Title

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Journal

Menopause: The Journal of the Menopause Society, 27(6)

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Publication Date

2020-06-01

DOI

10.1097/GME.0000000000001512

Peer reviewed

HHS Public Access

Author manuscript

Menopause. Author manuscript; available in PMC 2024 August 14.

Published in final edited form as:

Menopause. 2020 June ; 27(6): 640–647. doi:10.1097/GME.0000000000001512.

Incidence of diabetes according to metabolically healthy or unhealthy normal weight or overweight/obesity in postmenopausal women: the Women's Health Initiative

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Abstract

Objective: To determine the relationship of metabolic weight categories with incident diabetes mellitus (DM) in postmenopausal women.

Methods: The Women's Health Initiative (WHI) enrolled 161,808 postmenopausal women aged 50 to 79 years. We included those with cardiovascular disease (CVD) biomarkers and free of CVD and prevalent DM (n = 17,043) at baseline. Normal weight was defined as a body mass index (BMI) ≥18.5 and <25 kg/m^2, and waist circumference (WC) <88 cm and overweight/obesity as a BMI ≥25 kg/m^2 or WC ≥88 cm. Metabolically healthy was based on <2 and metabolically unhealthy ≥2 traits of the following: triglycerides ≥150 mg/dL, systolic blood pressure (BP) ≥130

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Abstract accepted/presented at the 2019 American Society for Preventive Cardiology Congress on CVD Prevention Conference in San Antonio, TX.

Supplemental digital content is available for this article. Direct URL citations are provided in the HTML and PDF versions of this article on the journal's Website (www.menopause.org).

mm Hg or diastolic BP ≥85 mm Hg, or antihypertensives or diuretics, fasting glucose ≥100 mg/dL or DM medication, and high-density lipoprotein cholesterol <50 mg/dL. Cox regression was performed to determine the risk of incident DM among metabolically healthy normal weight (MHNW), metabolically unhealthy normal weight (MUHNW), metabolically healthy overweight/obese (MHO), and metabolically unhealthy overweight/obese (MUHO).

Results: Among our sample, 2,253 (13.3%) participants developed DM over a mean ± standard deviation follow-up time of 15.6 ± 3.4 years. Compared with MHNW (n = 162 incident DM cases), an increased risk of incident DM was observed in MUHNW (n = 102 cases) (hazard ratio [HR] 2.24, 95% confidence interval [CI] 1.74–2.88, $P < 0.0001$), MHO (n = 624 cases) (HR 1.68, 95% CI 1.40–2.00, $P < 0.0001$), and MUHO (n = 1,365 cases) (HR 4.51, 95% CI 3.82–5.35, $P < 0.0001$).

Conclusions: Among postmenopausal women, MUHNW and MHO confer an approximate doubling in the risk and MUHO more than a four-fold increased risk for developing DM.

Keywords

Cardiometabolic; Diabetes; Obesity; Postmenopausal women; Women's Health Initiative

As reported by the Centers for Disease Control and Prevention's (CDC) National Diabetes Statistics Report,[1] the prevalence of diabetes mellitus (DM) (diagnosed and undiagnosed) for women aged 40 to 64 years, and 65 and older was 17.0% and 25.2%. During menopause, fat redistribution occurs in women, increasing insulin resistance and leading to an upward trend in the incidence of DM.[2] According to Lobo et al,[2] postmenopausal women who have increased abdominal fat are at risk for type 2 diabetes due to the development of insulin resistance and glucose intolerance. These changes in body fat composition of menopausal women are present in all ethnicities, and also in the obese and non-obese.[3] Metabolically healthy overweight/obese (MHO) individuals may not present with all of the cardiometabolic abnormalities that typically accompany obesity.[4] However, Aung et al[4] reports that MHO is not a benign condition, and it is correlated with an increased risk of developing DM and cardiovascular disease (CVD).

Metabolically unhealthy normal weight (MUHNW) people are also at an increased risk for type 2 diabetes, CVD, and mortality.[5–8] MUHNW may have more abdominal fat distribution and dyslipidemia than lean metabolically healthy individuals.[9] As reported by many recent studies, there appears to be a greater risk of developing DM for the MUHNW as compared with the metabolically healthy normal weight (MHNW).[4,10–14] It has been reported that the relationship between type 2 diabetes and waist circumference (WC) may be a better metabolic predictor among the normal weight as compared with overweight or obese people.[15] In addition, Peppa et al[16] reported that the metabolically unhealthy phenotype demonstrated results of weight fluctuations, increased biochemical markers of insulin resistance, hepatic steatosis, inflammation, and increased indices of central adiposity. Some studies have demonstrated that metabolically unhealthy overweight/obese (MUHO) individuals have increased visceral abdominal fat, which is directly correlated with metabolic disease.[17,18]

The purpose of this study was to determine the relationship between these metabolic weight categories and incident DM in the WHI postmenopausal women participant population without diabetes at baseline. Our hypothesis was that the incidence of DM would be greater among postmenopausal women with MUHNW, MUHO, and MHO in comparison with postmenopausal women with MHNW.

