				**Black (n=160) vs. White (n=315)**			
	Mean difference	**SE**		***P***	**Mean difference**	**SE**		***P***	**Mean difference**	**SE**		***P***
Model 1	**24.12**	**5.76**		**<0.001**	-13.33	7.08		0.06	-8.48	5.92		0.15
Model 2	**22.72**	**5.68**		**<0.001**	-9.44	7.00		0.18	-9.71	5.86		0.10
	Males											
	Hispanic (n=161) vs. White (n=326)				**Chinese (n=102) vs. White (n=326)**				**Black (n=122) vs. White (n=326)**			

	Mean difference	SE	*P*	Mean difference	SE	*P*	Mean difference	SE	*P*
Model 1	0.22	7.25	0.98	**-79.12**	**8.54**	**<0.001**	**-56.52**	**7.99**	**<0.001**
Model 2	1.66	7.34	0.38	**-77.56**	**8.47**	**<0.001**	**-57.57**	**8.11**	**<0.001**

Visceral fat (10 cm^2) and T2D[§]

Females

	White (n=315)				Chinese (n=97)				Black (n=122)				Hispanic (n=161)			
	HR	**95%CI**		***P***	**HR**	**95%CI**		***P***	**HR**	**95%CI**		***P***	**HR**	**95%CI**		***P***
Model 1	**1.12**	**1.07**	**1.16**	**<0.001**	**1.11**	**1.02**	**1.20**	**0.01**	**1.10**	**1.05**	**1.16**	**<0.001**	**1.09**	**1.04**	**1.14**	**0.001**
Model 2	**1.11**	**1.02**	**1.20**	**0.01**	1.07	0.88	1.29	0.52	**1.31**	**1.12**	**1.53**	**0.001**	**1.19**	**1.08**	**1.33**	**0.001**

Males

	White (n=315)				Chinese (n=97)				Black (n=122)				Hispanic (n=161)			
	HR	**95%CI**		***P***	**HR**	**95%CI**		***P***	**HR**	**95%CI**		***P***	**HR**	**95%CI**		***P***
Model 1	**1.06**	**1.03**	**1.10**	**<0.001**	1.07	0.97	1.17	0.17	1.03	0.98	1.07	0.29	**1.06**	**1.02**	**1.10**	**0.004**
Model 2	1.01	0.96	1.07	0.62	1.60	0.95	2.69	0.08	1.05	0.95	1.16	0.33	**1.10**	**1.03**	**1.19**	**0.01**

[§]For race and T2D, visceral fat and T2D, cox proportional hazard regression models were used. Hazard ratio (HR), 95% confidence interval (CI) and P-value were reported.

[ǂ]For race and visceral fat, linear regression models were used. Mean difference (SE) and P-value were reported.

Boldface indicated statistical significance after multiple testing [i.e., false-discovery rate (FDR) <0.05 using the Benjamini-Hochberg method].

Model 1: Crude model.

Model 2: Model 2 adjust for confounders. For race and T2D, race and visceral fat, model 2 adjusted for age and family history of diabetes. For visceral fat and T2D, model 2 adjusted for age, family history of diabetes, marital status, education, annual household income, stress, hypertension medication use, lipid-lowering medication use, smoking, alternative healthy eating index (AHEI)-2010, sedentary behavior, exercise, body mass index (BMI), total fat, muscle area and density, systolic blood pressure (SBP), total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides.

Model 3: Adjust for potential mediators for race and T2D, including marital status, education, annual household income, stress, hypertension medication use, lipid-lowering medication use, smoking, AHEI-2010, sedentary behavior, exercise, BMI, total fat, abdominal muscle area and density, SBP, total cholesterol, HDL cholesterol, triglycerides, and visceral fat.

Table 5.3. Decomposition of associations of race and ethnicity with type 2 diabetes by visceral fat

	iPSE (Visceralfat)					iPSE (notVisceralfat)				iTE			
	HR	**95%CI**		***P***	**Proportion explained (%)**	**HR**	**95%CI**		***P***	**HR**	**95%CI**		***P***
Female													
Hispanic vs. White	**1.20**	**1.04**	**1.54**	**<0.001**	20.3%	**2.08**	**1.30**	**3.90**	**0.01**	**2.50**	**1.50**	**5.43**	**0.01**
Chinese vs. White	0.92	0.77	1.03	0.20		**2.59**	**1.27**	**7.96**	**0.01**	2.38	1.19	7.37	0.03
Black vs. White	0.83	0.64	1.01	0.06		2.11	1.02	4.13	0.05	1.75	0.81	3.78	0.14
Male													
Hispanic vs. White	1.02	0.95	1.11	0.71		**1.95**	**1.23**	**4.42**	**<0.001**	**1.99**	**1.24**	**4.63**	**<0.001**
Chinese vs. White	0.91	0.55	1.29	0.54		0.99	0.32	2.98	0.98	0.91	0.30	2.11	0.80
Black vs. White	0.98	0.78	1.22	0.90		1.24	0.73	3.20	0.37	1.22	0.76	2.87	0.34

Interventional path specific effects (iPSEs) were used to assessed racial and ethnic differences in T2D explained by visceral fat. Hazard ratio (HR), 95% confidence interval (CI) and P-value were reported. Boldface indicated statistical significance (P<0.05). Boldface indicated statistical significance after multiple testing [i.e., false-discovery rate (FDR) <0.05 using the Benjamini-Hochberg method].
Continuous visceral fat (cm2) was used as the mediator.
Type 2 diabetes (T2D) was regressed on age, sex, family history of diabetes, race and ethnicity, marital status, education, annual household income, stress, hypertension medication use, lipid-lowering medication use, smoking, alternative healthy eating index (AHEI)-2010, sedentary behavior, exercise, body mass index (BMI), total fat mass, systolic blood pressure (SBP), total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, and visceral fat.
iPSE, interventional path specific effects; iTE, interventional total effect.

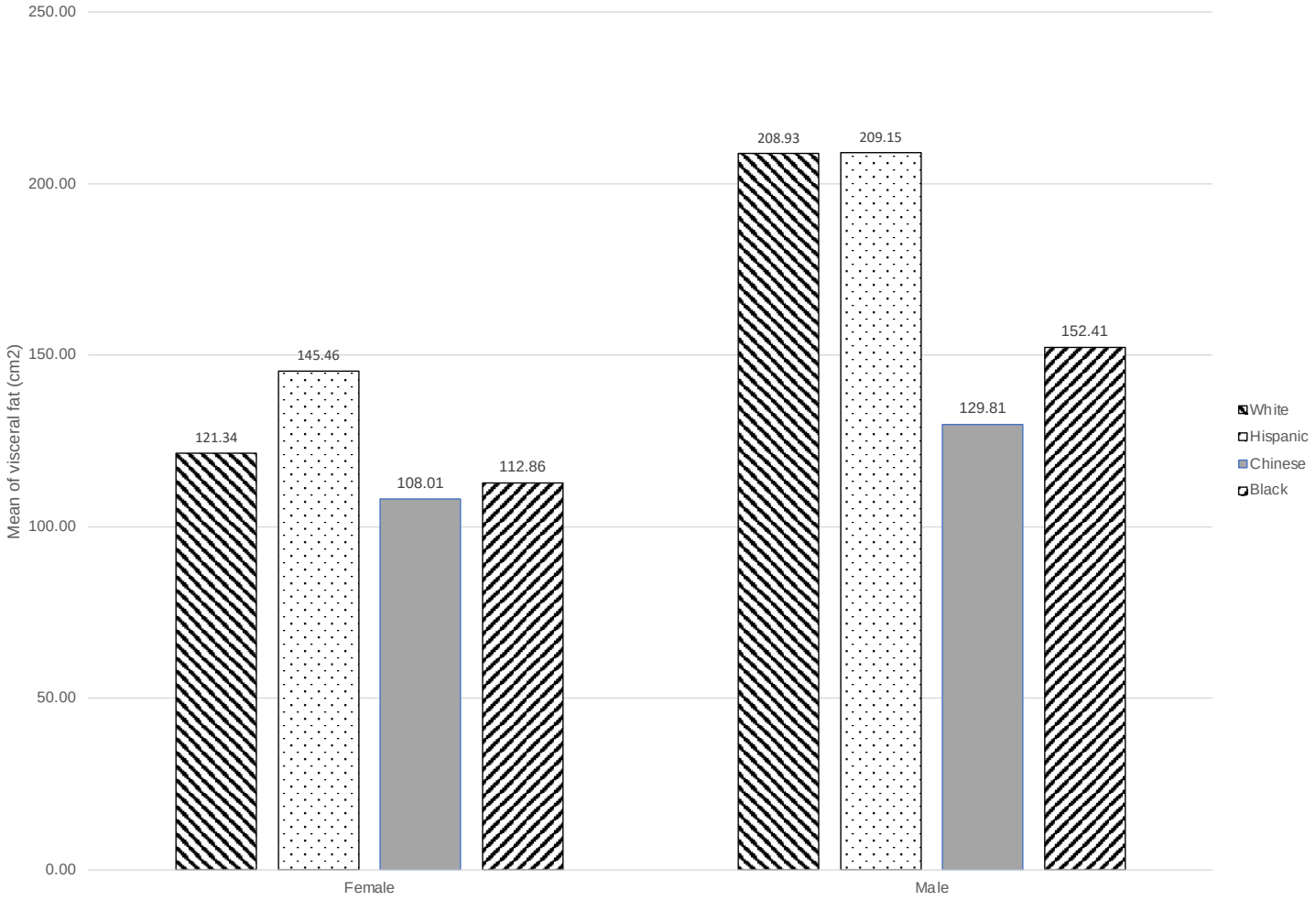


Figure 5.1. Visceral fat by racial and ethnic groups and sex groups in the Multi-Ethnic Study of Atherosclerosis ancillary study.

