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## Observational Study

## Impact of diabetes mellitus and cardiometabolic syndrome on the risk of Alzheimer's disease among postmenopausal women

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**Abstract****BACKGROUND**

In spite of an increase in the incidence and prevalence of diabetes mellitus (DM) and Alzheimer's disease (AD) in the aging population worldwide, limited attention has been paid to their potential association.

**AIM**

To investigate the association of DM and cardiometabolic syndrome (CMS, a precursor to DM) with risk of incident AD among postmenopausal women.

**METHODS**

Postmenopausal women aged 50-79 ( $n = 63117$ ) who participated in the U.S. Women's Health Initiative Observational Study (WHIOS), recruited in 1993-1998, without baseline AD and followed up through March 1, 2019, were analyzed. AD was classified by participant-reported history of doctor-diagnosis of incident AD in the WHIOS. DM was defined by participant-report or treated because of diabetes or serum glucose concentrations  $\geq 126$  mg/dL. CMS was defined as having  $\geq 3$  of five CMS components: large waist circumference, high blood pressure, elevated triglycerides, elevated glucose, and low high-density lipoprotein cholesterol. The associations of DM and CMS with AD were analyzed using Cox's proportional hazards regression analysis.

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## RESULTS

During a median follow-up of 20 years (range: 3.36 to 23.36 years), of 63117 participants, 8340 developed incident AD. Women with DM had significantly higher incidence of AD [8.5, 95% confidence interval (CI): 8.0-9.0 per 1000 person-years (PY)] than those without DM (7.1, 95%CI: 6.9-7.2 per 1000 PY). Multivariate Cox's regression analysis indicated that women with DM or CMS had a significantly higher risk of AD than those without DM or CMS. The corresponding hazard ratios [HR (95%CI)] were 1.22 (1.13-1.31,  $P < 0.001$ ) in subjects with DM, and 1.18 (1.09-1.27,  $P < 0.001$ ) in subjects with CMS. The HRs diminished with age and became non-significant in the oldest age group.

## CONCLUSION

During a median follow-up of 20 years, DM and CMS were significantly associated with the risk of AD among postmenopausal women. More specifically, women aged 50-69 with DM or CMS *vs* those without these conditions had significantly higher relative risks of AD than the relative risks of AD in those aged 70-79 with DM or CMS *vs* those without DM or CMS.

**Key Words:** Epidemiology; Diabetes mellitus; Cardiometabolic disorders; Alzheimer's disease; Aging population

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**Core Tip:** Data from population-based studies on the association of diabetes and cardiometabolic syndrome (CMS) with risk of Alzheimer's disease (AD) was limited. This study, using data from one of the largest population-based cohort studies in the United States women aged 50-79 at baseline to test a hypothesis that diabetes and CMS are significantly associated with the risk of AD. This analysis is one of the first studies to prospectively test this hypothesis using a large-scale longitudinal cohort data. Findings from the study add new evidence to the body of research literature and provide new insights into the prevention of AD through control of diabetes and CMS.

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## INTRODUCTION

Diabetes mellitus (DM) and Alzheimer's disease (AD, an irreversible, progressive brain disorder, which is the most common type of dementia among older adults) pose serious public health problems in the United States and worldwide. Today, about 34.1 million adults aged 18 years or older have DM (13.0% of United States adults). The prevalence rate of DM is 4.2% in United States adults aged 18-44 years old, 17.5% in adults aged 45-64, and 26.8% among the elderly aged 65 and older<sup>[1]</sup>. Similar to DM, increased incidence and prevalence of AD have been observed in the United States. An estimated 5.4 million Americans suffered from AD in 2016 and that number is likely to increase to 13.8 million by 2050<sup>[2-4]</sup>. AD affects one in nine people aged  $\geq 65$ . The risk of AD is one out of three in ages  $\geq 85$ . Meanwhile, about two thirds of patients diagnosed with AD are women, which is partly attributable to women having a longer life expectancy than men<sup>[5]</sup>. Furthermore, an estimated 121000 Americans died due to AD in 2017<sup>[3]</sup>. AD is the nation's sixth leading cause of death. In 2015, the direct cost of treating the disease totaled \$236 billion, and economists estimate that the unpaid labor provided by caregivers to AD's patients amounted to another \$220 billion in 2015<sup>[3,4]</sup>. AD mainly affects older people and it was traditionally viewed as a predominately inherited disease for many years. However, recent studies suggest that cardiovascular and metabolic disorders including hypertension, dysglycemia, central adiposity and dyslipidemia may play a pivotal role in the development of AD<sup>[6,7]</sup>. The cluster of these

risk factors is commonly called cardiometabolic syndrome (CMS or called metabolic syndrome)<sup>[8,9]</sup>. DM and CMS are the established risk factors for cardiovascular diseases (CVD)<sup>[10-14]</sup>. Consequently, whether AD or AD related dementia are similar to CVD as a brain complication of diabetes has been hypothesized and studied in the recent years<sup>[6,7,15,16]</sup>. Most of these results of the association of DM and CMS with risk of AD or AD related dementia were reported from hospital-based or small sample size of population-based observational studies<sup>[4,6,7,16-21]</sup>. Given the complex status of disease in participants in hospital-based studies and small sample sizes of the previous population-based studies, selection bias due to nonrepresentative participants and potential misclassification attributable to multiple comorbidities may occur using data from hospital-based studies and loss of statistical power in hypothesis testing from studies with small sample sizes. Furthermore, although two-thirds of patients with AD are women, only few studies were conducted in women. Studies of the associations between cardiometabolic disorders and AD are in their infancy compared to other areas of studies of diabetic complications. In the study, we hypothesize that women with DM or CMS have significantly higher risk of AD than those without DM or CMS. To test this hypothesis, we have two specific aims: (1) To examine the long-term effect of DM and CMS on the risk of incident AD, and (2) To examine whether there is a potential modifying effect of age on AD risk using data from a large-scale population-based observational cohort study among women aged 50 to 79 years.