METHODS

Study population

The Women's Health Initiative (WHI) consisted of two major components: a group of randomized clinical trials (CT) (N = 68,132) and an observational cohort study (N = 93,676).[19] The CT comprised of three concurrent, randomized controlled trials among postmenopausal women aged 50 to 79 years: Hormone Therapy Trials (HT), Dietary Modification Trial, and Calcium and Vitamin D Trial.[20] WHI recruitment was conducted from 1993 to 1998 by 40 clinical centers in 24 states and the District of Columbia.[20] Recruitment took place locally, at clinical centers, and nationally at the National Institutes of Health, the Clinical Coordinating Center, and various study-wide committees, including various recruitment strategies of mass mailings, community presentations, local newspaper ads, public service announcements (TV and radio), and health fairs (see appendix, Supplemental Digital Content 1, http://links.lww.com/MENO/A546).[20]

A baseline CVD risk factor and biomarker subset sample of approximately 25,000 participants was derived from three studies: CT 6% subsample, clinic complete blood counts, quality control pools; CVD biomarkers for 2010 to 2015 single-nucleotide polymorphisms health association resource cohort only; and CVD, DM, and renal biomarkers in the estrogen alone HT cohort were included as variables.[20] The measures consisted of glucose, total cholesterol, high-density lipoprotein cholesterol (HDL-C), triglycerides, insulin, and C-reactive protein (CRP).[20] We excluded women with prevalent DM (defined by self-report, fasting glucose of ≥126 mg/dL, insulin or oral diabetes medication use) or prevalent CVD (prior myocardial infarction, stroke, heart failure, peripheral arterial disease, or percutaneous intervention).

Measures

All measures were assessed at baseline for the purposes of this report.

Overweight/obesity was defined by a body mass index (BMI) ≥25 kg/m^2 or elevated WC (≥88 cm) which were measured by trained staff during clinic visits.[21–23] Normal body weight was defined as a BMI ≥18.5 and <25 kg/m^2, and without elevated WC (<88 cm) measured by trained staff during clinic visits.[21–23] Metabolically healthy was based on <2 and metabolically unhealthy ≥2 of the following traits: high triglycerides (≥150 mg/dL); elevated systolic blood pressure (BP) (≥130 mm Hg) or diastolic BP (≥85 mm Hg) measured by averaging two baseline measurements (if only one BP measurement was known, the single value was used)[20] or antihypertensive drugs (including diuretics); high fasting glucose (≥100 mg/dL) or medications for DM (insulin and oral antidiabetics); and low HDL-C (<50 mg/dL) for low HDL-C.[21–23]

Metabolically healthy normal was defined by having less than two of the above metabolic traits.[21–23] Metabolically unhealthy normal (MUHNW) was defined by having at least two of the four above metabolic traits.[21–23] MHO was defined by having less than two of the above metabolic traits.[21–23] MUHO was defined by having at least two of four metabolic traits.[21–23] Secondary analyses created six groups based on further subdividing overweight/obesity into overweight (BMI 25.0 to <30 kg/m^2) and obese (BMI ≥30.0 kg/m^2).

Or prevalent CVD (prior myocardial infarction, stroke, heart failure, peripheral arterial disease, or percutaneous intervention).

Incident DM was based on self-reported treatment with insulin or oral hypoglycemic medication (pills or shots) as prescribed by a physician during the WHI Core Study 1993 to 1998,[24] and validated for predictive value for self-reported incident DM.[25] Also, a follow-up medical history update questionnaire was used for self-reported treatment with insulin shots or oral hypoglycemic medication (pills).[20]

CVD risk factor and biomarker assays were all measured from blood samples at baseline, and consisted of glucose, total cholesterol, HDL-C, triglycerides, insulin, and CRP, and were measured at MRL/PPD and University of Minnesota laboratories.[20] All of the biomarkers used in the analyses were collected as blood samples with participants fasting for at least 12 hours before draws.[20] Glucose was measured in serum via the hexokinase method on the Hitachi 747 (Boehringer Mannheim Diagnostics, Indianapolis, IN) and the Gluco-quant Glucose/hexokinase reagent (Roche Diagnostics, Indianapolis, IN) on the Roche Modular P Chemistry analyzer (Roche Diagnostics Corporation, Indianapolis, IN).[20] Total cholesterol was analyzed by enzymatic methods on a Hitachi 747 analyzer (Boehringer Mannheim Diagnostics, Indianapolis, IN).[20] In 2006, the instrument changed from the Hitachi 747 to the Roche Modular.[20] It was also measured in serum using a cholesterol oxidase method (Roche Diagnostics Corporation, Indianapolis, IN) on the Roche Modular P Chemistry analyzer (Roche Diagnostics Corporation, Indianapolis, IN).[20] HDL-C was isolated using heparin manganese chloride with the supernate measured enzymatically on the Hitachi 747.[20] In 2006, the instrument changed from the Hitachi 747 to the Roche Modular.[20] HDL-C was also measured in serum using the HDL-C plus third-generation direct method (Roche Diagnostics Corporation, Indianapolis, IN) on the Roche Modular P Chemistry analyzer (Roche Diagnostics Corporation, Indianapolis, IN).[20] Triglycerides were analyzed by enzymatic methods on a Hitachi 747 analyzer (Boehringer Mannheim Diagnostics, Indianapolis, IN) and in serum using Triglyceride GB reagent (Roche Diagnostics, Indianapolis, IN 46250) on the Roche Modular P Chemistry analyzer (Roche Diagnostics Corporation, Indianapolis, IN).[20] Insulin was analyzed via sandwich immunoassay (Roche Diagnostics, Indianapolis, IN) on Roche Elecsys 2010 Analyzer.[20] Also, it was measured with the Pharmacia RIA method; then, starting on 8/10/98, they were measured in a step-wise sandwich ELISA procedure on an ES 300 (Boehringer Mannheim Diagnostics, Indianapolis, IN).[20] Insulin was also measured in serum by Roche 2010 Electrochemiluminescence.[20] In 2009, the instrument changed from the Roche 2010 to the ADVIA Centaur system.[20] CRP was measured in serum via immunoassay on a Roche Modular P Chemistry analyzer.[20] Information on quality control of the biomarker specimens has been previously described.[26,27]