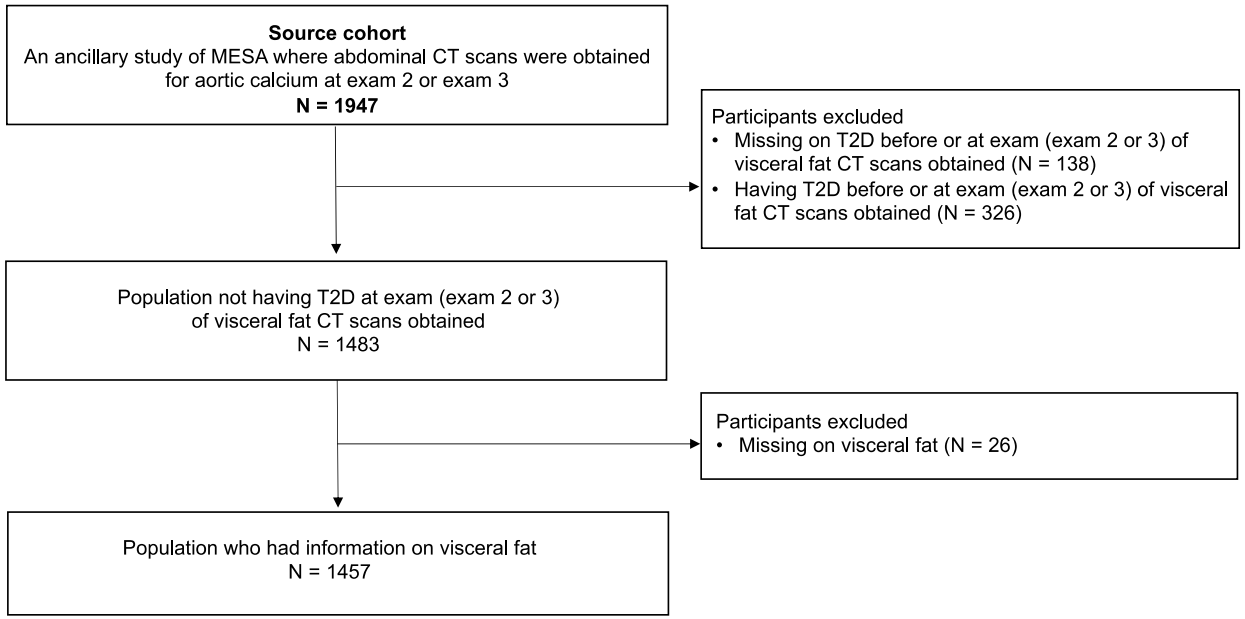


Figure S5.1. Participants flow chart

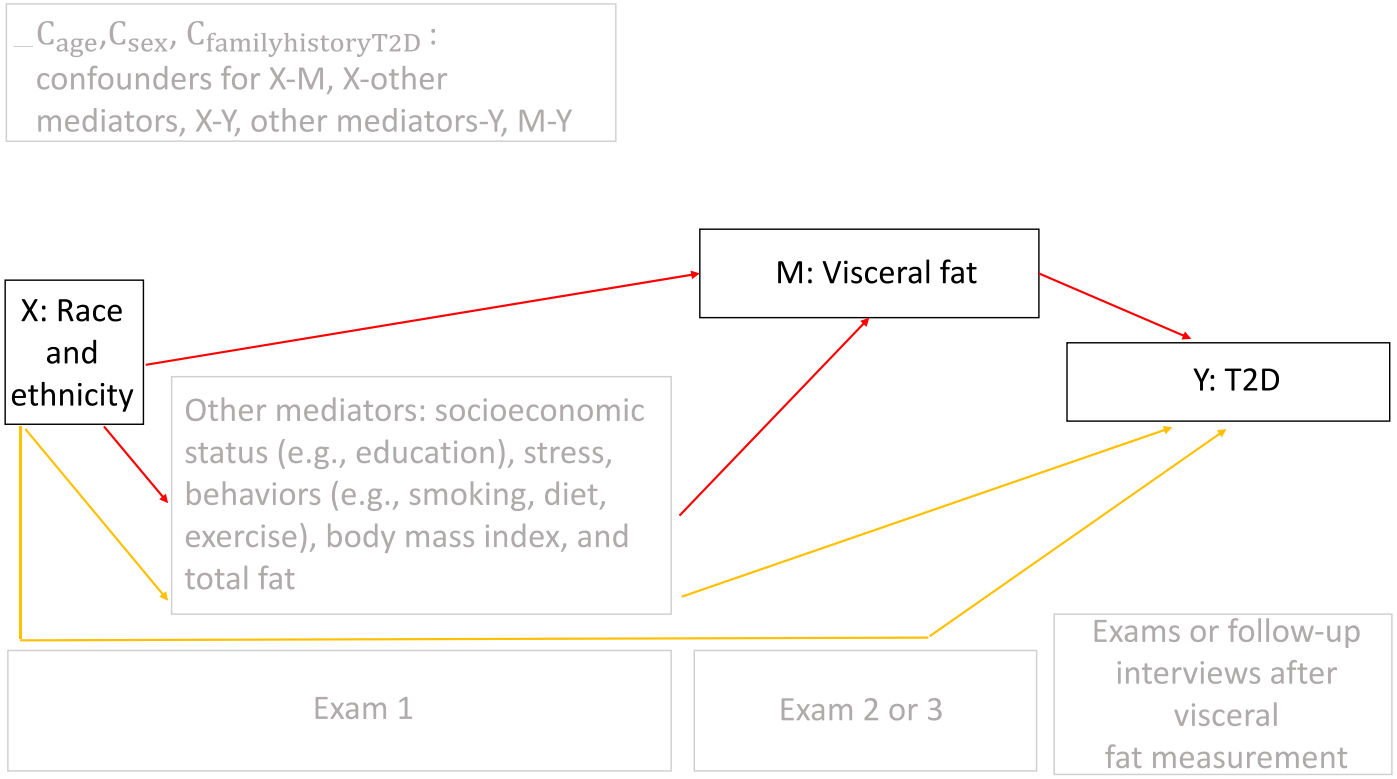


Figure S5.2. Directed acyclic graph (DAG) for racial and ethnic differences in type 2 diabetes through visceral fat

Table S5.1. Decomposition of associations of race and ethnicity with type 2 diabetes by visceral fat, adding interactions between race and visceral fat on type 2 diabetes

	iPSE (Visceralfat)				**iPSE (notVisceralfat)**				**iTE**			
	HR	**95%CI**		***P***	**Proportion explained (%)**	**HR**	**95%CI**		***P***	**HR**	**95%CI**		***P***
Female													
Hispanic vs. White	**1.26**	**1.05**	**1.80**	**<0.001**	25.6%	**1.97**	**1.07**	**3.96**	**0.02**	**2.49**	**1.35**	**4.90**	**<0.001**
Chinese vs. White	0.91	0.69	1.04	0.21		**2.85**	**1.35**	**7.46**	**<0.001**	**2.59**	**1.21**	**6.64**	**0.02**
Black vs. White	0.83	0.59	1.06	0.1		2.21	1.04	4.44	0.05	1.84	0.91	3.62	0.12
Male													
Hispanic vs. White	1.03	0.91	1.20	0.66		2.03	1.07	3.29	0.04	2.08	1.09	3.58	0.03
Chinese vs. White	0.52	0.09	1.78	0.16		1.57	0.30	7.25	0.36	0.81	0.28	1.74	0.59
Black vs. White	1.08	0.64	1.68	0.78		1.31	0.66	3.80	0.43	1.42	0.73	3.20	0.3

Interventional path specific effects (iPSEs) were used to assessed racial and ethnic differences in T2D explained by visceral fat. Hazard ratio (HR), 95% confidence interval (CI) and P-value were reported. Boldface indicated statistical significance (P<0.05). Boldface indicated statistical significance after multiple testing [i.e., false-discovery rate (FDR) <0.05 using the Benjamini-Hochberg method]. Continuous visceral fat (cm2) was used as the mediator.

Interactions between race and visceral fat on T2D were added in the mediation analysis.

Type 2 diabetes (T2D) was regressed on age, sex, family history of diabetes, race and ethnicity, marital status, education, annual household income, stress, hypertension medication use, lipid-lowering medication use, smoking, alternative healthy eating index (AHEI)-2010, sedentary behavior, exercise, body mass index (BMI), total fat mass, abdominal muscle area and density, systolic blood pressure (SBP), total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, and visceral fat.

Table S5.2. Associations of race and ethnicity with type 2 diabetes adjusting for mediators stepwise

Race/ethnicity and T2D												
Females												
	Hispanic vs. White				**Chinese vs. White**				**Black vs. White**			
	HR	**95%CI**		**P**	**HR**	**95%CI**		**P**	**HR**	**95%CI**		**P**
Model 1	**1.95**	**1.29**	**2.94**	**0.002**	**1.81**	**1.10**	**2.97**	**0.02**	**1.63**	**1.04**	**2.53**	**0.03**
Model 2	**1.77**	**1.17**	**2.69**	**0.01**	**1.91**	**1.15**	**3.15**	**0.01**	1.59	1.02	2.49	0.04
Model 3	1.31	0.84	2.05	0.24	1.49	0.89	2.51	0.13	1.59	1.01	2.50	0.05
Model 4	1.35	0.86	2.11	0.20	1.49	0.88	2.51	0.14	1.61	1.01	2.55	0.05
Model 5	1.30	0.83	2.05	0.25	1.42	0.83	2.45	0.20	1.60	1.00	2.55	0.05
Model 6	1.37	0.87	2.15	0.18	1.56	0.90	2.69	0.11	1.59	0.99	2.56	0.05
Model 7	1.44	0.91	2.29	0.12	1.69	0.95	3.02	0.08	1.61	1.00	2.59	0.05
Model 8	1.37	0.86	2.21	0.19	1.85	1.03	3.35	0.04	1.56	0.96	2.55	0.08
Model 9	1.33	0.82	2.15	0.25	1.79	0.99	3.25	0.06	1.58	0.97	2.59	0.07
Model 10	1.21	0.75	1.96	0.44	2.00	1.09	3.64	0.02	1.37	0.83	2.26	0.22
Model 11	1.25	0.76	2.06	0.38	2.04	1.11	3.73	0.02	1.39	0.84	2.30	0.20
Model 12	1.31	0.79	2.16	0.30	2.27	1.21	4.29	0.01	1.25	0.72	2.19	0.43
Model 13	1.29	0.78	2.15	0.32	2.11	1.10	4.04	0.03	1.77	1.00	3.13	0.05
Males												
	Hispanic vs. White				**Chinese vs. White**				**Black vs. White**			
	HR	**95%CI**		**P**	**HR**	**95%CI**		**P**	**HR**	**95%CI**		**P**
Model 1	**2.04**	**1.36**	**3.04**	**0.001**	0.85	0.47	1.53	0.58	**1.74**	**1.11**	**2.73**	**0.02**
Model 2	**1.82**	**1.20**	**2.76**	**0.005**	0.86	0.48	1.55	0.62	1.48	0.92	2.38	0.10
Model 3	1.31	0.82	2.09	0.25	0.72	0.38	1.36	0.31	1.33	0.81	2.18	0.27
Model 4	1.35	0.84	2.15	0.21	0.71	0.37	1.36	0.30	1.34	0.81	2.21	0.25
Model 5	1.33	0.83	2.13	0.23	0.70	0.36	1.35	0.29	1.34	0.81	2.20	0.26

Model 6	1.33	0.83	2.14	0.23	0.74	0.38	1.44	0.38	1.37	0.82	2.27	0.23
Model 7	1.34	0.83	2.14	0.23	0.75	0.38	1.46	0.39	1.37	0.82	2.28	0.23
Model 8	1.28	0.79	2.07	0.32	0.74	0.38	1.46	0.39	1.37	0.82	2.28	0.23
Model 9	1.37	0.84	2.22	0.21	0.77	0.40	1.50	0.44	1.40	0.84	2.35	0.20
Model 10	1.27	0.78	2.08	0.34	0.99	0.50	1.98	0.98	1.42	0.85	2.37	0.18
Model 11	1.46	0.88	2.42	0.15	1.16	0.57	2.35	0.68	1.44	0.86	2.41	0.16
Model 12	1.47	0.88	2.47	0.15	1.18	0.59	2.39	0.64	1.65	0.95	2.86	0.08
Model 13	1.53	0.91	2.59	0.11	1.40	0.68	2.87	0.36	1.98	1.12	3.50	0.02

Cox proportional hazard regression models were used. Hazard ratio (HR), 95% confidence interval (CI) and P-value were reported. Boldface indicated statistical significance after multiple testing [i.e., false-discovery rate (FDR) <0.05 using the Benjamini-Hochberg method].
Model 1: Crude model.
Model 2: Adjust for confounders, age and family history of diabetes.
From model 3, mediators were additionally adjusted.
Model 3: Adjust for age, gender, family history of diabetes, education, and annual household income.
Model 4: Adjust for age, gender, family history of diabetes, education, annual household income, and marital status.
Model 5: Adjust for age, gender, family history of diabetes, education, annual household income, marital status, and stress.
Model 6: Adjust for age, gender, family history of diabetes, education, annual household income, marital status, stress, and hypertension medication use, lipid-lowering medication use.
Model 7: Adjust for age, gender, family history of diabetes, education, annual household income, marital status, stress, hypertension medication use, lipid-lowering medication use, and smoking.
Model 8: Adjust for age, gender, family history of diabetes, education, annual household income, marital status, stress, hypertension medication use, lipid-lowering medication use, smoking, and AHEI-2010.
Model 9: Adjust for age, gender, family history of diabetes, education, annual household income, marital status, stress, hypertension medication use, lipid-lowering medication use, smoking, AHEI-2010, exercise, and sedentary behavior.
Model 10: Adjust for age, gender, family history of diabetes, education, annual household income, marital status, stress, hypertension medication use, lipid-lowering medication use, smoking, AHEI-2010, exercise, sedentary behavior, and BMI.
Model 11: Adjust for age, gender, family history of diabetes, education, annual household income, marital status, stress, hypertension medication use, lipid-lowering medication use, smoking, AHEI-2010, exercise, sedentary behavior, BMI, and total fat.
Model 12: Adjust for age, gender, family history of diabetes, education, annual household income, marital status, stress, hypertension medication use, lipid-lowering medication use, smoking, AHEI-2010, exercise, sedentary behavior, BMI, total fat, muscle area and density, SBP, total cholesterol, HDL cholesterol, and triglycerides.
Model 13: Adjust for age, gender, family history of diabetes, education, annual household income, marital status, stress, hypertension medication use, lipid-lowering medication use, smoking, AHEI-2010, exercise, sedentary behavior, BMI, total fat, muscle area and density, SBP, total cholesterol, HDL cholesterol, triglycerides, and visceral fat.
AHEI-2010, alternative healthy eating index-2010; BMI, body mass index; HDL cholesterol, high-density lipoprotein cholesterol; SBP, systolic blood pressure.