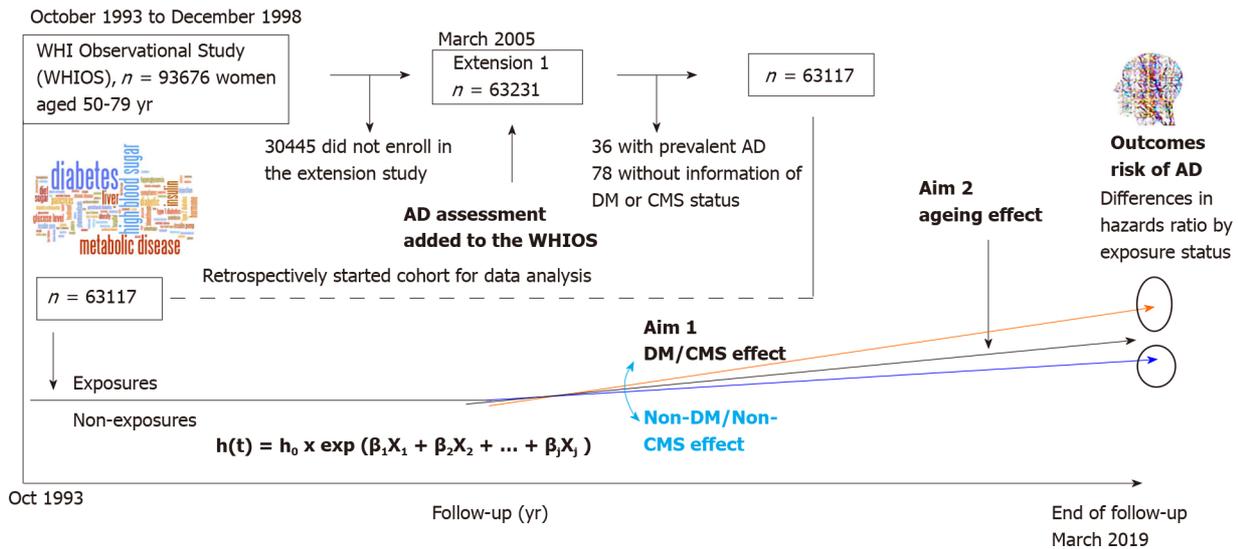
## MATERIALS AND METHODS

### *Study design and population*

The study used data from the U.S. Women's Health Initiative Observational Study (WHIOS) with a prospective analysis design<sup>[22-24]</sup>. The WHIOS, launched in 1993 is a longitudinal population-based observational study. The study design and materials were approved by institutional review boards at each survey center. Details of the scientific rationale, eligibility requirements and survey designs have been published<sup>[25]</sup>. In brief, a total of 93676 postmenopausal women aged 50-79 were enrolled from October 1, 1993 to December 31, 1998 at 40 United States clinical centers nationwide and participated in the study to examine risk factors for cardiovascular disease, cancers, diabetes and osteoporotic fractures. The inclusion criteria of the participants were those who planned to reside in the survey area for at least 3 years and had medical conditions predictive of survival more than 3 years, and no complicating conditions such as alcoholism, drug dependency and no baseline AD and dementia. Participants received annual follow-ups *via* mailings sent from the Clinical Coordinating Center (CCC) and were invited to have Clinical Center visits at year 3 after enrollment to update selected baseline data, obtain additional risk factor data, and collect a blood specimen. The annual mailing follow-ups consisted of a cover letter, a self-administered medical history update (*i.e.*, health outcomes) and assessment of exposures to risk factors. Non-responders received two additional mailings and telephone contacts by clinical center staff. When these efforts were not successful, clinical center staff contacted proxies to determine the location and status of the participant and to collect information on health outcomes. The initial WHIOS ended in March 2005. Then it continued to follow up the study participants who stay in the survey cohort, that it is designed as the WHIOS extension studies, with its Extension 1 from 2005 to 2010, and Extension 2 from 2010 to 2020. In the Extension studies, participants' health outcomes are followed by mails using self-administrated survey questionnaires. The assessments of incident AD started from the WHIOS Extension 1 and continued to its Extension 2<sup>[23,24]</sup>. Starting from the Extension 1, there were 63231 participants who had the assessments of AD status using a self-administered survey instrument. In the analysis, we used the recently available ended-follow-up data through March 1, 2019. This study was reviewed and approved by Drexel University Institutional Review Board and data was obtained from the U.S. National Heart, Lung, and Blood Institute (NHLBI) Biologic Specimen and Data Repository. In the analysis, of 63231 participants, 36 with prevalent AD and 78 without information on DM or CMS were excluded. The final analysis sample size is 63117 in the report (listed in the rectangular box of **Figure 1**).