Covariates—Variables hypothesized to be associated with DM, MHO, MUHO, MHNW, and MUHNW in postmenopausal women were included as covariates: age, race/ethnicity, income, cigarette smoking status, and family history (relatives with adult diabetes). All of the biomarkers used in the analyses were collected as blood samples with participants fasting for at least 12 hours before draws.[20] The residual blood samples were stored at 48C for up to 1 hour until plasma or serum was separated from the cells.[20]

Statistical analysis

The demographic, health, and metabolic characteristics of participants with and without incident DM were compared using Pearson's chi-square test for the categorical variables and an independent-samples *t* test for continuous dependent variables. To display the descriptive analyses across the four groups, Pearson's chi-square test for the categorical variables and an analysis of variance for the continuous dependent variables were used. The CVD biomarkers were log-transformed to account for skewed distributions and standardized to account for multiple labs utilizing different techniques and various instruments. The rates per 1,000 person-years for incident DM (among those free of DM at baseline) were shown according to disease grouping. Cox regression was performed to determine the risk of incident DM (among those without known DM at baseline) among the MHO, MUHO, MUHNW, and MHNW (as the reference group) adjusting for covariates of age, race/ethnicity, income, cigarette smoking status, and family history (relatives with adult diabetes). Analyses provided hazard ratios (HRs) and 95% confidence intervals (CIs). Time to development of incident DM was defined as the number of days from enrollment to DM treatment (days were converted to years in the analysis). All statistical tests were two-sided, and all statistical analyses were performed using SAS software Version 9.4.[28]

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee, and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

RESULTS

Comparisons of the general characteristics of the WHI postmenopausal women with incident DM (n = 2,253 [13.3%]) versus without incident DM (n = 14,739 [86.7%]) at baseline (see flow chart, Supplemental Digital Content 2, http://links.lww.com/MENO/A547) showed that women with incident DM had a mean age of 61.8 years, whereas those without incident DM reported a mean age of 63.5 years (Table 1). Both groups (with and without incident DM) were predominately White women (not of Hispanic origin), and had some college, vocational training, or an associate degree. In addition, those with incident DM had a higher prevalence of family history (relatives with adult diabetes). Also, those with incident DM had higher WCs, BMIs, systolic and diastolic BPs, glucose, total cholesterol, triglycerides, insulin, and CRP levels. Whereas those without incident DM had increased levels of physical activity and HDL-C (Table 1).

Table 2 reports the distributions of the general characteristics of the analysis sample as follows: MHNW (reference group) (18.8%), MUHNW (5.9%), MHO (38.7%), and MUHO

(36.5%). The MHNW had the lowest incidence of DM, were predominately White (not of Hispanic origin), had a baccalaureate degree or higher, had increased alcohol consumption, and had increased levels of physical activity and HDL-C. The MUHNW had the highest mean age, were mainly White, had some college, vocational training or an associate degree, reported a low income, and had a higher prevalence of current smoking, an increased systolic BP, and total cholesterol levels. The MHO had the lowest mean age, were mostly Black or African-American, had some college, vocational training or an associate degree, reported a low to moderate income, and a lower prevalence of current smoking. The MUHO had the highest incidence of DM, the majority were non-Hispanic White, had some college, vocational training, or an associate degree, reported a low to moderate income, had a higher prevalence of past smoking and family history of diabetes, had higher WCs, BMIs, and diastolic BPs, and increased levels of glucose, triglycerides, insulin, and CRP (Table 2).

The incident DM rates per 1,000 person-years among WHI postmenopausal women without known DM at baseline (Fig. 1) according to metabolic weight groups were: MHNW 3.11, MUHNW 6.41, MHO 5.94, and MUHO 14.97. The MUHO had the highest incident DM rates per 1,000 person-years. Conversely, the MHNW had the lowest incident DM rates per 1,000 person-years (Fig. 1).