Table S5.3. Characteristics of participants by race and sex in Multi-Ethnic Study of Atherosclerosis ancillary study

Characteristics	Non-Hispanic White females [21.6% (315)]		Hispanic females [11.9% (174)]		P-values compared to White females	Non-Hispanic Black females [11.0% (160)]		P-values compared to White females	Non-Hispanic Chinese American females [6.7% (97)]		P-values compared to White females
Age (years)	65.77	(9.07)	64.15	(9.24)	0.06	64.99	(9.99)	0.39	64.39	(9.49)	0.20
Family history of diabetes, % (N)	32.6	(102)	46.2	(80)	0.003	41.3	(64)	0.06	23.2	(22)	0.08
Married/living with a partner, % (N)	59.2	(186)	48.8	(83)	0.03	34.4	(55)	<0.001	70.1	(68)	0.05
Education, % (N)					<0.001			0.59			<0.001
High school or less	26.4	(81)	67.2	(117)		25.0	(40)		47.4	(48)	
Associates	32.2	(102)	21.3	(37)		36.9	(59)		25.8	(25)	
Bachelor's or higher	41.4	(134)	11.5	(20)		38.1	(61)		26.8	(26)	
Annual household income, % (N)					<0.001			<0.001			<0.001
<$25,000	17.1	(51)	49.1	(85)		27.9	(41)		52.1	(50)	
$25,000–$49,999	26.8	(80)	34.7	(60)		37.4	(55)		30.2	(29)	
≥$50,000	56.2	(168)	16.2	(28)		34.7	(51)		17.7	(17)	
Stress, % (N)					0.08			0.04			<0.001
Low	25.1	(79)	34.5	(60)		34.4	(55)		56.7	(55)	
Medium	40.6	(128)	37.4	(65)		30.0	(48)		22.7	(22)	
High	34.3	(108)	28.2	(49)		35.6	(57)		20.6	(20)	
Hypertension medication use, % (N)	32.8	(103)	29.3	(51)	0.43	50.0	(80)	<0.001	24.7	(24)	0.13
Lipid-lowering medication use, % (N)	17.2	(54)	16.7	(29)	0.88	12.7	(20)	0.20	15.5	(15)	0.69
Cigarettes smoking, % (N)					0.01			0.67			<0.001
Never	44.3	(139)	58.6	(102)		47.5	(76)		99.0	(96)	
Former	43.0	(135)	34.5	(60)		38.8	(62)		1.0	(1)	
Current	12.7	(40)	6.9	(12)		13.8	(22)		0.0	(0)	
Alternative healthy eating index (AHEI)-2010	56.31	(10.17)	52.38	(8.82)	<0.001	54.00	(9.70)	0.02	56.46	(7.93)	0.88
Sedentary behavior (MET-hours/day)	4.48	(2.96)	3.52	(2.31)	<0.001	4.91	(2.85)	0.12	3.45	(2.36)	0.001

Exercise (MET-hour/day)	3.37	(3.39)	2.56	(3.03)	0.01	3.34	(3.42)	0.94	3.18	(3.48)	0.64
Body mass index (BMI, kg/m^2)	26.65	(5.23)	29.08	(5.29)	<0.001	29.84	(6.05)	<0.001	23.88	(3.42)	<0.001
Total fat mass (kg)	29.31	(9.65)	31.54	(8.59)	0.01	33.94	(10.98)	<0.001	23.21	(5.49)	<0.001
Abdominal muscle area (cm2)	82.58	(13.62)	81.50	(15.45)	0.43	92.81	(17.42)	<0.001	75.13	(13.10)	<0.001
Abdominal muscle density (HU)	40.29	(4.45)	40.30	(4.96)	0.98	42.78	(5.56)	<0.001	41.63	(4.80)	0.01
Systolic blood pressure (SBP, mmHg)	123.70	(22.01)	128.90	(24.91)	0.02	132.70	(22.37)	<0.001	21.77	(2.21)	0.76
Diastolic blood pressure (DBP, mmHg)	67.22	(9.60)	69.86	(9.66)	0.00	73.36	(10.26)	<0.001	68.88	(8.64)	0.13
Total cholesterol (mg/dl)	203.40	(34.48)	206.50	(35.10)	0.34	195.60	(31.33)	0.02	195.90	(28.96)	0.03
High-density lipoprotein (HDL) cholesterol (mg/dl)	59.96	(16.57)	53.60	(13.81)	<0.001	59.81	(16.28)	0.93	54.96	(12.99)	0.002
Low-density lipoprotein (LDL) cholesterol (mg/dl)	115.40	(28.90)	125.80	(32.81)	<0.001	117.40	(28.58)	0.49	115.40	(28.60)	0.98
Triglycerides (mg/dl)	137.90	(80.92)	138.50	(70.68)	0.94	89.29	(38.85)	<0.001	129.20	(68.57)	0.34

	Non-Hispanic White males [22.4% (326)]		**Hispanic males [11.1% (161)]**			**Non-Hispanic Black males [8.4% (122)]**			**Non-Hispanic Chinese American males [7.0% (102)]**		
					P-values compared to White males			**P-values compared to White males**			**P-values compared to White males**
Age (years)	64.92	(9.99)	61.60	(9.62)	0.001	64.37	(10.07)	0.60	64.98	(10.57)	0.96
Family history of diabetes, % (N)	22.2	(72)	39.5	(62)	<0.001	45.3	(53)	<0.001	19.0	(19)	0.49
Married/living with a partner, % (N)	76.6	(76)	73.6	(117)	0.47	67.2	(82)	0.04	91.2	(93)	0.001
Education, % (N)					<0.001			<0.001			0.01
High school or less	12.9	(42)	53.4	(86)		23.8	(29)		24.8	(25)	
Associates	26.4	(86)	28.6	(46)		37.7	(46)		19.8	(20)	
Bachelor's or higher	60.7	(198)	18.0	(29)		38.5	(47)		55.5	(56)	
Annual household income, % (N)					<0.001			<0.001			<0.001
<$25,000	8.8	(28)	30.2	(48)		21.8	(24)		40.6	(41)	
$25,000–$49,999	25.9	(82)	39.6	(63)		32.7	(36)		21.8	(22)	
≥$50,000	65.3	(207)	30.2	(48)		45.5	(50)		37.6	(38)	
Stress, % (N)					0.22			0.77			0.03

Low	34.7	(113)	41.0	(66)		31.2	(38)		49.0	(50)	
Medium	37.4	(122)	29.8	(48)		38.5	(47)		31.4	(32)	
High	27.9	(91)	29.2	(47)		30.3	(37)		19.6	(20)	
Hypertension medication use, % (N)	29.5	(96)	28.0	(45)	0.73	37.7	(46)	0.09	22.6	(23)	0.17
Lipid-lowering medication use, % (N)	18.2	(59)	11.2	(18)	0.05	7.4	(9)	0.01	12.8	(13)	0.20
Cigarettes smoking, % (N)					0.55			0.35			0.11
Never	36.7	(118)	35.0	(56)		33.1	(40)		48.0	(49)	
Former	51.9	(167)	50.0	(80)		50.4	(61)		44.1	(45)	
Current	11.5	(37)	15.0	(24)		16.5	(20)		7.8	(8)	
Alternative healthy eating index (AHEI)-2010	52.63	(9.46)	49.17	(9.05)	<0.001	50.86	(10.13)	0.09	54.45	(7.77)	0.05
Sedentary behavior (MET-hours/day)	3.65	(2.35)	3.46	(2.31)	0.41	4.36	(2.78)	0.01	3.40	(2.26)	0.34
Exercise (MET-hour/day)	4.26	(4.50)	3.66	(3.95)	0.15	4.97	(6.87)	0.29	3.17	(3.19)	0.01
Body mass index (BMI, kg/m^2)	27.44	(3.66)	28.43	(4.04)	0.01	27.62	(3.71)	0.65	23.64	(2.77)	<0.001
Total fat mass (kg)	24.51	(6.14)	24.78	(6.61)	0.66	24.19	(6.61)	0.63	16.86	(4.57)	<0.001
Abdominal muscle area (cm2)	123.70	(23.96)	125.70	(22.10)	0.37	136.40	(26.09)	<0.001	111.80	(18.53)	<0.001
Abdominal muscle density (HU)	43.95	(5.32)	44.73	(4.29)	0.08	46.42	(4.57)	<0.001	45.99	(3.65)	<0.001
Systolic blood pressure (SBP, mmHg)	124.70	(18.34)	122.80	(19.48)	0.29	129.90	(20.20)	0.01	123.30	(20.53)	0.52
Diastolic blood pressure (DBP, mmHg)	75.24	(8.77)	75.13	(9.59)	0.90	76.56	(10.17)	0.21	74.12	(9.14)	0.26
Total cholesterol (mg/dl)	189.30	(33.27)	196.10	(34.98)	0.04	187.20	(36.43)	0.55	190.90	(30.71)	0.68
High-density lipoprotein (HDL) cholesterol (mg/dl)	45.90	(11.88)	43.61	(10.18)	0.03	49.45	(13.54)	0.01	47.69	(11.15)	0.18
Low-density lipoprotein (LDL) cholesterol (mg/dl)	118.10	(29.29)	123.10	(31.04)	0.08	119.20	(32.75)	0.72	117.80	(26.91)	0.92
Triglycerides (mg/dl)	128.30	(75.27)	148.60	(77.89)	0.01	92.57	(40.17)	<0.001	126.00	(66.70)	0.78

Data were presented as mean (standard deviation, SD) for continuous variables, and percentage, % (frequency, N) for categorical variables.
When comparing each racial/ethnic minority group to White group, P-values were compared using t-test for continuous variables and $\chi 2$-tests for categorical variables.
When comparing categorical variables, if the frequency < 5, Fisher's exact test was used.

Table S5.4. Characteristics among included and excluded participants

Characteristics		Included participants (n=1457)		Excluded participants (n=490)		P-values
Age (years)		64.58	(9.73)	64.90	(9.41)	0.53
Female, % (N)		51.2	(746)	44.3	(217)	0.01
Family history of diabetes, % (N)		33.1	(474)	52.3	(241)	<0.001
Race and ethnicity						<0.001
	White	44.0	(641)	29.4	(144)	
	Chinese	13.7	(199)	10.8	(53)	
	Black	19.4	(282)	25.3	(124)	
	Hispanic	23.0	(335)	34.5	(169)	
Married/living with a partner, % (N)		64.8	(941)	64.0	(313)	0.94
Education, % (N)						<0.001
	High school or less	32.2	(468)	45.5	(223)	
	Associates	28.9	(420)	27.6	(135)	
	Bachelor's or higehr	39.0	(567)	26.9	(132)	
Annual household income, % (N)						<0.001
	<$25,000	27.5	(389)	38.5	(181)	
	$25,000–$49,999	28.6	(404)	32.8	(154)	
	≥$50,000	44.0	(622)	28.7	(135)	
Stress, % (N)						0.10
	Low	42.1	(613)	36.5	(179)	
	Middle	29.0	(423)	31.6	(155)	

	High	28.9	(421)	31.8	(156)	
Hypertension medication use, % (N)		32.1	(468)	46.4	(227)	<0.001
Lipid-lowering medication use, % (N)		14.9	(217)	19.6	(96)	0.01
Cigerettes smoking, % (N)						0.60
	Never	50.3	(733)	51.0	(250)	
	Former	37.2	(542)	35.1	(172)	
	Current	12.5	(182)	13.9	(68)	
Alternative healthy eating index (AHEI)-2010		53.40	(9.64)	52.98	(8.60)	0.37
Sedentary behavior (MET- hours/day)		3.96	(2.62)	3.96	(2.53)	0.97
Exercise (MET-hour/day)		3.61	(4.12)	3.10	(3.82)	0.01
Body mass index (BMI, kg/m^2)		27.34	(4.81)	29.59	(5.36)	<0.001
Total fat mass (kg)		26.84	(9.07)	30.14	(10.00)	<0.001
Abdominal muscle area (cm2)		103.60	(28.89)	104.30	(29.24)	0.65
Abdominal muscle density (HU)		42.88	(5.27)	42.39	(5.52)	0.08
Systolic blood pressure (SBP, mmHg)		21.33	(0.56)	22.02	(1.00)	<0.001
Diastolic blood pressure (DBP, mmHg)		72.25	(10.04)	73.32	(10.64)	0.05
Total cholesterol (mg/dl)		196.20	(34.14)	193.20	(33.93)	0.09
High-density lipoprotein (HDL) cholesterol (mg/dl)		52.15	(15.09)	46.92	(13.58)	<0.001
Low-density lipoprotein (LDL) cholesterol (mg/dl)		118.80	(29.99)	116.10	(31.28)	0.10
Triglycerides (mg/dl)		126.50	(72.14)	157.50	(96.08)	<0.001

Data were presented as mean (standard deviation, SD) for continuous variables, and percentage, % (frequency, N) for categorical variables.

P-values were compared using t-test for continuous variables and χ2-tests for categorical variables

Table S5.5. Decomposition of associations of race and ethnicity with type 2 diabetes by visceral fat, applying inverse probability weighting

	iPSE (Visceralfat)					**iPSE (notVisceralfat)**				**iTE**			
	HR	**95%CI**		***P***	**Proportion explained (%)**	**HR**	**95%CI**		***P***	**HR**	**95%CI**		***P***
Female													
Hispanic vs. White	1.20	1.01	1.57	0.04	16.7%	**2.51**	**1.47**	**6.36**	**<0.001**	**3.02**	**1.94**	**7.90**	**<0.001**
Chinese vs. White	0.99	0.88	1.07	0.79		**3.15**	**1.47**	**9.93**	**0.02**	**3.11**	**1.44**	**9.91**	**0.02**
Black vs. White	1.02	0.90	1.19	0.80		**3.02**	**1.77**	**7.92**	**<0.001**	**3.08**	**1.79**	**8.30**	**<0.001**
Male													
Hispanic vs. White	1.07	0.97	1.22	0.21		1.96	0.95	4.30	0.07	2.10	1.01	4.77	0.05
Chinese vs. White	0.85	0.52	1.12	0.12		1.26	0.38	1.00	0.62	1.07	0.32	2.84	0.99
Black vs. White	0.93	0.70	1.11	0.38		1.68	0.75	4.88	0.17	1.55	0.71	4.31	0.22

Interventional path specific effects (iPSEs) were used to assessed racial and ethnic differences in T2D explained by visceral fat. Hazard ratio (HR), 95% confidence interval (CI) and P-value were reported. Boldface indicated statistical significance (P<0.05). Boldface indicated statistical significance after multiple testing [i.e., false-discovery rate (FDR) <0.05 using the Benjamini-Hochberg method]. Continuous visceral fat (cm2) was used as the mediator.