### *Measures of outcomes and comorbid conditions*

In the WHIOS, AD and chronic conditions, including hypertension, hypercholesteremia, diabetes, heart attack, coronary heart disease, heart failure and AD were classified by self-administered standard survey instruments<sup>[23,24]</sup>. These chronic



**Figure 1 Study sample size and analysis framework.** Cox proportional hazards regression model:  $h(t)$  is the hazard function determined by a set of  $X_j$  covariates.

conditions were determined by the WHIOS participants' self-reported answers to questions "have you been diagnosed or treated because of the disease?" An answer "yes" was classified as having the disease. The survey assessment of incident AD started from WHIOS Extension 1 (2005) and ongoing. Annual survey self-administered questionnaires were mailed to the WHIOS participants' households to collect major health outcomes data through participants self-report or a family member or those who knew the study participants' health status. The assessment of AD was classified by a question that asked, "has a doctor told you for the first time that you have moderate or severe memory problems, for example, dementia or Alzheimer's?" Of the total classified incident AD cases, 40% were reported by the WHIOS participants (*i.e.*, self-report), 13% by a family member or friend of the WHIOS study participants, 2% by a healthcare provider of the WHIOS study participants, and 45% by any others who knew the participants' AD status. Duration (days) of follow-up for each participant was calculated from the participant's enrollment in the survey to the date of their first physician-diagnosis of AD or to the date of the end of the follow-up for those who had no AD or for those who ended the survey earlier due to any other reasons, whatever which came first<sup>[26]</sup>.

**Predictors**

Diabetes was determined by WHIOS participants' self-reported answer to, "have you been diagnosed or treated because of diabetes?" The answer "yes" was classified as having diabetes. In addition, subjects who had a blood sample with fasting glucose  $\geq 126$  mg/dL or those using glucose-lowering medication were also classified as DM. For CMS, there are several definitions<sup>[8,9,27,28]</sup>. We used the criteria proposed by the U.S. National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) with a minor modification by the American Heart Association (AHA), because this definition is most frequently used in the United States<sup>[28]</sup>. The AHA defines CMS as having  $\geq 3$  of the following five components: (1) Central adiposity (assessed by waist circumference  $> 88$  cm in women); (2) Elevated fasting blood triglyceride (TG  $\geq 150$  mg/dL); (3) Reduced blood high-density lipoprotein cholesterol (HDL-C  $< 50$  mg/dL in women); (4) Elevated blood pressure (systolic blood pressure  $\geq 130$  or diastolic blood pressure  $\geq 85$  mmHg) or those who are taking antihypertensive medications; and (5) Elevated blood fasting glucose ( $\geq 110$  mg/dL) or those who had self-reports of physician-diagnosis of pre-diabetes or who have glucose-lowering medication use. In the WHIOS participants with AD status assessments, blood TG, HDL-C and glucose were tested in a subsample of 4443 participants. To estimate the total prevalent CMS, we applied the WHIOS participants' self-reports of physician-diagnosis of hypercholesterolemia as a surrogate for the estimate of elevated TG among those who had no blood sample measures of TG<sup>[29,30]</sup>. Meanwhile, the WHIOS participants' self-reported angina was applied to serve as a surrogate for the estimate of reduced HDL-C for those who had no blood sample measures of HDL-C because there is a well-

established association between reduced HDL-C and angina risk<sup>[29]</sup>. This method of using a surrogate to estimate CMS has been applied and accepted by several large-scale observational population-based studies<sup>[9,29,30]</sup>.

### Covariates

Covariates included participants' age (years), race/ethnicity (self-reported, White, African American, the other race/ethnicity group), current marital status (never or separated, widowed, or married), educational attainments (grouped as  $\leq$  high school,  $>$  higher school or completed associate degree, and  $\geq$  college), average annual family income (grouped as  $<$  35000, 35000-49999, 50000-74999, and  $\geq$  75000 US \$/year), health insurance status (including Medicare and pre-paid private health insurance), hormone therapy use (yes/no), smoking (defined as never, former (irrespective of the time since quitting) and current)), and self-reported physician-diagnosis of chronic conditions (myocardial infarction, stroke and peripheral artery disease).

### Statistical analyses

To test the study hypothesis, we conducted a serial analysis. In the first analysis, baseline characteristics of participants were described by DM and CMS status. Differences in demographic characteristics, socioeconomic status, smoking, and medical history of chronic conditions by DM and CMS status were tested using Student *t*-tests for continuous variables, and Chi-square tests for categorical variables. In the second analysis, the incidence rates of AD per 1000 person-years of follow-up, and 95% confidence intervals (95%CI) of the incidence rates, were estimated using SAS Proc GEMOND. Differences in incident AD rates between participants with DM or with CMS and those without DM or without CMS were tested using Wald Chi-square tests<sup>[31,32]</sup>. In the third analysis, multivariate-adjusted Cox's proportional hazards (PH) regression was applied to estimate the associations of DM and CMS with the risk of AD. Cox's PH assumption were tested by using Kaplan-Meier curves [*i.e.*, assessed by the graph of the  $\log(-\log(\text{survival}))$  vs  $\log$  of survival time], and including time dependent covariates in the Cox models<sup>[33,34]</sup>. Hazard ratios (HRs) and their 95%CI of DM and CMS associated with the risk of incident AD were estimated in three multivariate-adjusted models for key covariates because these covariates are strongly correlated with both the study exposures and the outcomes. Model 1 adjusted for age, race/ethnicity, and marital status. Model 2 adjusted for covariates that were included in Model 1 plus education, family income, health insurance, smoking, and history of hormone therapy use. Model 3 adjusted for covariates that were included in Model 2 plus medical history of myocardial infarction, stroke, and peripheral arterial disease.