Table 3 presents the Cox proportional HRs risk of incident DM according to metabolic weight group (with MHNW as the reference) along with risk factors and biomarkers in WHI postmenopausal women. The mean ± standard deviation (SD) follow-up time to event was 15.6 ± 3.4 years. The adjusted HRs for the MUHNW (n = 102 cases) (HR 2.24, 95% CI 1.74–2.88, $P < 0.0001$), MHO (n = 624 cases) (HR 1.68, 95% CI 1.40–2.00, $P < 0.0001$), and MUHO (n = 1,365 cases) (HR 4.51, 95% CI 3.82–5.35, $P < 0.0001$) were statistically significant as compared with MHNW (reference group) after adjusting for covariates. Lastly, the covariates age, ethnicity Black/African-American, and family history (relative with adult diabetes) were significantly associated with incident DM (Table 3). In sensitivity analyses, further adjusting for total cholesterol (which greatly reduced the sample size of the entire model) had a negligible effect on our estimates. In addition, pair-wise comparisons revealed the following relationships: MUHNW versus MHO (HR 1.34, 95% CI 1.08–1.66), MUHO versus MUHNW (HR 2.02, 95% CI 1.64–2.48), MHO versus MUHO (HR 0.37, 95% CI 0.34–0.41), and MUHO versus MHO (HR 2.69, 95% CI 2.44–2.97).

A secondary analysis was conducted by additional adjustment for BMI. This revealed that BMI slightly attenuated relationships of metabolic weight groups with incident DM (HRs for MUHNW, MHO, and MHNW of 2.19, 1.32, and 3.37 respectively; all $P < 0.001$); however, our findings remained robust and significant.

Furthermore, Table 4 shows results of metabolic weight groups by subdividing overweight/obese separately into overweight and obese in addition to normal weight stratified by metabolically healthy versus unhealthy (six groups total). The adjusted HRs for the MUHNW (HR 2.22, 95% CI 1.73–2.86, $P < 0.0001$), metabolically healthy (MH) overweight (HR 1.35, 95% CI 1.11–1.62, $P = 0.03$), metabolically unhealthy (MUH) overweight (HR 3.69, 95% CI 3.08–4.43, $P < 0.0001$), MH obese (HR 2.13, 95% CI 1.76–2.58, $P < 0.0001$), and MUH obese (HR 5.21, 95% CI 4.38–6.19, $P < 0.0001$) were

statistically significant as compared with MHNW (reference group) after adjusting for covariates (Table 4).

DISCUSSION

Our study showed that among postmenopausal women, those who are metabolically unhealthy, despite being of normal weight, carry a two-fold greater incidence of DM as those who are metabolically healthy and normal weight; those who are overweight or obese and metabolically unhealthy have nearly a four-fold greater risk of developing incident DM. Overall, incident DM rates were approximately twice as high for those who were MUHNW and nearly four times as high for those who were MUHO compared with MHNW.

Metabolically unhealthy overweight/obese is known to be associated with impaired glucose tolerance, dyslipidemia, and hypertension.[29] Also, a few research studies have demonstrated that MUHO individuals have increased visceral abdominal fat, which is directly associated with metabolic disease.[17,18] This is consistent with our findings of WHI postmenopausal women with incident DM who also had increased WCs, BMIs, and systolic and diastolic BPs. Also, it has been described that the metabolically unhealthy phenotype experiences weight fluctuations, increased biochemical markers of insulin resistance, inflammation, and increased indices of central adiposity.[16] Lastly, this also coincides with the MUHO with incident DM having higher levels of glucose, triglyceride, insulin, and CRP in our study.

Furthermore, the MUHO group was more likely to have a higher incidence of DM, smoke, be less physically active, have a larger WC or BMI, higher diastolic BP, and the highest biomarkers of glucose, triglyceride, insulin, and CRP. Central adiposity is associated with an increased risk of insulin resistance, which ultimately leads to the increased risk of type 2 diabetes.[30] Also, it has been noted that the higher the BMI or WC, the more substantial the risk of becoming insulin-resistant.[31] During menopause, a decline in estrogen occurs, which may contribute to increased abdominal fat.[32] These changes occur in all women regardless of their cardiometabolic status[3] and may alter their risk of insulin resistance, DM, obesity, and depression during menopause.[2] Finally, lifestyle modifications were reported to be one of the most beneficial intervention strategies to combat risk during menopause.[2]

Additionally, a meta-analysis including the MEDLINE and Embase databases, and the NAGALA (NAfld in Gifu Area, Longitudinal Analysis) study, consisting of over 130,000 men and women participants, revealed that the MHO with and without fatty liver presented with higher relative risks of developing incident DM than the MHNW.[33] Also, a 12-year population-based cohort of men and women from the Tehran Lipid and Glucose Study reported a 50% and 70% increased risk of incident DM in the metabolically healthy abdominal obese (MHAO) for men and women.[34] A cohort study of rural Chinese adults noted a 1.94-fold, 3.10-fold, and 6.63-fold increased risk of incident DM among the MHO, MUHNW, and MUHO.[35] Similarly, a study examined the risk of incident DM among nondiabetic first-degree relatives of patients with type 2 diabetes in Iran; the MHO and MUHO show a 2.96 and 2.75 increased odds of developing incident DM, respectively, as compared with the MHNW.[36] However, limited research has been conducted regarding cardiometabolic disease and incident DM among postmenopausal women.