Inverse probability weighting was applied to address potential selection bias due to excluding participants.

Type 2 diabetes (T2D) was regressed on age, sex, family history of diabetes, race and ethnicity, marital status, education, annual household income, stress, hypertension medication use, lipid-lowering medication use, smoking, alternative healthy eating index (AHEI)-2010, sedentary behavior, exercise, body mass index (BMI), total fat mass, abdominal muscle area and density, systolic blood pressure (SBP), total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, and visceral fat.

6. Chapter six: Discussion

6.1. Objectives

The overall goal of the studies within this dissertation was to gain a better understanding of why racial and ethnic minorities have excess risk of developing T2D by examining modifiable pathways and to give implications for public health interventions. Gaps in the literature were identified, including no studies examining comprehensive SDOH with T2D and no studies quantifying mediation effects of exercise and visceral fat for racial differences in T2D.

This dissertation focused on three main objectives:

1) To examine the association between comprehensive SDOH and T2D, and the associations in racial and ethnic subgroups.

2) To investigate whether and to what degree racial and ethnic differences in T2D are explained by exercise.

3) To assess whether and to what degree racial and ethnic differences in T2D are explained by visceral fat in sex subgroups.

This dissertation used the data from MESA, a population-based, prospective and longitudinal cohort including multiple racial and ethnic groups, and assessed associations of SDOH from several domains with T2D and applied modern casual mediation analyses to examine exercise and visceral fat as mediators for racial differences in T2D. MESA included 6814 adults aged 45–84 years and free of CVD. Study participants were recruited in 2000–2002 and followed to 2020. We also used the other MESA ancillary study measuring abdominal aortic calcification in a subset of participants (n=1947) who obtained abdominal CT scans of visceral fat at either exam 2 or exam 3[163–166]

6.2. Main findings

The dissertation collectively illustrated a picture of how SDOH, exercise, and visceral fat influence racial differences in T2D risk. Like the conceptual framework demonstrating, racial differences in disadvantaged SDOH, influenced by systemic inequities, may lead to increased stress and unhealthy behaviors such as lower exercise. These factors, in turn, contributed to higher obesity and visceral fat levels, which elevated insulin resistance and impaired β-cell function, ultimately increasing T2D risk among minorities.

The first study highlighted that disadvantaged SDOH were significantly associated with increased T2D risk in overall participants and specifically among Whites and Hispanics when stratified by race and ethnicity. This association was not observed in Chinese and Blacks, potentially due to insufficient sample size. Racial and ethnic minorities often experience higher levels of disadvantaged SDOH, influenced by systemic inequities. These adverse conditions may contribute to T2D disparities through mechanisms such as increased stress, unhealthy behaviors (e.g., less exercise), and higher levels of obesity and visceral fat accumulation. In next two studies, we examined the racial differences in T2D through the downstream factors exercise and visceral fat.

The second study examined the role of exercise in racial differences in T2D and found that exercise accounted for about one-tenth of the racial differences in T2D risk when comparing Hispanics and Chinese to Whites. These findings align with the conceptual model, illustrating the critical role of exercise in higher T2D risks among Hispanics and Chinese, who are more likely to face disadvantaged SDOH due to systemic racism and policies, leading to lower exercise levels, later on higher obesity, and increased visceral fat.

The third study focused on the role of visceral fat in T2D disparities and found that visceral fat mediated the higher T2D risk in Hispanic females, explaining about one-fifth of the racial and ethnic differences in T2D risk among this group. This finding underscores the important role of visceral fat in the development of T2D among Hispanic females, who often face higher levels of disadvantaged SDOH due to structural inequities, resulting in lower exercise levels. These conditions contribute to higher visceral fat accumulation compared to White females, leading to increased hepatic and peripheral insulin resistance and, consequently, a higher risk of T2D.

Social determinants of health and type 2 diabetes

We assessed the SDOH based on a widely applied method in the NHIS studies[111,112,167]. We included 9 variables across four domains: economic stability domain, education domain, neighborhood, physical environment and social cohesion domain, and health and system domain. We found that disadvantaged SDOH was associated with increased T2D risk in a dose-response manner in overall participants, and Whites and Hispanics in the stratified analysis by race and ethnicity. We did not observe the associations in Chinese and Blacks in this dissertation.

Our findings are in line with two studies examined personal sociodemographic factors or neighborhood SES with T2D in the US and Finland[27,31], which showed a positive association of cumulative personal sociodemographic variables[27] or cumulative neighborhood factors[31] with T2D. However, these two studies did not investigate interplays between personal and neighborhood factors[27,31]. Our study expanded such work by prospectively assessing SDOH integrating several domains with T2D, and examining the associations in racial and ethnic subgroups. Our findings suggested the aggregated SDOH as an important risk factor for T2D and prioritizing prevention resources for vulnerable groups exposed to social disadvantages. It is

critical for the Hispanics at heightened risk, as targeted interventions may be needed for T2D disparities and promoting health equity.

Racial and ethnic disparities of type 2 diabetes in the United States: the pathways through exercise

We used iPSEs to examine whether and to what degree the association of race and ethnicity with T2D can be explained by exercise. We confirmed that Hispanics, Blacks and Chinese had higher risks of T2D, and found only Hispanics and Chinese had lower levels of exercise than Whites. In addition, we observed that exercise may be a mediator of the T2D risk differences for Hispanics and Chinese, but not for Blacks, as compared to Whites. Exercise explained about one-tenth of racial differences in T2D when comparing Hispanics and Chinese to Whites.

Our findings were consistent with one study regarding the role of exercise in explaining the T2D risk difference between Hispanics and Whites[56]. The study among postmenopausal women examined baseline mixed activities as a mediator for racial differences in T2D[56]. It found that combined exercise and household activities explained 6% of racial differences (Hispanic or Black vs. White) in T2D[56]. However, the limitation of the study was that the exercise was combined with household activities, thus, it was unable to differentiate the mediation effect of exercise and household activities[56]. Additionally, the study only assessed baseline activities which were likely to change over time. Moreover, the study did not have data for Asian subpopulations[56]. Our study provided new evidence that habitual exercise explained about one-tenth of higher T2D risk in Chinese as compared to Whites. Our findings suggest that culture-appropriated exercise interventions to increase exercise in Hispanics and Chinese may help to reduce their higher T2D risks.

Racial and ethnic disparities of type 2 diabetes in the United States: the pathways through visceral fat

We used iPSEs to examine whether and to which degree the association of race and ethnicity with T2D can be explained by visceral fat in sex subgroups. We found that controlling for confounders, Hispanic, Black and Chinese females, as well as Hispanic and Black males had higher risks of T2D than White counterparts, but Chinese males had similar T2D risk compared to White males. Only Hispanic females had higher visceral fat than White females. In addition, we found that visceral fat may be a mediator of the Hispanic females' higher T2D risk, but not for other minorities' higher risk of T2D. Visceral fat explained about one-fifth of racial and ethnic differences in T2D when comparing Hispanics females to White females.

Our findings for the mediation effects of visceral fat were inconsistent with one study regarding the mediation effects of waist circumstance in explaining the risk difference of T2D, which may be due to that study using waist circumstance not estimating visceral fat well[56]. It found that Blacks had higher, Asians had lower, and Hispanics had similar percentages of high waist circumstance compared to Whites, meanwhile, waist circumstance explained 19% of Blacks' higher T2D risk relative to Whites, but not for Asians' and Hispanics' higher T2D risk[56]. However, waist circumstance could not distinguish visceral fat from subcutaneous fat then may not accurately estimate visceral fat[75]. We found that Hispanic females had higher visceral fat than White females, which was also found in a previous study in the US showing that Hispanic females had higher visceral fat mass than White females[79]. We provided new evidence that visceral fat explained about one-fifth of higher T2D risk among Hispanic females as compared to White females. Our study grasping how visceral fat contributes to the higher T2D risk among Hispanic females improves understanding of the biological factor at play.

6.3. Strengths and limitations

The study using MESA, a population-based, prospective cohort study with multiple racial and ethnic groups, provides the opportunity to examine comprehensive SDOH with T2D and quantify mediation effects of exercise and visceral fat for racial differences in T2D. First, this cohort has rich data on sociodemographic variables, medications, behaviors, anthropometrics, and lab results. Second, the time sequence of SDOH, exercise, visceral fat and T2D ensured the temporality of associations.

In addition to the strengths of the data, there are several analytical strengths. First, we created comprehensive SDOH using a score which included multiple domains of personal and neighborhood risk factors. Second we used cumulative exercise not only capturing the habitual levels of exercises over time but also reducing measurement errors. Third, we used visceral fat measured by CT, which is better than using waist circumstance to assess visceral fat. Fourth, we applied rigorous causal mediation analysis method to examine mediation effects.

Nonetheless, some potential limitations of our study exist. First, as it was an observational study, although we tried to control for confounders, there might be residual confounders. Second, as we only had Chinese in MESA, more studies including more Asian subgroups are needed. Third, systemic racism and related public policies are fundamental causes of racial health disparities in T2D, and racial discrimination is also an important factor in measuring SDOH, however, we did not have the related variables. More studies including these variables are needed. Additionally, while our dissertation focused on SDOH, exercise, and visceral fat, other factors such as psychological factors and diet available in our dataset may also explain racial and ethnic differences in T2D. Future studies should examine the roles of these factors in the disparities.

6.4. Conclusions and public health implications

The findings from the dissertation bridge the gaps by assessing associations between comprehensive social disadvantages and T2D and using causal mediation analysis to quantitively understand the etiology pathways through exercise and visceral fat for racial disparities in T2D. It found that SDOH may contribute to Hispanics' higher risk of T2D; exercise may explain one-tenth of Hispanics' and Chinese' higher risk of T2D; and visceral fat may explain one-fifth of Hispanic females' higher risk of T2D. These findings suggested that disadvantaged SDOH influenced by systemic inequities, reduced exercise influenced by worse SDOH, and increased visceral fat due to worse SDOH and less exercise are interlinked factors contributing to the elevated T2D risk in racial and ethnic minorities (e.g., Hispanics). As T2D is largely preventable, the findings from this dissertation expand the understanding of the modifiable pathways of racial disparities in T2D. These insights could give implications for future effective interventions for higher T2D risks among racial and ethnic groups .

This dissertation contributes to give public health implications. First, as systemic racism and the related policies (e.g., education systems, housing policy, land ownership, labor protections) are the root cause for racial disparities, leading to minorities' disadvantaged SDOH, systemic public health interventions or policies are needed for the upstream factor SDOH. It is critical to prioritize resources and allocate targeted resource for vulnerable groups affected by social disadvantages, particularly at-risk Hispanics. This involves implementing policies to expand to healthcare coverage, improving educational opportunities, employment conditions, living conditions, enhancing access to healthy foods, and creating safe spaces for exercise, as well as community-based interventions that address the specific needs of these populations. Second, develop and implement culturally appropriate exercise interventions aimed at increasing

exercise levels for all racial and ethnic groups, especially among Hispanics and Chinese. These interventions should consider cultural preferences and barriers to exercise, promoting sustainable and enjoyable exercise routines. For example, support community-based exercise programs tailored to the cultural preferences and needs of different racial and ethnic groups. Third, increase awareness about the risks of visceral fat and its link to T2D through targeted public health campaigns for all racial and ethnic groups, especially in Hispanic communities. These campaigns should educate the public on the importance of maintaining a healthy weight, regular exercise, and healthy eating to prevent visceral fat accumulation. In addition, enact some nutritional policies to increase access to healthy, affordable food options in communities, and decrease visceral fat. Support initiatives such as farmers' markets, community gardens, and subsidies for healthy food purchases are needed. Implement stricter regulations on food labeling and marketing to help consumers make informed choices and reduce the consumption of unhealthy foods.

Racial disparities in T2D are fundamentally linked to systemic racism, and are also linked to its influenced SDOH, exercise and visceral fat levels. This dissertation opens new horizons by not only providing information for prioritizing resources for vulnerable groups affected by social disadvantages, but also for targeted interventions in modifiable factor, exercise, and a deeper understanding of the biological impacts of visceral fat. The findings from this dissertation highlight the importance of a multifaceted approach that integrates SDOH improvement, exercise promotion, and nutritional education and community support for visceral fat to address the complex factors contributing to racial and ethnic differences in T2D.