To test whether there are modifying effects of age differences on the associations of DM and CMS with risks of AD, stratification analyses were performed by three 10-year age groups (50-59, 60-69, and 70-79). Interaction effects between age stratum (the 3 10-year groups), DM and CMS (age  $\times$  DM and age  $\times$  CMS) on the risk of AD were examined based on a 1-degree-of-freedom test using maximum likelihood estimates using the total combined sample dataset. The analysis framework is shown in **Figure 1**.

**Sensitivity analysis:** We performed sensitivity analyses to take into consideration the accuracy of the assessment of AD by repeating the analysis separately for the data sources who completed the self-administered survey questionnaire: (1) For those who completed the survey questionnaire themselves, (2) For those with surveys completed by a family member or a friend of the WHIOS study participants, (3) For those with surveys completed by a health care provider for the WHIOS study participants, and (4) For those with surveys completed by others who knew the participant's health conditions. Of them, groups 2 and 3 had relatively small number of AD reports.

All statistical analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC 2018). A two-sided *P* value  $\leq$  0.05 was considered statistically significant.

## RESULTS

### Baseline characteristics of participants

Of 63117 participants, **Table 1** shows that participants with DM ( $n = 7255$ ) had a significantly higher mean age than those without DM ( $n = 55862$ ), (ages 63.2 vs 62.8 years old,  $P < 0.001$ ). African Americans had the highest prevalence of DM (24.4%) followed by the "other" race/ethnicity group (16.5%) and White (10.3%) ( $P < 0.001$ ). Married participants, those who had educational attainments of college or higher, or those who had the highest family average incomes had the lowest prevalence of DM

**Table 1** Baseline characteristics of participants by diabetes mellitus status

	By DM status				P value
	Non-DM		DM		
	n	mean, %	n	mean, %	
Age, mean (SD), yr	55862	62.9 (7.2)	7255	63.2 (7.0)	< 0.001
Age group, No., %					< 0.001
50-59	19398	89.4	2295	10.6	
60-69	25068	87.9	3467	12.2	
70-79	11396	88.4	1493	11.6	
Race/ethnicity, No., %					< 0.001
White	49927	89.7	5745	10.3	
Africa American	2706	75.7	871	24.4	
Others	3229	83.5	639	16.5	
Marital status <sup>1</sup> , No., %					< 0.001
Never or separated	10645	87.1	1579	12.9	
Widowed	8139	86.3	1296	13.7	
Presently married	36869	89.5	4341	10.5	
Education level <sup>2</sup> , No., %					< 0.001
≤ High School	9484	84.7	1707	15.3	
> HS and Associate	19398	87.1	2873	12.9	
≥ College	26589	91.1	2608	8.9	
Annual family income (US\$), No., %					< 0.001
< 35000	17099	84.8	3073	15.2	
35000-49999	10809	88.5	1401	11.5	
50000-74999	11685	89.9	1306	10.1	
≥ 75000	12902	92.4	1055	7.6	
Medicare, No., %					< 0.001
No	35403	88.9	4402	11.1	
Yes	20034	87.8	2787	12.2	
Pre-paid private insurance, No., %					0.13
No	32403	88.4	4269	11.6	
Yes	23034	88.7	2920	11.3	
Hormone usage status, No., %					< 0.001
Never used	20552	86.6	3180	13.4	
Past user	7901	87.7	1104	12.3	
Current user	27368	90.2	2963	9.8	
Smoking status, No., %					0.46
Never	28078	88.6	3609	11.4	
Past	24222	88.5	3140	11.5	
Current	2908	87.9	401	12.1	
Medical history, No., %					
Hypertension	20494	81.8	4566	18.2	< 0.001
Myocardial infarction	1746	78.9	467	21.1	< 0.001

Angina	1080	79.1	285	20.9	< 0.001
Stroke	1802	81.1	421	18.9	< 0.001
Peripheral artery disease	766	75.6	247	24.4	< 0.001

<sup>1</sup>Never/separated includes divorced; presently married includes marriage-like relationship.

<sup>2</sup>Associate: Included vocational or training school, some college or associate degree. DM: Diabetes mellitus; SD: Standard deviation.

compared to their counterparts ( $P < 0.001$ ). Participants with Medicare (a federal health insurance program for adults aged 65 and older in the United States) had higher prevalence of DM than those without Medicare (12.2% *vs* 11.1%,  $P < 0.001$ ). Women with current hormone therapy use had the lowest prevalence of DM compared to those who never used or used before. Participants with hypertension, myocardial infarction, angina, stroke or peripheral artery disease had significantly higher prevalence of DM than those without these conditions. Similar to DM, there were significant differences in mean age and the other factors between participants with CMS and those without CMS (Table 2).