A strength of this study was that the CVD biomarkers presented with a wide demographic of participants, large sample size, clinical measures, measured weights, and use of a validated endpoint of incident DM. The major limitation of the study is that incident DM depended on self-reported initiation of insulin or antidiabetic medication, as fasting glucose or glycated hemoglobin measures were unavailable for the duration of follow-up. Also, there were some differences in the assays measuring the CVD biomarkers depending on the WHI substudy source, which may affect internal validity.

Another potential limitation is that study participants may not be representative of a population-based sample. Thus, this may limit generalizability to the general US population. However, a strength of this study is that the sample size is large and stems from multicultural, multiethnic, and multiracial recruitment efforts. Although the participants were recruited nationally and from various geographic and socio-economic backgrounds, the majority were non-Hispanic White. The WHI population also consists of only postmenopausal women, and therefore, may not be generalizable to younger women and men. Also, as a secondary data analysis, not all potential variables of interest may have been collected during the original study sample data collection to address particular issues or hypotheses. Lastly, use of all of our predictors at baseline may be a potential limitation as we did not have sufficient repeated measures to look at effects of changes in these predictors on outcomes (eg, as time-dependent covariates).

CONCLUSIONS

In conclusion, our findings provide evidence that MUHNW and MHO confer an approximate two-fold increased risk for developing DM, with MUHO associated with more than a four-fold elevated risk compared with those who are MHNW. This indicates that there is significant increased risk of DM in those who are metabolically unhealthy, despite being of normal weight. Apart from the need for improved DM education models to provide current education to patients,[37] greater patient education regarding the importance of weight loss and control of cardiometabolic risk factors for prevention of diabetes can be recommended.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Funding/support:

The WHI program is funded by the National Heart, Lung, and Blood Institute, National Institutes of Health, US Department of Health and Human Services through contracts HHSN268201600018C, HHSN268201600001C, HHSN268201600002C, HHSN268201600003C, and HHSN268201600004C.

Financial disclosure/conflicts of interest:

Dr Lawrence S. Phillips is supported in part by VA awards I01-CX001025, and I01CX001737, NIH awards R21DK099716, U01 DK091958, U01 DK098246, P30DK111024, and R03AI133172, and a Cystic Fibrosis Foundation award PHILLI12A0. The sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript. Dr Phillips declares that there is no duality of interest associated with this manuscript. With regard to potential conflicts of interest, within the past several years, Dr Phillips has served on Scientific Advisory Boards for Janssen,

and has or had research support from Abbvie, 899ck, Amylin, Eli Lilly, Novo Nordisk, Sanofi, PhaseBio, Roche, Abbvie, Vascular Pharmaceuticals, Janssen, Glaxo SmithKline, Pfizer, Kowa, and the Cystic Fibrosis Foundation. In the past, he was a speaker for Novartis and Merck, but not for the past 5 years. Dr Phillips is also a cofounder and Officer and Board member and stockholder of a company, DIASYST, Inc., which is developing software aimed to help improve diabetes management. Dr Phillips is also supported in part by the Veterans Health Administration (VA). This work is not intended to reflect the official opinion of the VA or the US government. Dr Nathan Wong has received research support through his institution from Amgen, Amarin, Boehringer-Ingelheim, and Novartis, and is on the speakers bureau for Amarin and Sanofi. The other authors have nothing to disclose.

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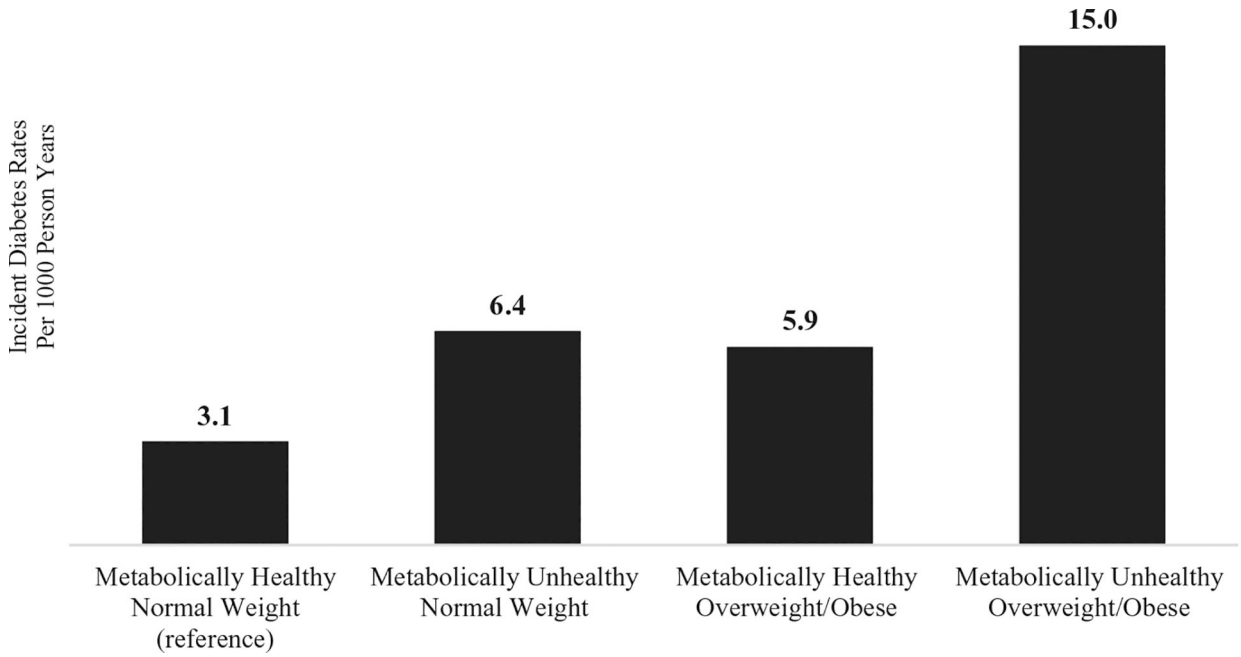