7. Chapter seven: References

1. National Diabetes Statistics Report 2020. Estimates of diabetes and its burden in the United States. Published online 2020:32.
2. National Diabetes Statistics Report. Centers for Disease Control and Prevention. November 29, 2023. Accessed April 2, 2024. https://www.cdc.gov/diabetes/data/statistics-report/index.html.
3. Boyle JP, Thompson TJ, Gregg EW, Barker LE, Williamson DF. Projection of the year 2050 burden of diabetes in the US adult population: dynamic modeling of incidence, mortality, and prediabetes prevalence. Popul Health Metrics. 2010;8(1):29. doi:10.1186/1478-7954-8-29
4. Parker ED, Lin J, Mahoney T, et al. Economic costs of diabetes in the U.S. in 2022. Diabetes Care. 2023;47(1):26-43. doi:10.2337/dci23-0085
5. Rowley WR, Bezold C, Arikan Y, Byrne E, Krohe S. Diabetes 2030: Insights from Yesterday, Today, and Future Trends. Population Health Management. 2017;20(1):6-12. doi:10.1089/pop.2015.0181
6. Shariff-Marco S, Klassen AC, Bowie JV. Racial/Ethnic Differences in Self-Reported Racism and Its Association With Cancer-Related Health Behaviors. Am J Public Health. 2010;100(2):364-374. doi:10.2105/AJPH.2009.163899
7. Cheng YJ, Kanaya AM, Araneta MRG, et al. Prevalence of Diabetes by Race and Ethnicity in the United States, 2011-2016. JAMA. 2019;322(24):2389. doi:10.1001/jama.2019.19365
8. Menke A, Casagrande S, Geiss L, Cowie CC. Prevalence of and Trends in Diabetes Among Adults in the United States, 1988-2012. JAMA. 2015;314(10):1021. doi:10.1001/jama.2015.10029

9. Morales J, Glantz N, Larez A, et al. Understanding the impact of five major determinants of health (genetics, biology, behavior, psychology, society/environment) on type 2 diabetes in U.S. Hispanic/Latino families: Mil Familias - a cohort study. BMC Endocr Disord. 2020;20(1):4. doi:10.1186/s12902-019-0483-z
10. Galicia-Garcia U, Benito-Vicente A, Jebari S, et al. Pathophysiology of Type 2 Diabetes Mellitus. IJMS. 2020;21(17):6275. doi:10.3390/ijms21176275
11. Reed J, Bain S, Kanamarlapudi V. A Review of Current Trends with Type 2 Diabetes Epidemiology, Aetiology, Pathogenesis, Treatments and Future Perspectives. DMSO. 2021;Volume 14:3567-3602. doi:10.2147/DMSO.S319895
12. on behalf of the Feel4Diabetes-study Group, Kyrou I, Tsigos C, et al. Sociodemographic and lifestyle-related risk factors for identifying vulnerable groups for type 2 diabetes: a narrative review with emphasis on data from Europe. BMC Endocr Disord. 2020;20(S1):134. doi:10.1186/s12902-019-0463-3
13. Hill-Briggs F, Adler NE, Berkowitz SA, et al. Social Determinants of Health and Diabetes: A Scientific Review. Diabetes Care. 2021;44(1):258-279. doi:10.2337/dci20-0053
14. Clark ML. Social determinants of type 2 diabetes and health in the United States. WJD. 2014;5(3):296. doi:10.4239/wjd.v5.i3.296
15. Hill J, Nielsen M, Fox MH. Understanding the Social Factors That Contribute to Diabetes: A Means to Informing Health Care and Social Policies for the Chronically Ill. TPJ. 2013;17(2):67-72. doi:10.7812/TPP/12-099
16. Kelly SJ, Ismail M. Stress and Type 2 Diabetes: A Review of How Stress Contributes to the Development of Type 2 Diabetes. Annu Rev Public Health. 2015;36(1):441-462. doi:10.1146/annurev-publhealth-031914-122921

17. Banaji MR, Fiske ST, Massey DS. Systemic racism: individuals and interactions, institutions and society. Cogn Research. 2021;6(1):82. doi:10.1186/s41235-021-00349-3
18. Melton-Fant C. Health Equity and the Dynamism of Structural Racism and Public Policy. Milbank Quarterly. 2022;100(3):628-649. doi:10.1111/1468-0009.12581
19. Bailey ZD, Feldman JM, Bassett MT. How Structural Racism Works — Racist Policies as a Root Cause of U.S. Racial Health Inequities. Malina D, ed. N Engl J Med. 2021;384(8):768-773. doi:10.1056/NEJMms2025396
20. Bonilla-Silva E. Rethinking Racism: Toward a Structural Interpretation. American Sociological Review. 1997;62(3):465. doi:10.2307/2657316
21. Ogunwole SM, Golden SH. Social Determinants of Health and Structural Inequities—Root Causes of Diabetes Disparities. Diabetes Care. 2021;44(1):11-13. doi:10.2337/dci20-0060
22. Hill JO, Galloway JM, Goley A, et al. Scientific Statement: Socioecological Determinants of Prediabetes and Type 2 Diabetes. Diabetes Care. 2013;36(8):2430-2439. doi:10.2337/dc13-1161
23. Agardh E, Allebeck P, Hallqvist J, Moradi T, Sidorchuk A. Type 2 diabetes incidence and socio-economic position: a systematic review and meta-analysis. International Journal of Epidemiology. 2011;40(3):804-818. doi:10.1093/ije/dyr029
24. Maskarinec G, Erber E, Grandinetti A, et al. Diabetes Incidence Based on Linkages With Health Plans: The Multiethnic Cohort. Diabetes. 2009;58(8):1732-1738. doi:10.2337/db08-1685
25. Socioeconomic status and type 2 diabetes in African American and non-Hispanic white women and men: evidence from the Third National Health and Nutrition Examination Survey. Am J Public Health. 2001;91(1):76-83. doi:10.2105/AJPH.91.1.76

26. Schneiderman N, Llabre M, Cowie CC, et al. Prevalence of Diabetes Among Hispanics/Latinos From Diverse Backgrounds: The Hispanic Community Health Study/Study. 2014;37.
27. Echouffo-Tcheugui JB, Caleyachetty R, Muennig PA, Narayan K, Golden SH. Cumulative social risk and type 2 diabetes in US adults: The National Health and Nutrition Examination Survey (NHANES) 1999–2006. Eur J Prev Cardiolog. 2016;23(12):1282-1288. doi:10.1177/2047487315627036
28. Doubleday A, Knott CJ, Hazlehurst MF, Bertoni AG, Kaufman JD, Hajat A. Neighborhood greenspace and risk of type 2 diabetes in a prospective cohort: the Multi-Ethnic Study of Atherosclerosis. Environ Health. 2022;21(1):18. doi:10.1186/s12940-021-00824-w
29. Christine PJ, Auchincloss AH, Bertoni AG, et al. Longitudinal Associations Between Neighborhood Physical and Social Environments and Incident Type 2 Diabetes Mellitus: The Multi-Ethnic Study of Atherosclerosis (MESA). JAMA Intern Med. 2015;175(8):1311. doi:10.1001/jamainternmed.2015.2691
30. Auchincloss AH. Neighborhood Resources for Physical Activity and Healthy Foods and Incidence of Type 2 Diabetes Mellitus: The Multi-Ethnic Study of Atherosclerosis. Arch Intern Med. 2009;169(18):1698. doi:10.1001/archinternmed.2009.302
31. Kivimäki M, Vahtera J, Tabák AG, et al. Neighbourhood socioeconomic disadvantage, risk factors, and diabetes from childhood to middle age in the Young Finns Study: a cohort study. The Lancet Public Health. 2018;3(8):e365-e373. doi:10.1016/S2468-2667(18)30111-7

32. Reshetnyak E, Ntamatungiro M, Pinheiro LC, et al. Impact of Multiple Social Determinants of Health on Incident Stroke. Stroke. 2020;51(8):2445-2453. doi:10.1161/STROKEAHA.120.028530

33. Safford MM, Reshetnyak E, Sterling MR, et al. Number of Social Determinants of Health and Fatal and Nonfatal Incident Coronary Heart Disease in the REGARDS Study. Circulation. 2021;143(3):244-253. doi:10.1161/CIRCULATIONAHA.120.048026

34. Spanakis EK, Golden SH. Race/Ethnic Difference in Diabetes and Diabetic Complications. Curr Diab Rep. 2013;13(6):814-823. doi:10.1007/s11892-013-0421-9

35. Golden SH, Brown A, Cauley JA, et al. Health Disparities in Endocrine Disorders: Biological, Clinical, and Nonclinical Factors—An Endocrine Society Scientific Statement. The Journal of Clinical Endocrinology & Metabolism. 2012;97(9):E1579-E1639. doi:10.1210/jc.2012-2043

36. Palmer RC, Ismond D, Rodriquez EJ, Kaufman JS. Social Determinants of Health: Future Directions for Health Disparities Research. Am J Public Health. 2019;109(S1):S70-S71. doi:10.2105/AJPH.2019.304964

37. Gary-Webb TL, Suglia SF, Tehranifar P. Social Epidemiology of Diabetes and Associated Conditions. Curr Diab Rep. 2013;13(6):850-859. doi:10.1007/s11892-013-0427-3

38. Steptoe A, Hackett RA, Lazzarino AI, et al. Disruption of multisystem responses to stress in type 2 diabetes: Investigating the dynamics of allostatic load. Proc Natl Acad Sci USA. 2014;111(44):15693-15698. doi:10.1073/pnas.1410401111

39. Torres S, Han HR. Psychological distress in non-hispanic white and hispanic abused women. Archives of Psychiatric Nursing. 2000;14(1):19-29. doi:10.1016/S0883-9417(00)80005-9

40. Sternthal MJ, Slopen N, Williams DR. RACIAL DISPARITIES IN HEALTH: How Much Does Stress Really Matter? Du Bois Rev. 2011;8(1):95-113. doi:10.1017/S1742058X11000087

41. Stress and Health Disparities: Contexts, Mechanisms, and Interventions Among Racial/Ethnic Minority and Low Socioeconomic Status Populations: (500202018-001). Published online 2017. doi:10.1037/e500202018-001

42. Bromberger JT, Harlow S, Avis N, Kravitz HM, Cordal A. Racial/Ethnic Differences in the Prevalence of Depressive Symptoms Among Middle-Aged Women: The Study of Women's Health Across the Nation (SWAN). American Journal of Public Health. 2004;94(8):8.

43. Oquendo MA, Ellis SP, Greenwald S, Malone KM, Weissman MM, Mann JJ. Ethnic and Sex Differences in Suicide Rates Relative to Major Depression in the United States. AJP. 2001;158(10):1652-1658. doi:10.1176/appi.ajp.158.10.1652

44. Rickert VI, Wiemann CM, Berenson AB. Ethnic Differences in Depressive Symptomatology Among Young Women. 2000;95(1):6.

45. Hatch SL, Dohrenwend BP. Distribution of Traumatic and Other Stressful Life Events by Race/Ethnicity, Gender, SES and Age: A Review of the Research. American J of Comm Psychol. 2007;40(3-4):313-332. doi:10.1007/s10464-007-9134-z

46. Pan A, Wang Y, Talaei M, Hu FB, Wu T. Relation of active, passive, and quitting smoking with incident type 2 diabetes: a systematic review and meta-analysis. The Lancet Diabetes & Endocrinology. 2015;3(12):958-967. doi:10.1016/S2213-8587(15)00316-2

47. Yuan S, Xue H liang, Yu H jie, et al. Cigarette smoking as a risk factor for type 2 diabetes in women compared with men: a systematic review and meta-analysis of prospective cohort studies. Journal of Public Health. 2019;41(2):e169-e176. doi:10.1093/pubmed/fdy106

48. Yuan S, Larsson SC. A causal relationship between cigarette smoking and type 2 diabetes mellitus: A Mendelian randomization study. Sci Rep. 2019;9(1):19342. doi:10.1038/s41598-019-56014-9

49. Willi C, Bodenmann P, Ghali WA, Faris PD, Cornuz J. Active Smoking and the Risk of Type 2 Diabetes: A Systematic Review and Meta-analysis. JAMA. 2007;298(22):2654. doi:10.1001/jama.298.22.2654

50. Jannasch F, Kröger J, Schulze MB. Dietary Patterns and Type 2 Diabetes: A Systematic Literature Review and Meta-Analysis of Prospective Studies. J Nutr. 2017;147(6):1174-1182. doi:10.3945/jn.116.242552

51. Esposito K, Maiorino MI, Bellastella G, Panagiotakos DB, Giugliano D. Mediterranean diet for type 2 diabetes: cardiometabolic benefits. Endocrine. 2017;56(1):27-32. doi:10.1007/s12020-016-1018-2

52. Salas-Salvado J. Prevention of Diabetes With Mediterranean Diets. :13.

53. Koloverou E, Panagiotakos DB, Pitsavos C, et al. Adherence to Mediterranean diet and 10-year incidence (2002-2012) of diabetes: correlations with inflammatory and oxidative stress biomarkers in the ATTICA cohort study: Mediterranean Diet and Diabetes. Diabetes Metab Res Rev. 2016;32(1):73-81. doi:10.1002/dmrr.2672

54. Hammershaimb B, Goitia J, Gyurjian K, et al. Racial and Ethnic Differences in Risk Factors and Outcomes in Adults With Acute Myocardial Infarction. TPJ. 2023;27(1):113-121. doi:10.7812/TPP/22.100

55. Gasevic D, Ross ES, Lear SA. Ethnic Differences in Cardiovascular Disease Risk Factors: A Systematic Review of North American Evidence. Canadian Journal of Cardiology. 2015;31(9):1169-1179. doi:10.1016/j.cjca.2015.06.017

56. Ma Y, Hébert JR, Manson JE, et al. Determinants of Racial/Ethnic Disparities in Incidence of Diabetes in Postmenopausal Women in the U.S. Diabetes Care. 2012;35(11):2226-2234. doi:10.2337/dc12-0412

57. Long T, Zhang K, Chen Y, Wu C. Trends in Diet Quality Among Older US Adults From 2001 to 2018. JAMA Netw Open. 2022;5(3):e221880. doi:10.1001/jamanetworkopen.2022.1880

58. Haffner M, Ava J, Hazuda P, Stem P, Young A. among Mexican the San Antonio. :10.

59. Gao X. Longitudinal associations between objective and perceived healthy food environment and diet: The Multi-Ethnic Study of Atherosclerosis. Social Science. Published online 2022:9.