### Incidence of Alzheimer's disease

With a median follow-up of 20 years, of 63117 participants who had no AD at baseline, 8340 women reported that they had incident AD. The cumulative incidence rate (95% CI) of AD was 8.5 (8.0-9.0) per 1000 person-years in participants with DM and 7.1 (6.9-7.2) per 1000 person-years in those without DM ( $P < 0.001$ ). Similar to DM, women with CMS had significantly higher incidence rates of AD (8.6 per 1000 person-years, 95% CI: 8.1-9.1) than those without CMS (7.0 per 1000 person-years, 95% CI: 6.9-7.2),  $P < 0.001$ .

The cumulative incidence rates (95% CI) of AD were 2.7 (2.5-2.9), 8.1 (7.8-8.3), and 14.5 (14.0-15.0) per 1000 person-years among women ages 50-59, 60-69, and 70-79 respectively (age differences in AD rates,  $P < 0.001$ ).

### Multivariate-adjusted Cox regression analyses

Figure 2 shows that DM was significantly associated with risk of AD. After adjusting for all the study covariates, Model 3 indicates that women with DM had 22% higher risk of AD than those without DM. The hazard ratio (95% CI) was 1.22 (1.13-1.31,  $P < 0.001$ ). Women aged 50-59 at baseline had the largest hazard ratio (HR) of DM *vs* absence of DM for AD (HR = 1.52, 95% CI: 1.27-1.82,  $P < 0.001$ ), followed by 1.26 (1.14-1.39,  $P < 0.001$ ) and 1.04 (0.92-1.19,  $P = 0.53$ ) in those aged 60-69 and 70-79. Women with CMS had 18% higher risk of AD than those without CMS, with corresponding HR (95% CI) of 1.18 (1.09-1.27,  $P < 0.001$ ). Of five CMS components, Model 3 indicates that high BP (HR = 1.07, 95% CI: 1.02-1.13,  $P = 0.004$ ), elevated TG (1.14, 1.07-1.21,  $P < 0.001$ ), and elevated glucose concentrations (1.21, 1.13-1.30,  $P < 0.001$ ) were significantly associated with increased risks of AD. Similar to DM, the relative risk of CMS *vs* absence of CMS for AD were greater in the younger age groups than that in the older. No significant association between CMS and AD risk was observed in the oldest age group (ages 70-79), with HR (95% CI) of 1.00 (0.87-1.14,  $P = 0.97$ ). No significant interaction effects of age with DM, and age with CMS on the risk of AD were observed.

Figure 3 shows that overall increase in age was significantly associated with an increased incidence rate of AD in individuals with or without DM. Individuals with diabetes had significantly higher relative risk (*i.e.*, hazards) of AD in those aged 50-59 and 60-69 as compared to their corresponding counterparts without diabetes (Figure 3A). The incidence rates (95% CI) of AD for DM *vs* non-DM individuals were 4.3 (3.7-4.8) *vs* 2.5 (2.4-2.8) per 1000 person-years,  $P < 0.001$  in those aged 50-59, and 9.3 (8.6-10.1) *vs* 7.9 (7.7-8.2) per 1000 person-years,  $P < 0.001$  in those aged 60-69. This difference in AD by DM status was not significant among those aged 70-79 [14.4 (12.9-16.0) *vs* 14.5 (13.9-15.0) per 1000 person-years,  $P = 0.88$ , Figure 3B]. Similar to DM, the relative risks of those with CMS *vs* non-CMS for incident AD were higher among the younger age groups (data not shown).

### Sensitivity analysis

Supplementary Table 1 shows that the HRs (95% CI) remained statistically significant for those who completed the survey instrument on AD conditions by themselves (HR = 1.33, 95% CI: 1.19-1.49,  $P < 0.001$ , Model 3) and those whose AD status was reported

**Table 2** Baseline characteristics of participants by cardiometabolic syndrome status

	By CMS status				P value
	Non-CMS		CMS		
	n	mean, %	n	mean, %	
Age, mean (SD), yr	55485	62.8 (7.2)	7632	63.7 (6.9)	< 0.001
Age group, No., %					< 0.001
50-59	19522	90.0	2171	10.0	
60-69	24771	86.8	3764	13.2	
70-79	11192	86.8	1697	13.2	
Race/ethnicity, No., %					< 0.001
White	50415	90.6	5257	9.4	
Africa American	1996	55.8	1581	44.2	
Others	3074	79.5	794	20.5	
Marital status <sup>1</sup> , No., %					< 0.001
Never or separated	10472	85.7	1752	14.3	
Widowed	7946	84.2	1489	15.8	
Presently married	36852	89.4	4358	10.6	
Education level <sup>2</sup> , No., %					< 0.001
≤ High School	9207	82.3	1984	17.7	
> HS and Associate	19253	86.4	3018	13.6	
≥ College	26641	91.2	2556	8.8	
Annual family income (US\$), No., %					< 0.001
< 35000	16660	82.6	3512	17.4	
35000-49999	10710	87.7	1500	12.3	
50000-74999	11734	90.3	1257	9.7	
≥ 75000	13056	93.5	901	6.5	
Medicare, No., %					< 0.001
No	35329	88.8	4476	11.2	
Yes	19741	86.5	3080	13.5	
Pre-paid private insurance, No., %					0.084
No	32178	87.7	4494	12.3	
Yes	22892	88.2	3062	11.8	
Hormone usage status, No., %					< 0.001
Never used	20136	84.8	3596	15.2	
Past user	7802	86.6	1203	13.4	
Current user	27502	90.7	2829	9.3	
Smoking status, No., %					0.027
Never	27885	88.0	3802	12.0	
Past	24092	88.0	3270	12.0	
Current	2861	86.5	448	13.5	
Medical history, No., %					
Diabetes	2740	37.8	4515	62.2	< 0.001
Hypertension	18928	75.5	6142	24.5	< 0.001

Myocardial infarction	1695	76.6	518	23.4	< 0.001
Angina	629	46.1	736	53.9	< 0.001
Stroke	1758	79.1	465	20.9	< 0.001
Peripheral artery disease	721	71.2	292	28.8	< 0.001

<sup>1</sup>Never/separated includes divorced; presently married includes marriage-like relationship.