FIG. 1.

Incident diabetes rates per 1,000 person-years among WHI postmenopausal women without known diabetes at baseline.

TABLE 1.

Baseline sociodemographic and other metabolic risk factor characteristics of WHI postmenopausal women according to incident diabetes

	Incident Diabetes (n = 2,253) (13.3%)	No Incident Diabetes (n = 14,739) (86.7%)	*P*
Age (y) (n = 17,043)	61.8 ± 7.0	63.5 ± 7.4	<0.0001
Race/ethnicity (n = 17,043)			<0.0001
Asian or Pacific Islander	30 (1.3)	232 (1.6)	
Black or African-American	885 (39.3)	4,708 (31.9)	
Hispanic/Latino	394 (17.5)	2,446 (16.6)	
White (not of Hispanic origin)	924 (41.0)	7,227 (49.0)	
Other	20 (0.9)	126 (0.9)	
Education (n = 16,908)			<0.0001
<12th grade	237 (10.6)	1,231 (8.4)	
High school diploma or GED	427 (19.1)	2,589 (17.7)	
Some college/associate degree/vocational training	923 (41.3)	5,696 (39.0)	
Baccalaureate Degree or higher	650 (29.1)	5,111 (35.0)	
Income (n = 16,425)			0.12
Less than $19,999	522 (24.0)	3,177 (22.4)	
$20,000 to $34,999	578 (26.6)	3,638 (25.6)	
$35,000 to $49,999	425 (19.6)	2,790 (19.7)	
$50,000 to $74,999	367 (16.9)	2,457 (17.3)	
$75,000 or more	231 (10.6)	1,749 (12.3)	
Don’t know	51 (2.4)	391 (2.8)	
Smoking (n = 16,804)			0.28
Never smoked	1,180 (53.1)	7,723 (53.1)	
Current smoker	220 (9.9)	1,294 (8.9)	
Past smoker	823 (37.0)	5,516 (38.0)	
Alcohol (drank 12 alcoholic drinks ever) (n = 16,928)	1,880 (84.2)	12,551 (85.7)	0.05
Family history (relative with adult diabetes) (n = 16,942)			<0.0001
Yes	1,109 (49.5)	4,947 (33.8)	
No	1,013 (45.2)	8,826 (60.2)	
Don’t know	119 (5.3)	878 (6.0)	
Total energy expend rec phys act (MET-hrs/wk) (n = 16,113)	9.5 ± 12.2	11.3 ± 13.6	<00.0001
Waist (cm) (n = 17,001)	94.0 ± 13.3	87.2 ± 12.8	<0.0001
Body mass index (BMI) (kg/m^2) (n = 17,043)	31.5 ± 6.2	28.7 ± 5.7	<0.0001
Systolic blood pressure (mm Hg) (n = 17,043)	131.0 ± 17.0	128.5 ± 17.5	<0.0001
Diastolic blood pressure (mm Hg) (n = 17,043)	77.7 ± 9.2	76.2 ± 9.2	<0.0001
Biomarkers			
Glucose (mg/dL) (n = 17,034)	100.9 ± 11.9	92.6 ± 9.5	<0.0001
Total cholesterol (mg/dL) (n = 17,043)	230.3 ± 41.9	230.1 ± 40.1	0.85
HDL cholesterol (mg/dL) (n = 17,043)	50.2 ± 12.6	55.7 ± 13.6	<0.0001
Triglyceride (mg/dL) (n = 17,043)	152.6 ± 95.4	127.0 ± 71.2	<0.0001

	Incident Diabetes (n = 2,253) (13.3%)	**No Incident Diabetes (n = 14,739) (86.7%)**	***P***
Insulin (pmol/L) (n = 16,555)	76.7 ± 50.2	53.7 ± 35.1	<0.0001
C-reactive protein (CRP) (mg/L) (n = 15,432)	1.3 ± 1.0	0.9 ± 1.1	<0.0001

N (percentage) reported for categorical variables. Mean ± standard deviation are reported for continuous variables. Pearson's Chi-square test for categorical dependent variables. Independent *t* test for continuous dependent variables.

GED, general education development; HDL, high-density lipoprotein; total energy expend rec phys act (MET-hrs/wk), total energy expenditure from recreational physical activity (MET-hrs/wk); WHI, Women's Health Initiative.

$P < 0.05$.