60. Rodriguez LA, Jin Y, Talegawkar SA, et al. Differences in Diet Quality among Multiple US Racial/Ethnic Groups from the Mediators of Atherosclerosis in South Asians Living in America (MASALA) Study and the Multi-Ethnic Study of Atherosclerosis (MESA). The Journal of Nutrition. 2020;150(6):1509-1515. doi:10.1093/jn/nxaa050

61. Aune D, Norat T, Leitzmann M, Tonstad S, Vatten LJ. Physical activity and the risk of type 2 diabetes: a systematic review and dose–response meta-analysis. Eur J Epidemiol. 2015;30(7):529-542. doi:10.1007/s10654-015-0056-z

62. Uusitupa M, Louheranta A, Lindström J, et al. The Finnish Diabetes Prevention Study. Br J Nutr. 2000;83(S1):S137-S142. doi:10.1017/S0007114500001070

63. Shai I, Jiang R, Manson JE, et al. Ethnicity, Obesity, and Risk of Type 2 Diabetes in Women. Diabetes Care. 2006;29(7):1585-1590. doi:10.2337/dc06-0057

64. Brancati FL, Kao WHL, Folsom AR, Watson RL, Szklo M. Incident Type 2 Diabetes Mellitus in African American and White Adults: The Atherosclerosis Risk in Communities Study. JAMA. 2000;283(17):2253. doi:10.1001/jama.283.17.2253

65. Li K, Wen M. Racial and Ethnic Disparities in Leisure-time Physical Activity in California: Patterns and Mechanisms. Race Soc Probl. 2013;5(3):147-156. doi:10.1007/s12552-013-9087-9

66. Carlson SA, Fulton JE, Schoenborn CA, Loustalot F. Trend and Prevalence Estimates Based on the 2008 Physical Activity Guidelines for Americans. American Journal of Preventive Medicine. 2010;39(4):305-313. doi:10.1016/j.amepre.2010.06.006

67. Barnes PM, Adams PF, Powell-Griner E. Health Characteristics of the Asian Adult Population: United States, 2004-2006: (407192008-001). Published online 2008. doi:10.1037/e407192008-001

68. Mikhail N, Wali S, Brown AF. Ethnic Disparities in Diabetes. Endocrinology and Metabolism Clinics of North America. 2021;50(3):475-490. doi:10.1016/j.ecl.2021.05.006

69. Golden SH, Yajnik C, Phatak S, Hanson RL, Knowler WC. Racial/ethnic differences in the burden of type 2 diabetes over the life course: a focus on the USA and India. Diabetologia. 2019;62(10):1751-1760. doi:10.1007/s00125-019-4968-0

70. Gastaldelli A. Abdominal fat: does it predict the development of type 2 diabetes? The American Journal of Clinical Nutrition. 2008;87(5):1118-1119. doi:10.1093/ajcn/87.5.1118

71. Montague CT, O'Rahilly S. The perils of portliness: causes and consequences of visceral adiposity. Diabetes. 2000;49(6):883-888. doi:10.2337/diabetes.49.6.883

72. Kabir M, Catalano KJ, Ananthnarayan S, et al. Molecular evidence supporting the portal theory: a causative link between visceral adiposity and hepatic insulin resistance. American

Journal of Physiology-Endocrinology and Metabolism. 2005;288(2):E454-E461. doi:10.1152/ajpendo.00203.2004

73. Vettor R, Milan G, Rossato M, Federspil G. Review article: adipocytokines and insulin resistance. Aliment Pharmacol Ther. 2005;22(s2):3-10. doi:10.1111/j.1365-2036.2005.02587.x

74. Pittas AG, Joseph NA, Greenberg AS. Adipocytokines and Insulin Resistance. The Journal of Clinical Endocrinology & Metabolism. 2004;89(2):447-452. doi:10.1210/jc.2003-031005

75. Tchernof A, Després JP. Pathophysiology of Human Visceral Obesity: An Update. Physiological Reviews. 2013;93(1):359-404. doi:10.1152/physrev.00033.2011

76. Xu F, Earp JE, Blissmer BJ, Lofgren IE, Delmonico MJ, Greene GW. The Demographic Specific Abdominal Fat Composition and Distribution Trends in US Adults from 2011 to 2018. IJERPH. 2022;19(19):12103. doi:10.3390/ijerph191912103

77. Garg SK, Lin F, Kandula N, et al. Ectopic Fat Depots and Coronary Artery Calcium in South Asians Compared With Other Racial/Ethnic Groups. JAHA. 2016;5(11):e004257. doi:10.1161/JAHA.116.004257

78. Flowers E, Lin F, Kandula NR, et al. Body Composition and Diabetes Risk in South Asians: Findings From the MASALA and MESA Studies. Diabetes Care. 2019;42(5):946-953. doi:10.2337/dc18-1510

79. Carroll JF, Fulda KG, Chiapa AL, et al. Impact of Race/Ethnicity on the Relationship Between Visceral Fat and Inflammatory Biomarkers. Obesity. 2009;17(7):1420-1427. doi:10.1038/oby.2008.657

80. Araneta MRG, Barrett-Connor E. Ethnic Differences in Visceral Adipose Tissue and Type 2 Diabetes: Filipino, African-American, and White Women. Obesity Research. 2005;13(8):1458-1465. doi:10.1038/oby.2005.176

81. Anand SS, Tarnopolsky MA, Rashid S, et al. Adipocyte Hypertrophy, Fatty Liver and Metabolic Risk Factors in South Asians: The Molecular Study of Health and Risk in Ethnic Groups (mol-SHARE). Stanojevic S, ed. PLoS ONE. 2011;6(7):e22112. doi:10.1371/journal.pone.0022112

82. Panchu P, Bahuleyan B, Babu R, Vijayan V. Age and sex variation in visceral adipose tissue. Int J Adv Med. 2019;6(1):101. doi:10.18203/2349-3933.ijam20190113

83. Baarts RB, Jensen MR, Hansen OM, et al. Age- and sex-specific changes in visceral fat mass throughout the life-span. Obesity. 2023;31(7):1953-1961. doi:10.1002/oby.23779

84. Kammerlander AA, Lyass A, Mahoney TF, et al. Sex Differences in the Associations of Visceral Adipose Tissue and Cardiometabolic and Cardiovascular Disease Risk: The Framingham Heart Study. JAHA. 2021;10(11):e019968. doi:10.1161/JAHA.120.019968

85. Demerath EW, Sun SS, Rogers N, et al. Anatomical Patterning of Visceral Adipose Tissue: Race, Sex, and Age Variation. Obesity. 2007;15(12):2984-2993. doi:10.1038/oby.2007.356

86. Hoffman DJ, Wang Z, Gallagher D, Heymsfield SB. Comparison of Visceral Adipose Tissue Mass in Adult African Americans and Whites **. Obesity Research. 2005;13(1):66-74. doi:10.1038/oby.2005.9

87. Després JP, Couillard C, Gagnon J, et al. Race, Visceral Adipose Tissue, Plasma Lipids, and Lipoprotein Lipase Activity in Men and Women: The Health, Risk Factors, Exercise Training, and Genetics (HERITAGE) Family Study. ATVB. 2000;20(8):1932-1938. doi:10.1161/01.ATV.20.8.1932

88. Warnecke RB, Oh A, Breen N, et al. Approaching Health Disparities From a Population Perspective: The National Institutes of Health Centers for Population Health and Health Disparities. Am J Public Health. 2008;98(9):1608-1615. doi:10.2105/AJPH.2006.102525

89. Brown AF. Socioeconomic Position and Health among Persons with Diabetes Mellitus: A Conceptual Framework and Review of the Literature. Epidemiologic Reviews. 2004;26(1):63-77. doi:10.1093/epirev/mxh002

90. Walker RJ, Gebregziabher M, Martin-Harris B, Egede LE. Relationship between social determinants of health and processes and outcomes in adults with type 2 diabetes: validation of a conceptual framework. BMC Endocr Disord. 2014;14(1):82. doi:10.1186/1472-6823-14-82

91. Appendix A: Detailed tables. Centers for Disease Control and Prevention. Accessed May 21, 2024. https://www.cdc.gov/diabetes/php/data-research/appendix.html?CDC_AAref_Val=https%3A%2F%2Fwww.cdc.gov%2Fdiabetes%2Fdata%2Fstatistics-report%2Fappendix.html.

92. Surveillance - United States Diabetes Surveillance System. Centers for Disease Control and Prevention. Accessed May 21, 2024. https://gis.cdc.gov/grasp/diabetes/diabetesatlas-surveillance.html.

93. Magliano DJ, Islam RM, Barr ELM, et al. Trends in incidence of total or type 2 diabetes: systematic review. BMJ. Published online September 11, 2019:l5003. doi:10.1136/bmj.l5003

94. Narayan KMV, Boyle JP, Geiss LS, Saaddine JB, Thompson TJ. Impact of Recent Increase in Incidence on Future Diabetes Burden. Diabetes Care. 2006;29(9):2114-2116. doi:10.2337/dc06-1136

95. Bertoni AG, Burke GL, Owusu JA, et al. Inflammation and the Incidence of Type 2 Diabetes. Diabetes Care. 2010;33(4):804-810. doi:10.2337/dc09-1679

96. Kaku K. Pathophysiology of Type 2 Diabetes and Its Treatment Policy. 2010;53(1):6.

97. Pyke DA. Diabetes: The genetic connections. Diabetologia. 1979;17(6):333-343. doi:10.1007/BF01236266

98. Aguayo-Mazzucato C, Diaque P, Hernandez S, Rosas S, Kostic A, Caballero AE. Understanding the growing epidemic of type 2 diabetes in the Hispanic population living in the United States. Diabetes Metab Res Rev. 2019;35(2):e3097. doi:10.1002/dmrr.3097

99. Caballero AE. Diabetes in the hispanic or latino population: Genes, environment, culture, and more. Curr Diab Rep. 2005;5(3):217-225. doi:10.1007/s11892-005-0012-5

100. Chang AM, Halter JB. Aging and insulin secretion. American Journal of Physiology-Endocrinology and Metabolism. 2003;284(1):E7-E12. doi:10.1152/ajpendo.00366.2002

101. Cho NH, Shaw JE, Karuranga S, et al. IDF Diabetes Atlas: Global estimates of diabetes prevalence for 2017 and projections for 2045. Diabetes Research and Clinical Practice. 2018;138:271-281. doi:10.1016/j.diabres.2018.02.023

102. McCarthy MI. Genomics, Type 2 Diabetes, and Obesity. Feero WG, Guttmacher AE, eds. N Engl J Med. 2010;363(24):2339-2350. doi:10.1056/NEJMra0906948

103. Fuchsberger C, Flannick J, Teslovich TM, et al. The genetic architecture of type 2 diabetes. Nature. 2016;536(7614):41-47. doi:10.1038/nature18642

104. Dimas AS, Lagou V, Barker A, et al. Impact of Type 2 Diabetes Susceptibility Variants on Quantitative Glycemic Traits Reveals Mechanistic Heterogeneity. Diabetes. 2014;63(6):2158-2171. doi:10.2337/db13-0949

105. Cerf ME. Beta Cell Dysfunction and Insulin Resistance. Front Endocrinol. 2013;4. doi:10.3389/fendo.2013.00037

106. Waters KM, Stram DO, Hassanein MT, et al. Consistent Association of Type 2 Diabetes Risk Variants Found in Europeans in Diverse Racial and Ethnic Groups. McCarthy MI, ed. PLoS Genet. 2010;6(8):e1001078. doi:10.1371/journal.pgen.1001078