<sup>2</sup>Associate: included vocational or training school, some college or associate degree. CMS: Cardiometabolic syndrome; SD: Standard deviation.

	Model 1		Model 2		Model 3	
	HR (95%CI)	P value	HR (95%CI)	P value	HR (95%CI)	P value
<b>Diabetes</b>						
Yes <i>vs</i> no	1.26 (1.18-1.34)	< 0.001	1.22 (1.14-1.31)	< 0.001	1.22 (1.13-1.31)	< 0.001
Stratification by age <sup>a</sup>						
50-59						
DM (yes <i>vs</i> no)	1.74 (1.48-2.04)	< 0.001	1.58 (1.33-1.87)	< 0.001	1.52 (1.27-1.82)	< 0.001
60-69						
DM (yes <i>vs</i> no)	1.28 (1.17-1.39)	< 0.001	1.28 (1.16-1.40)	< 0.001	1.26 (1.14-1.39)	< 0.001
70-79						
DM (yes <i>vs</i> no)	1.06 (0.95-1.19)	0.30	1.03 (0.91-1.16)	0.66	1.04 (0.92-1.19)	0.53
<b>CMS</b>						
Yes <i>vs</i> no	1.26 (1.18-1.34)	< 0.001	1.22 (1.14-1.30)	< 0.001	1.18 (1.09-1.27)	< 0.001
CMS components						
Large WC (yes <i>vs</i> no)	1.12 (1.07-1.17)	< 0.001	1.08 (1.03-1.14)	0.001	1.05 (0.99-1.10)	0.09
HBP (yes <i>vs</i> no)	1.15 (1.10-1.20)	< 0.001	1.10 (1.05-1.15)	< 0.001	1.07 (1.02-1.13)	0.004
Elevated TG	1.16 (1.10-1.23)	< 0.001	1.14 (1.08-1.21)	< 0.001	1.14 (1.07-1.21)	< 0.001
Elevated glucose	1.25 (1.17-1.33)	< 0.001	1.21 (1.14-1.30)	< 0.001	1.21 (1.13-1.30)	< 0.001
Low HDL	1.23 (1.11-1.36)	< 0.001	1.18 (1.06-1.31)	0.003	1.10 (0.92-1.33)	0.30
Stratification by age <sup>a</sup>						
50-59						
CM (yes <i>vs</i> no)	1.06 (0.95-1.19)	0.30	1.48 (1.23-1.78)	< 0.001	1.37 (1.12-1.68)	0.003
60-69						
CM (yes <i>vs</i> no)	1.26 (1.18-1.34)	< 0.001	1.32 (1.20-1.44)	< 0.001	1.26 (1.14-1.40)	< 0.001
70-79						
CM (yes <i>vs</i> no)	1.04 (0.93-1.17)	0.47	1.01 (0.90-1.14)	0.89	1.00 (0.87-1.14)	0.97

Model 1: Adjusted for age, race/ethnicity and marital status.

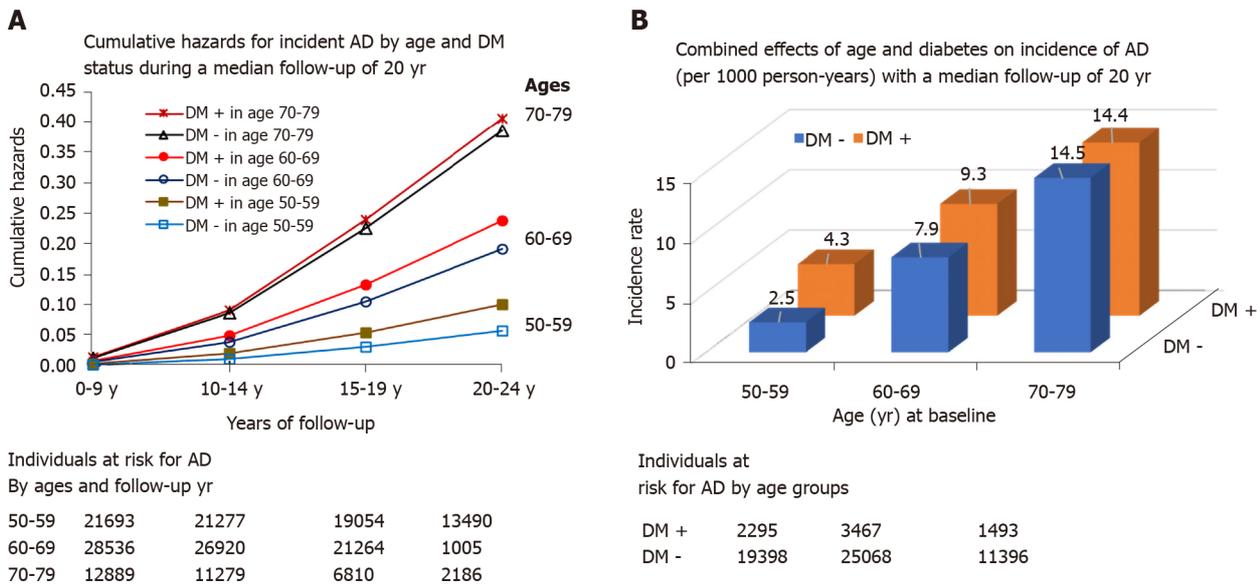
Model 2: Adjusted for Model 1 plus Medicare, pre-paid private insurance, education, income, smoking status, and hormone therapy use.