TABLE 2.

Baseline sociodemographic and other metabolic risk factor characteristics of normal and overweight/obese in WHI postmenopausal women

	MHNW (n = 3,203) (18.8%) (reference)	MUHNW (n = 1,010) (5.9%)	MHO (n = 6,603) (38.7%)	MUHO (n = 6,227) (36.5%)	*P*
Age (y)	63.7 ± 7.7	65.8 ± 7.1	62.4 ± 7.3	63.6 ± 7.1	<0.0001
Diabetes incidence	162 (5.1)	102 (10.1)	624 (9.5)	1,365 (22.0)	<0.0001
Race/ethnicity					<0.0001
Asian or Pacific Islander	85 (2.7)	45 (4.5)	49 (0.7)	84 (1.4)	
Black or African-American	791 (24.7)	171 (16.9)	2,872 (43.5)	1,773 (28.5)	
Hispanic/Latino	562 (17.6)	186 (18.4)	1,004 (15.2)	1,102 (17.7)	
White (not of Hispanic origin)	1,740 (54.3)	601 (59.5)	2,618 (39.7)	3,213 (51.6)	
Other	25 (0.8)	7 (0.7)	60 (0.9)	55 (0.9)	
Education					<0.0001
<12th grade	173 (5.4)	95 (9.5)	528 (8.1)	679 (11.0)	
High school diploma/GED	485 (15.2)	215 (21.5)	1,114 (17.0)	1,211 (19.6)	
Some Coll/Assoc Deg/Voc Trn	1,199 (37.6)	384 (38.4)	2,504 (38.2)	2,549 (41.3)	
Baccalaureate Deg/Higher	1,332 (41.8)	305 (30.5)	2,402 (36.7)	1,733 (28.1)	
Income					<0.0001
Less than $19,999	514 (16.6)	262 (26.9)	1,379 (21.6)	1,563 (26.1)	
$20,000 to $34,999	717 (23.2)	247 (25.4)	1,633 (25.6)	1,632 (27.3)	
$35,000 to $49,999	642 (20.8)	181 (18.6)	1,255 (19.7)	1,144 (19.1)	
$50,000 to $74,999	620 (20.1)	146 (15.0)	1,128 (17.7)	932 (15.6)	
$75,000 or more	519 (16.8)	108 (11.1)	826 (13.0)	534 (8.9)	
Don’t know	80 (2.6)	30 (3.8)	156 (2.5)	177 (3.0)	
Smoking					<0.0001
Never smoked	1,698 (53.8)	534 (53.5)	3,456 (53.1)	3,239 (52.8)	
Current smoker	343 (10.9)	149 (14.9)	467 (7.2)	565 (9.2)	
Past smoker	1,475 (46.5)	469 (46.8)	3,093 (47.2)	2,936 (47.6)	
Alcohol (12 drinks ever)	2,790 (87.7)	841 (83.8)	5,656 (86.3)	5,185 (83.9)	<0.0001
Family history (relative with adult diabetes)					<0.0001
Yes	921 (28.9)	336 (33.4)	2,375 (36.2)	2,443 (39.4)	
No	2,088 (65.6)	621 (61.7)	3,757 (57.3)	3,399 (54.9)	
Don’t know	174 (5.5)	50 (5.0)	426 (6.5)	352 (5.7)	
Total energy expend (MET-hrs/wk)	14.6 ± 15.4	12.9 ± 14.2	10.9 ± 13.4	9.1 ± 11.8	<0.0001
Waist (cm)	74.0 ± 5.5	76.6 ± 5.6	90.1 ± 11.3	95.1 ± 11.7	<0.0001
Body mass index (BMI) (kg/m^2)	22.6 ± 1.6	23.1 ± 1.5	30.5 ± 5.0	31.8 ± 5.4	<0.0001
Systolic BP (mm Hg)	122.1 ± 16.8	135.5 ± 17.8	125.1 ± 16.1	135.1 ± 16.7	<0.0001
Diastolic BP (mm Hg)	73.0 ± 8.8	76.9 ± 9.5	75.5 ± 8.8	78.9 ± 9.1	<0.0001
Biomarkers:					
Glucose (mg/dL)	88.8 ± 8.0	95.6 ± 10.9	90.7 ± 8.2	99.1 ± 10.7	<0.0001

	MHNW (n = 3,203) (18.8%) (reference)	**MUHNW (n = 1,010) (5.9%)**	**MHO (n = 6,603) (38.7%)**	**MUHO (n = 6,227) (36.5%)**	***P***
Cholesterol (mg/dL)	224.2 ± 36.3	238.7 ± 44.4	226.2 ± 38.4	236.0 ± 42.6	<0.0001
HDL cholesterol (mg/dL)	64.3 ± 13.3	50.1 ± 12.9	59.4 ± 11.6	46.2 ± 9.8	<0.0001
Triglyceride (mg/dL)	93.2 ± 36.6	169.0 ± 114.1	100.6 ± 36.8	174.8 ± 86.2	<0.0001
Insulin (pmol/L)	32.0 ± 16.7	44.0 ± 22.1	52.7 ± 32.3	75.9 ± 44.2	<0.0001
Log CRP (mg/L)	0.2 ± 1.0	0.6 ± 1.1	1.0 ± 1.0	1.3 ± 1.0	<0.0001

N (percentage) reported for categorical variables. Mean ± standard deviation are reported for continuous variables.