107. Saxena R, Elbers CC, Guo Y, et al. Large-Scale Gene-Centric Meta-Analysis across 39 Studies Identifies Type 2 Diabetes Loci. The American Journal of Human Genetics. 2012;90(3):410-425. doi:10.1016/j.ajhg.2011.12.022

108. Mikhail N, Wali S, Brown AF. Ethnic Disparities in Diabetes. Endocrinology and Metabolism Clinics of North America. 2021;50(3):475-490. doi:10.1016/j.ecl.2021.05.006

109. Umpierrez GE, Gonzalez A, Umpierrez D, Pimentel D. Diabetes Mellitus in the Hispanic/Latino Population: An Increasing Health Care Challenge in the United States. The American Journal of the Medical Sciences. 2007;334(4):274-282. doi:10.1097/MAJ.0b013e3180a6efe3

110. Social Determinants of Health [Internet]. World Health Organization; [cited 2024 Feb 20]. Available from: https://www.who.int/health-topics/social-determinants-of-health#tab=tab_1

111. Javed Z, Valero-Elizondo J, Maqsood MH, et al. Social determinants of health and obesity: Findings from a national study of US adults. Obesity. 2022;30(2):491-502. doi:10.1002/oby.23336

112. Khan SU, Acquah I, Javed Z, et al. Social Determinants of Health Among Non-Elderly Adults With Stroke in the United States. Mayo Clinic Proceedings. 2022;97(2):238-249. doi:10.1016/j.mayocp.2021.08.024

113. Zheng Y, Ley SH, Hu FB. Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. Nat Rev Endocrinol. 2018;14(2):88-98. doi:10.1038/nrendo.2017.151

114. Weisman A, Fazli GS, Johns A, Booth GL. Evolving Trends in the Epidemiology, Risk Factors, and Prevention of Type 2 Diabetes: A Review. Canadian Journal of Cardiology. 2018;34(5):552-564. doi:10.1016/j.cjca.2018.03.002

115. Ley SH, Hamdy O, Mohan V, Hu FB. Prevention and management of type 2 diabetes: dietary components and nutritional strategies. The Lancet. 2014;383(9933):1999-2007. doi:10.1016/S0140-6736(14)60613-9

116. Jeon CY, Lokken RP, Hu FB, van Dam RM. Physical Activity of Moderate Intensity and Risk of Type 2 Diabetes. Diabetes Care. 2007;30(3):744-752. doi:10.2337/dc06-1842

117. Kasuga M. Insulin resistance and pancreatic cell failure. Journal of Clinical Investigation. 2006;116(7):1756-1760. doi:10.1172/JCI29189

118. Bellou V, Belbasis L, Tzoulaki I, Evangelou E. Risk factors for type 2 diabetes mellitus: An exposure-wide umbrella review of meta-analyses. Nerurkar PV, ed. PLoS ONE. 2018;13(3):e0194127. doi:10.1371/journal.pone.0194127

119. Kyrou I, Weickert MO. CHAPTER 14: CLINICAL PROBLEMS CAUSED BY OBESITY. :93.

120. Golay A, Ybarra J. Link between obesity and type 2 diabetes. Best Practice & Research Clinical Endocrinology & Metabolism. 2005;19(4):649-663. doi:10.1016/j.beem.2005.07.010

121. Bonora E, Kiechl S, Willeit J, et al. Population-Based Incidence Rates and Risk Factors for Type 2 Diabetes in White Individuals. Diabetes. 2004;53(7):1782-1789. doi:10.2337/diabetes.53.7.1782

122. Gujral UP, Mohan V, Pradeepa R, et al. Ethnic variations in diabetes and prediabetes prevalence and the roles of insulin resistance and β-cell function: The CARRS and NHANES studies. Journal of Clinical & Translational Endocrinology. 2016;4:19-27. doi:10.1016/j.jcte.2016.02.004

123. Han TS, Al-Gindan YY, Govan L, Hankey CR, Lean MEJ. Associations of BMI, waist circumference, body fat, and skeletal muscle with type 2 diabetes in adults. Acta Diabetol. 2019;56(8):947-954. doi:10.1007/s00592-019-01328-3

124. Lee DH, Keum N, Hu FB, et al. Comparison of the association of predicted fat mass, body mass index, and other obesity indicators with type 2 diabetes risk: two large prospective studies in US men and women. Eur J Epidemiol. 2018;33(11):1113-1123. doi:10.1007/s10654-018-0433-5

125. Fernández JR, Heo M, Heymsfield SB, et al. Is percentage body fat differentially related to body mass index in Hispanic Americans, African Americans, and European Americans? The American Journal of Clinical Nutrition. 2003;77(1):71-75. doi:10.1093/ajcn/77.1.71

126. Prasad DS, Kabir Z, Dash AK, Das BC. Abdominal obesity, an independent cardiovascular risk factor in Indian subcontinent: A clinico epidemiological evidence summary. Journal of Cardiovascular Disease Research. 2011;2(4):199-205. doi:10.4103/0975-3583.89803

127. Hsieh CJ, Wang PW, Chen TY. The relationship between regional abdominal fat distribution and both insulin resistance and subclinical chronic inflammation in non-diabetic adults. Diabetol Metab Syndr. 2014;6(1):49. doi:10.1186/1758-5996-6-49

128. Castro AVB, Nunes VS, Ionut V, Bergman RN, El Dib R. Is Visceral Fat a Better Predictor of the Incidence of Impaired Glucose Tolerance or Type 2 Diabetes Mellitus than Subcutaneous Abdominal Fat: A Systematic Review and Meta-Analysis of Cohort Studies. PeerJ PrePrints; 2014. doi:10.7287/peerj.preprints.199v1

129. Fox CS, Massaro JM, Hoffmann U, et al. Abdominal Visceral and Subcutaneous Adipose Tissue Compartments: Association With Metabolic Risk Factors in the Framingham Heart Study. Circulation. 2007;116(1):39-48. doi:10.1161/CIRCULATIONAHA.106.675355

130. Jung SH, Ha KH, Kim DJ. Visceral Fat Mass Has Stronger Associations with Diabetes and Prediabetes than Other Anthropometric Obesity Indicators among Korean Adults. Yonsei Med J. 2016;57(3):674. doi:10.3349/ymj.2016.57.3.674

131. Zhang F, Li Y, Zhao Y, Zhou X, Ji L. Is visceral abdominal fat area a better indicator for hyperglycemic risk? Results from the Pinggu Metabolic Disease Study. J Diabetes Investig. 2020;11(4):888-895. doi:10.1111/jdi.13217

132. Karlsson T, Rask-Andersen M, Pan G, et al. Contribution of genetics to visceral adiposity and its relation to cardiovascular and metabolic disease. Nat Med. 2019;25(9):1390-1395. doi:10.1038/s41591-019-0563-7

133. Boyko EJ, Fujimoto WY, Leonetti DL, Newell-Morris L. Visceral adiposity and risk of type 2 diabetes: a prospective study among Japanese Americans. Diabetes Care. 2000;23(4):465-471. doi:10.2337/diacare.23.4.465

134. Hoyer D, Boyko EJ, McNeely MJ, Leonetti DL, Kahn SE, Fujimoto WY. Subcutaneous thigh fat area is unrelated to risk of type 2 diabetes in a prospective study of Japanese Americans. Diabetologia. 2011;54(11):2795-2800. doi:10.1007/s00125-011-2275-5

135. Kanaya AM, Wassel Fyr C, Vittinghoff E, et al. Adipocytokines and Incident Diabetes Mellitus in Older Adults: The Independent Effect of Plasminogen Activator Inhibitor 1. Arch Intern Med. 2006;166(3):350. doi:10.1001/archinte.166.3.350

136. Hanley AJG, Wagenknecht LE, Norris JM, et al. Insulin resistance, beta cell dysfunction and visceral adiposity as predictors of incident diabetes: the Insulin Resistance Atherosclerosis Study (IRAS) Family Study. Diabetologia. 2009;52(10):2079-2086. doi:10.1007/s00125-009-1464-y

137. Neeland IJ, Turer AT, Ayers CR, et al. Dysfunctional Adiposity and the Risk of Prediabetes and Type 2 Diabetes in Obese Adults. JAMA. 2012;308(11):1150. doi:10.1001/2012.jama.11132

138. Haffner SM, D'Agostino R, Saad MF, et al. Increased Insulin Resistance and Insulin Secretion in Nondiabetic African-Americans and Hispanics Compared With Non-Hispanic Whites. Physical activity. 1996;45.

139. Lillioja S, Nyomba BL, Saad MF, et al. Exaggerated Early Insulin Release and Insulin Resistance in a Diabetes-Prone Population: A Metabolic Comparison of Pima Indians and Caucasians. The Journal of Clinical Endocrinology & Metabolism. 1991;73(4):866-876. doi:10.1210/jcem-73-4-866

140. Chiu KC. Comparison of Measured and Estimated Indices of Insulin Sensitivity and Cell Function: Impact of Ethnicity on Insulin Sensitivity and Cell Function in Glucose-Tolerant and Normotensive Subjects. Journal of Clinical Endocrinology & Metabolism. 2001;86(4):1620-1625. doi:10.1210/jc.86.4.1620

141. Jensen CC, Cnop M, Hull RL, Fujimoto WY, Kahn SE. Beta-Cell Function Is a Major Contributor to Oral Glucose. 2002;51.

142. DeLany JP, Dubé JJ, Standley RA, et al. Racial Differences In Peripheral Insulin Sensitivity and Mitochondrial Capacity in the Absence of Obesity. The Journal of Clinical Endocrinology & Metabolism. 2014;99(11):4307-4314. doi:10.1210/jc.2014-2512

143. Lee S, Boesch C, Kuk JL, Arslanian S. Effects of an overnight intravenous lipid infusion on intramyocellular lipid content and insulin sensitivity in African–American versus Caucasian adolescents. Metabolism. 2013;62(3):417-423. doi:10.1016/j.metabol.2012.09.007

144. Bacha F, Gungor N, Lee S, Arslanian SA. Type 2 diabetes in youth: are there racial differences in β-cell responsiveness relative to insulin sensitivity? Pediatric Diabetes. 2012;13(3):259-265. doi:10.1111/j.1399-5448.2011.00820.x

145. Arslanian SA, Saad R, Lewy V, Danadian K, Janosky J. Hyperinsulinemia in African-American Children. Diabetes. 2002;51(10):3014-3019. doi:10.2337/diabetes.51.10.3014

146. Goff LM, Ladwa M, Hakim O, Bello O. Ethnic distinctions in the pathophysiology of type 2 diabetes: a focus on black African-Caribbean populations. Proc Nutr Soc. 2020;79(2):184-193. doi:10.1017/S0029665119001034

147. Hasson BR, Apovian C, Istfan N. Racial/Ethnic Differences in Insulin Resistance and Beta Cell Function: Relationship to Racial Disparities in Type 2 Diabetes among African Americans versus Caucasians. Curr Obes Rep. 2015;4(2):241-249. doi:10.1007/s13679-015-0150-2

148. Torrens JI, Skurnick J, Davidow AL, et al. Ethnic Differences in Insulin Sensitivity and Beta-Cell Function in Premenopausal or Early Perimenopausal Women Without Diabetes. DIABETES CARE. 2004;27(2).