Model 3: Adjusted for Model 2 plus medical history of myocardial infarction, stroke and peripheral artery disease.

<sup>a</sup>: Age was not adjusted in the age stratification analysis.

**Figure 2 Hazard ratios (95% confidence interval) of diabetes, cardiometabolic syndrome and individual cardiometabolic syndrome components associated with incident Alzheimer's disease.** HR: Hazard ratio; CI: Confidence interval; CMS: Cardiometabolic syndrome; DM: Diabetes mellitus; TG: Triglyceride; HDL: High-density lipoprotein.

by others (1.14, 1.02-1.28,  $P = 0.022$ ). Similar to DM, subjects with CMS had a significantly increased risk of AD among these two subgroups (Model 3). The corresponding HRs (95%CI) are 1.19 (1.05-1.34,  $P = 0.006$ ) and 1.19 (1.07-1.34,  $P = 0.002$ ). However, the associations were statistically non-significant among the other two subgroups who completed the survey questionnaire on behalf of the study participants. The corresponding HRs (95%CI) of DM associated with AD are 1.14 (0.93-1.39,  $P = 0.20$ ) and 1.57 (0.96-2.56,  $P = 0.07$ ) among those whose survey questionnaires were answered by a family member or friend, or a healthcare provider. The corresponding HRs (95%CI) of CMS associated with AD are 1.09 (0.89-1.33,  $P = 0.41$ ) and 1.36 (0.82-2.27,  $P = 0.24$ ) in the two subgroups. It should be noted that restricting to these subgroups greatly decreased the available sample size for these analyses. The resulting estimated HRs had wider 95%CI's, suggesting that further studies with increased sample sizes are needed (Supplementary Table 1).



**Figure 3** Increase in age was significantly associated with the risk of Alzheimer's disease in subjects with or without diabetes mellitus. A and B: Cumulative hazards for incident Alzheimer's disease by age and DM status during the follow-up (A) and combined effects of age and diabetes on incidence rates of Alzheimer's disease (B).

## DISCUSSION

To the best of our knowledge, this study is one of the first reports on the association of DM and CMS with AD risk among postmenopausal women. The main findings indicate that with a median follow-up of 20-years, postmenopausal women aged 50-79 with DM or CMS had an overall significantly higher incidence rate of AD than their corresponding counterparts in the total study participants. Although the absolute risk of AD increased with age, the relative risks of AD with DM or CMS among younger women aged 50-69 with DM or CMS *vs* those without DM or CMS were much stronger than the relative risk of AD among older women aged 70-79.

AD is an irreversible and progressive brain disorder that slowly destroys memory and thinking skills, and eventually the ability to carry out the simplest tasks. Therefore, early prevention of this disease becomes important if any preventable risk factors prior to the development of AD can be identified. In recent decades a rapidly increasing number of studies have examined the association of diabetes, obesity, hypertension, dyslipidemia and dysglycemia with risk of cognitive impairment and AD<sup>[20]</sup>. For example, the Rotterdam study observed a significant association of diabetes *vs* non-DM with AD risk (relative risk, RR = 1.9, 95%CI: 1.2-3.1) in a prospective population-based cohort study of 6,370 adults aged 55 and older during an average of 2.1 years of follow-up<sup>[16,35]</sup>. Findings from the Rochester study, a prospective cohort study of 1455 subjects aged 20 and older, indicated a significant association between adult onset diabetes and risk of AD in men (relative risk: 2.27, 95%CI: 1.55-3.31), and a positive but nonsignificant association among women (RR = 1.37, 95%CI: 0.94-2.01)<sup>[36]</sup>. Findings from the Canadian Study of Health and Aging (CSHA) in participants (*n* = 5574) aged 65 and over in a 5-year follow-up indicate that the relative risk of DM *vs* non-DM for incident AD was 1.30 (0.83-2.03) in their combined sample of both genders (results are not presented by gender in their report)<sup>[16]</sup>. Our results are in general consistent with these previous reports, with a 22% higher risk of AD in those with DM *vs* those without DM in women aged 50 and older (HR = 1.22, 95%: 1.13-1.31, *P* < 0.001). Our study extends the previous studies by using a larger sample size and addressing AD risk by age groups. Of individual CMS components, findings from Nägga *et al*<sup>[21]</sup> study indicate a significant association between increased midlife triglycerides and risk of beta-amyloid (A $\beta$ ) and tau pathology. Several review articles have also examined the associations of CMS and diabetes with the development of AD<sup>[20,37,38]</sup>. However, studies on the development of AD were limited. Data from the WHIOS fills the gap to assess the metabolic disorders and risk of AD among postmenopausal women. Findings of this study contribute evidence to the body of literature by demonstrating a significant association of DM and CMS with AD. Given the potentially preventable risk of DM and CMS, we expect that the risk of AD can be reduced if we focus on the control and prevention of DM and CMS as early as

possible.