Pearson's Chi-square test for categorical variables and analysis of variance for continuous dependent variables ($P < 0.05$).

Assoc Deg, associate degree; BP, blood pressure; Coll, college; CRP, C-reactive protein; Deg, degree; GED, general education development; HDL, high-density lipoprotein; MHNW, metabolically healthy normal weight; MHO, metabolically healthy overweight/obese; MI, myocardial infarction; MUHNW, metabolically unhealthy normal weight; MUHO, metabolically unhealthy overweight/obese; total energy expend (MET-hrs/wk), total energy expenditure from recreational physical activity (MET-hrs/wk); Voc Trn, vocational training; WHI, Women's Health Initiative.

TABLE 3.

Cox proportional hazard ratios in WHI postmenopausal women

	HR (95% CI)	*P*
MUHNW vs MHNW	2.24 (1.74–2.88)	<0.0001
MHO vs MHNW	1.68 (1.40–2.00)	<0.0001
MUHO vs MHNW	4.51 (3.82–5.35)	<0.0001
Age (y)	0.97 (0.96–0.98)	<0.0001
Race/ethnicity		
Asian or Pacific Islander vs White	1.01 (0.70–1.46)	0.96
Black/African-American vs White	1.23 (1.11–1.36)	0.0001
Hispanic/Latino vs White	0.95 (0.83–1.08)	0.42
Other vs White	0.97 (0.60–1.56)	0.88
Income		
Less than $19,999 vs $20,000 to $34,999	0.98 (0.87–1.11)	0.78
$35,000 to $49,999 vs $20,000 to $34,999	0.96 (0.85–1.09)	0.55
$50,000 to $74,999 vs $20,000 to $34,999	0.94 (0.82–1.07)	0.37
$75,000 or more vs $20,000 to $34,999	0.87 (0.75–1.02)	0.08
Don’t know vs $20,000 to $34,999	0.80 (0.59–1.06)	0.12
Smoking		
Current smoker vs never smoked	1.01 (0.87–1.17)	0.92
Past smoker vs never smoked	0.96 (0.88–1.05)	0.37
Family history (relative with adult diabetes)		
Yes vs no	1.65 (1.51–1.80)	<0.0001
Don’t know vs no	1.14 (0.94–1.39)	0.19

Variables included in the adjusted model: metabolic groups, age, race/ethnicity, income, smoking, and family history of diabetes ($P < 0.05$).

CI, confidence intervals; HR, hazard ratio; MHNW, metabolically healthy normal weight; MHO, metabolically healthy overweight/obese; MUHNW, metabolically unhealthy normal weight; MUHO, metabolically unhealthy overweight/obese; WHI, Women’s Health Initiative.

TABLE 4.

Cox proportional hazard ratios in WHI postmenopausal women among separate overweight and obese groups

	HR (95% CI)	*P*
MUHNW vs MHNW	2.22 (1.73–2.86)	<0.0001
MHOW vs MHNW	1.35 (1.11–1.65)	0.03
MUHOW vs MHNW	3.69 (3.08–4.43)	<0.0001
MHOB vs MHNW	2.13 (1.76–2.58)	<0.0001
MUHOB vs MHNW	5.21 (4.38–6.19)	<0.0001
Age (years)	0.97 (0.97–0.98)	<0.0001
Race/Ethnicity		
Asian or Pacific Islander vs White	1.08 (0.75–1.56)	0.69
Black/African-American vs White	1.20 (1.08–1.33)	0.0005
Hispanic/Latino vs White	0.98 (0.86–1.12)	0.73
Other vs White	0.98 (0.61–1.59)	0.94
Income		
Less than $19,999 vs $20,000 to $34,999	0.97 (0.86–1.10)	0.65
$35,000 to $49,999 vs $20,000 to $34,999	0.97 (0.85–1.10)	0.63
$50,000 to $74,999 vs $20,000 to $34,999	0.96 (0.84–1.10)	0.58
$75,000 or more vs $20,000 to $34,999	0.90 (0.75–1.05)	0.19
Don’t know vs $20,000 to $34,999	0.79 (0.59–1.06)	0.12
Smoking		
Current smoker vs never smoked	1.05 (0.90–1.22)	0.54
Past smoker vs never smoked	0.96 (0.88–1.05)	0.37
Family history (relative with adult diabetes)		
Yes vs no	1.63 (1.49–1.78)	<0.0001
Don’t know vs no	1.14 (0.94–1.38)	0.20

Variables included in the adjusted model: metabolic groups, age, race/ethnicity, income, smoking, and family history of diabetes ($P < 0.05$).

CI, confidence intervals; HR, hazard ratio; MHNW, metabolically healthy normal weight; MHOB, metabolically healthy obese; MHOW, metabolically healthy overweight; MUHNW, metabolically unhealthy normal weight; MUHOB, metabolically unhealthy obese; MUHOW, metabolically unhealthy overweight; WHI, Women’s Health Initiative.