149. Narayan KMV, Kanaya AM. Why are South Asians prone to type 2 diabetes? A hypothesis based on underexplored pathways. Diabetologia. 2020;63(6):1103-1109. doi:10.1007/s00125-020-05132-5

150. Raygor V, Abbasi F, Lazzeroni LC, et al. Impact of race/ethnicity on insulin resistance and hypertriglyceridaemia. Diabetes and Vascular Disease Research. 2019;16(2):153-159. doi:10.1177/1479164118813890

151. Sharma A, Lee-Ødegård S, Qvigstad E, et al. β-Cell Function, Hepatic Insulin Clearance, and Insulin Sensitivity in South Asian and Nordic Women After Gestational Diabetes Mellitus. Diabetes. 2022;71(12):2530-2538. doi:10.2337/db22-0622

152. Kodama K, Tojjar D, Yamada S, Toda K, Patel CJ, Butte AJ. Ethnic Differences in the Relationship Between Insulin Sensitivity and Insulin Response: A systematic review and meta-analysis. Diabetes Care. 2013;36(6):1789-1796. doi:10.2337/dc12-1235

153. Ma RCW, Chan JCN. Type 2 diabetes in East Asians: similarities and differences with populations in Europe and the United States. Ann NY Acad Sci. 2013;1281(1):64-91. doi:10.1111/nyas.12098

154. Yabe D, Seino Y, Fukushima M, Seino S. β Cell Dysfunction Versus Insulin Resistance in the Pathogenesis of Type 2 Diabetes in East Asians. Curr Diab Rep. 2015;15(6):36. doi:10.1007/s11892-015-0602-9

155. Kanaya AM, Herrington D, Vittinghoff E, et al. Understanding the High Prevalence of Diabetes in U.S. South Asians Compared With Four Racial/Ethnic Groups: The MASALA and MESA Studies. Diabetes Care. 2014;37(6):1621-1628. doi:10.2337/dc13-2656

156. Colberg SR, Sigal RJ, Fernhall B, et al. Exercise and Type 2 Diabetes. Diabetes Care. 2010;33(12):e147-e167. doi:10.2337/dc10-9990

157. Petersen AMW, Pedersen BK. The anti-inflammatory effect of exercise. Journal of Applied Physiology. 2005;98(4):1154-1162. doi:10.1152/japplphysiol.00164.2004

158. Strasser B. Physical activity in obesity and metabolic syndrome. Ann NY Acad Sci. 2013;1281(1):141-159. doi:10.1111/j.1749-6632.2012.06785.x

159. Syeda USA, Battillo D, Visaria A, Malin SK. The importance of exercise for glycemic control in type 2 diabetes. American Journal of Medicine Open. 2023;9:100031. doi:10.1016/j.ajmo.2023.100031

160. Freitas Lima LC, Braga V de A, do Socorro de França Silva M, et al. Adipokines, diabetes and atherosclerosis: an inflammatory association. Front Physiol. 2015;6. doi:10.3389/fphys.2015.00304

161. Kojta I, Chacińska M, Błachnio-Zabielska A. Obesity, Bioactive Lipids, and Adipose Tissue Inflammation in Insulin Resistance. Nutrients. 2020;12(5):1305. doi:10.3390/nu12051305

162. Bild DE. Multi-Ethnic Study of Atherosclerosis: Objectives and Design. American Journal of Epidemiology. 2002;156(9):871-881. doi:10.1093/aje/kwf113

163. Vella CA, Allison MA, Cushman M, et al. Physical Activity and Adiposity-related Inflammation: The MESA. Medicine & Science in Sports & Exercise. 2017;49(5):915-921. doi:10.1249/MSS.0000000000001179

164. Rao VN, Zhao D, Allison MA, et al. Adiposity and Incident Heart Failure and its Subtypes. JACC: Heart Failure. 2018;6(12):999-1007. doi:10.1016/j.jchf.2018.07.009

165. Forbang NI, McClelland RL, Remigio-Baker RA, et al. Associations of cardiovascular disease risk factors with abdominal aortic calcium volume and density: The Multi-Ethnic Study of Atherosclerosis (MESA). Atherosclerosis. 2016;255:54-58. doi:10.1016/j.atherosclerosis.2016.10.036

166. Neeland IJ, Boone SC, Mook-Kanamori DO, et al. Metabolomics Profiling of Visceral Adipose Tissue: Results From MESA and the NEO Study. JAHA. 2019;8(9):e010810. doi:10.1161/JAHA.118.010810

167. Taccheri C, Jordan J, Tran D, et al. The Impact of Social Determinants of Health on Eye Care Utilization in a National Sample of People with Diabetes. Ophthalmology. 2023;130(10):1037-1045. doi:10.1016/j.ophtha.2023.06.007

168. VanderWeele TJ. Mediation Analysis: A Practitioner's Guide. Annu Rev Public Health. 2016;37(1):17-32. doi:10.1146/annurev-publhealth-032315-021402

169. VanderWeele TJ. A Unification of Mediation and Interaction: A 4-Way Decomposition. Epidemiology. 2014;25(5):749-761. doi:10.1097/EDE.0000000000000121

170. VanderWeele TJ, Vansteelandt S, Robins JM. Effect Decomposition in the Presence of an Exposure-Induced Mediator-Outcome Confounder: Epidemiology. 2014;25(2):300-306. doi:10.1097/EDE.0000000000000034

171. Lin SH, VanderWeele T. Interventional Approach for Path-Specific Effects. Journal of Causal Inference. 2017;5(1):20150027. doi:10.1515/jci-2015-0027

172. Tai AS, Huang YT, Yang HI, Lan LV, Lin SH. G-Computation to Causal Mediation Analysis With Sequential Multiple Mediators—Investigating the Vulnerable Time Window of HBV Activity for the Mechanism of HCV Induced Hepatocellular Carcinoma. Front Public Health. 2022;9:757942. doi:10.3389/fpubh.2021.757942

173. Wang A, Arah OA. G-computation demonstration in causal mediation analysis. Eur J Epidemiol. 2015;30(10):1119-1127. doi:10.1007/s10654-015-0100-z

174. Braveman P, Gottlieb L. The Social Determinants of Health: It's Time to Consider the Causes of the Causes. Public Health Rep. 2014;129(1_suppl2):19-31. doi:10.1177/00333549141291S206

175. Tucker JM, Welk GJ, Beyler NK. Physical Activity in U.S. Adults. American Journal of Preventive Medicine. 2011;40(4):454-461. doi:10.1016/j.amepre.2010.12.016

176. Kolb H, Martin S. Environmental/lifestyle factors in the pathogenesis and prevention of type 2 diabetes. BMC Med. 2017;15(1):131. doi:10.1186/s12916-017-0901-x

177. American Diabetes Association standards of medical care in diabetes–2020 https://www.sochob.cl/web1/wp-content/uploads/2019/12/Standards-of-MEdical-Care-in-Diabetes-2020.pdf. Accessed March 16, 2023.

178. Ebong IA, Watson KE, Hairston KG, et al. Body fat distribution, menopausal hormone therapy and incident type 2 diabetes in postmenopausal women of the MESA study. Maturitas. 2016;91:147-152. doi:10.1016/j.maturitas.2016.06.020

179. Woolcott OO, Bergman RN. Relative fat mass (RFM) as a new estimator of whole-body fat percentage ─ A cross-sectional study in American adult individuals. Sci Rep. 2018;8(1):10980. doi:10.1038/s41598-018-29362-1

180. Friedewald WT, Levy RI, Fredrickson DS. Estimationof the Concentrationof Low-Density LipoproteinCholesteroiln Plasma,Without Useof the PreparativeUltracentrifuge.

181. Merkin SS, Coresh J, Roux AVD, Taylor HA, Powe NR. Area Socioeconomic Status and Progressive CKD: The Atherosclerosis Risk in Communities (ARIC) Study. American Journal of Kidney Diseases. 2005;46(2):203-213. doi:10.1053/j.ajkd.2005.04.033

182. Pérez-Escamilla R, Putnik P. The Role of Acculturation in Nutrition, Lifestyle, and Incidence of Type 2 Diabetes among Latinos. The Journal of Nutrition. 2007;137(4):860-870. doi:10.1093/jn/137.4.860

183. Composition of the labor force [Internet]. U.S. Bureau of Labor Statistics; 2023 [cited 2023 Dec 4]. Available from: https://www.bls.gov/opub/reports/race-and-ethnicity/2021/home.htm

184. Williams DR, Mohammed SA, Leavell J, Collins C. Race, socioeconomic status, and health: Complexities, ongoing challenges, and research opportunities: Race, SES, and health. Annals of the New York Academy of Sciences. 2010;1186(1):69-101. doi:10.1111/j.1749-6632.2009.05339.x

185. Springfield S, Qin F, Hedlin H, et al. Modifiable Resources and Resilience in Racially and Ethnically Diverse Older Women: Implications for Health Outcomes and Interventions. IJERPH. 2022;19(12):7089. doi:10.3390/ijerph19127089

186. Kawachi I, Berkman LF. Social Capital, Social Cohesion, and Health. In: Berkman LF, Kawachi I, Glymour MM, eds. Social Epidemiology. Oxford University Press; 2014:290-319. doi:10.1093/med/9780195377903.003.0008

187. Brancati L, Whelton PK, Kuller LH, Klag J. Diabetes MeWus, Race, and Socioeconomic Status.

188. Cowie CC, Harris MI, Silverman RE, Johnson EW, Rust KF. Effect of multiple risk factors on differences between blacks and whites in the prevalence of non-insulin-dependent diabetes mellitus in the United States. American Journal of Epidemiology. 1993 Apr 1;137(7):719–32. doi:10.1093/oxfordjournals.aje.a116732

189. Burke JP, Williams K, Gaskill SP, Hazuda HP, Haffner SM, Stern MP. Rapid Rise in the Incidence of Type 2 Diabetes From 1987 to 1996: Results From the San Antonio Heart Study. Arch Intern Med. 1999;159(13):1450. doi:10.1001/archinte.159.13.1450

190. Ainsworth BE, Irwin ML, Addy CL, Whitt MC, Stolarczyk LM. Moderate Physical Activity Patterns of Minority Women: The Cross-Cultural Activity Participation Study. Journal of Women's Health & Gender-Based Medicine. 1999;8(6):805-813. doi:10.1089/152460999319129

191. LaMonte MJ, Durstine JL, Addy CL, Irwin ML, Ainsworth BE. Physical activity, physical fitness, and Framingham 10-year risk score: The Cross-Cultural Activity Participation Study. Journal of Cardiopulmonary Rehabilitation. 2001;21(2):63–70

192. Hu FB, Stampfer MJ, Rimm E, et al. Dietary Fat and Coronary Heart Disease: A Comparison of Approaches for Adjusting for Total Energy Intake and Modeling Repeated Dietary Measurements. American Journal of Epidemiology. 1999;149(6):531-540. doi:10.1093/oxfordjournals.aje.a009849

193. American Diabetes Association standards of medical care in diabetes–2020 https://www.sochob.cl/web1/wp-content/uploads/2019/12/Standards-of-MEdical-Care-in-Diabetes-2020.pdf. Accessed March 16, 2023.

194. Kershaw KN, Lane-Cordova AD, Carnethon MR, Tindle HA, Liu K. Chronic Stress and Endothelial Dysfunction: The Multi-Ethnic Study of Atherosclerosis (MESA). AJHYPE. 2017;30(1):75-80. doi:10.1093/ajh/hpw103

195. Pencina MJ, Larson MG, D'Agostino RB. Choice of time scale and its effect on significance of predictors in longitudinal studies: CHOICE OF TIME SCALE AND ITS EFFECT. Statist Med. 2007;26(6):1343-1359. doi:10.1002/sim.2699

196. VanderWeele TJ, Vansteelandt S. Odds Ratios for Mediation Analysis for a Dichotomous Outcome. American Journal of Epidemiology. 2010;172(12):1339-1348. doi:10.1093/aje/kwq332

197. Lear SA, Humphries KH, Kohli S, Chockalingam A, Frohlich JJ, Birmingham CL. Visceral adipose tissue accumulation differs according to ethnic background: results of the Multicultural Community Health Assessment Trial (M-CHAT). The American Journal of Clinical Nutrition. 2007;86(2):353-359. doi:10.1093/ajcn/86.2.353

198. Joseph JJ, Echouffo-Tcheugui JB, Golden SH, et al. Physical activity, sedentary behaviors and the incidence of type 2 diabetes mellitus: the Multi-Ethnic Study of Atherosclerosis (MESA). BMJ Open Diab Res Care. 2016;4(1):e000185. doi:10.1136/bmjdrc-2015-000185

199. Zhang YB, Chen C, Pan XF, et al. Associations of healthy lifestyle and socioeconomic status with mortality and incident cardiovascular disease: two prospective cohort studies. BMJ. Published online April 14, 2021:n604. doi:10.1136/bmj.n604

200. Hupfeld CJ, Courtney CH, Olefsky JM. TYPE 2 DIABETES MELLITUS: diabetes mellitus.

201. Lovejoy JC, De La Bretonne JA, Klemperer M, Tulley R. Abdominal fat distribution and metabolic risk factors: Effects of race. Metabolism. 1996;45(9):1119-1124. doi:10.1016/S0026-0495(96)90011-6

202. Kalimeri M, Totman JJ, Baum T, et al. Postmenopausal Chinese-Singaporean Women Have a Higher Ratio of Visceral to Subcutaneous Adipose Tissue Volume than Caucasian Women of the Same Age and BMI. Diagnostics. 2021;11(11):2127. doi:10.3390/diagnostics11112127

203. Kadowaki S, Miura K, Kadowaki T, et al. International Comparison of Abdominal Fat Distribution Among Four Populations: The ERA-JUMP Study. Metabolic Syndrome and Related Disorders. 2018;16(4):166-173. doi:10.1089/met.2017.0132

204. Hill JO, Sidney S, Lewis CE, Tolan K, Scherzinger AL, Stamm ER. Racial differences in amounts of visceral adipose tissue in young adults: the CARDIA (Coronary Artery Risk Development in Young Adults) Study. The American Journal of Clinical Nutrition. 1999;69(3):381-387. doi:10.1093/ajcn/69.3.381

205. Mongraw-Chaffin M, Allison MA, Burke GL, et al. CT-Derived Body Fat Distribution and Incident Cardiovascular Disease: The Multi-Ethnic Study of Atherosclerosis. The Journal of Clinical Endocrinology & Metabolism. 2017;102(11):4173-4183. doi:10.1210/jc.2017-01113

206. Shah RV, Murthy VL, Abbasi SA, et al. Visceral Adiposity and the Risk of Metabolic Syndrome Across Body Mass Index. JACC: Cardiovascular Imaging. 2014;7(12):1221-1235. doi:10.1016/j.jcmg.2014.07.017