Although the mechanisms by which DM or CMS play a role in the development of AD remain poorly understood, some possible pathways have been proposed. Of these, insulin resistance, an impaired response of the body to insulin resulting in elevated levels of glucose in the blood, has been proposed to be an important cause of DM and its relationship to the development of AD, because severe neuropathological changes are common to diabetes and AD. For example, hyperglycemia in patients with DM can result in glycosylation of various receptors, leading to the formation of “receptors for advanced glycation end products” (RAGE). An affinity between RAGE and beta-amyloid (A $\beta$ ) peptides can trigger and propagate chronic brain inflammation<sup>[39]</sup>. Dyslipidemia and hypertension are also proposed as important risk factors associated with risk of AD. In a longitudinal study of 318 elderly individuals with normal cognition, the investigators found that higher fasting triglyceride levels in midlife were associated with increased risk of brain A $\beta$  and tau pathology 20 years later. This association was independent of age, sex, APOE  $\epsilon$ 4, and vascular risk factors<sup>[21]</sup>. The potential pathophysiologic effect of triglycerides on A $\beta$  pathology remains under study. In transgenic AD mouse models blood triglyceride concentrations have been shown to increase prior to A $\beta$  deposition, indicating a direct association between triglycerides and A $\beta$  homeostasis<sup>[40]</sup>. Lipids may influence membrane fluidity, which could directly affect secretase-mediated A $\beta$ <sup>[41]</sup>. In a meta-analysis of 18 prospective studies examining the relationship of total cholesterol with risk for AD and vascular dementia, midlife total cholesterol levels were consistently associated with an increased risk of AD and all dementia, whereas no increased risk was observed for late-life total cholesterol<sup>[42]</sup>. In our study, significant associations of central adiposity (assessed by large waist circumference) and low HDL-C with AD were observed after adjustment for age, race/ethnicity, marital status, insurance, education, family income, smoking and hormone therapy use (Models 1 and 2 of [Figure 2](#)). The associations of large WC and low HDL-C with risk of AD became nonsignificant after a further adjustment by including myocardial infarction (MI), stroke and peripheral arterial disease (PAD) (Model 3 of [Figure 2](#)). These attenuated associations in model 3 are possibly attributable to an over-adjustment because these cardiovascular conditions are likely on the pathway of the development of AD (large WC and dyslipidemia – cardiovascular diseases – AD). Several studies have indicated that MI, stroke, and PAD predict the risk of cognitive impairment and AD<sup>[43-46]</sup>. The association between hypertension and AD is complex and may involve direct and indirect effects with other risk factors, such as the fact that hypertension increases risk of arterial stiffness, A $\beta$  accumulation, and has interaction effect with insulin resistance<sup>[42,47,48]</sup>. Increased ages are significantly associated with increased risks of AD. However, it should be noted that in our study the relative risks (*i.e.*, HRs) of AD in younger women aged 50-69 with DM or CMS *vs* those without DM or CMS were higher compared to the relative risks of AD in older adults aged 70-79 without DM or CMS *vs* those without DM or CMS. The relative risks of DM and CMS *vs* those without DM or CMS for AD became nonsignificant in the older age group. Similar nonsignificant associations between those with and those without DM among the elderly were reported from previous studies as well<sup>[21,49]</sup>. The potential mechanisms are unclear. One of the explanations is that this nonsignificance in the older age group is possibly attributable to survivor bias. Individuals aged 70-79 may have better healthy conditions than those who died before their ages 70-79. The relative effect of DM or CMS on AD risk may become weaker in the older age group. Meanwhile, individuals aged 70-79 have a higher proportion of comorbidities, such as stroke and hypertension than the younger. Other, currently-unknown, age-related causes of AD may become more important in older age groups as well. Therefore, DM may have a relatively smaller impact on AD risk in the older patients. Further studies among the older age groups are warranted.

That there are several limitations when interpreting the results. First, the WHIOS included only women who were postmenopausal, which limits the generalizability to women earlier in their life cycle. Second, the classification of AD was based on a self-administered survey questionnaire. We had no access to more definitive measures such as imaging of brain structures (*i.e.*, magnetic resonance imaging and computerized tomography) or measures of the burden of amyloid deposits, and of neurofibrillary tangles in brain (such as Amyloid PET and Tau Pet imaging). Although it is common to define a disease status using a pre-designed self-administered questionnaire in most large-scale observational epidemiological studies, possible information bias may have occurred, which may lead to under- or over-estimate of the incidence of AD. In addition, based on the survey instrument on the question on AD, we thought that the classification of AD in the analysis might have included these with

AD or AD related dementia. In our sensitivity analysis, we tested DM-AD and CMS-AD associations separately for subgroups based on who completed the self-administered questionnaire. It shows that AD reported by a family member or friend or a healthcare provider of the study participant had nonsignificant associations with DM and CMS. However, this subsample analysis is questionable by their much smaller sample sizes (AD cases) reported by these two groups, which is also demonstrated by their wide 95% confidence intervals. Certainly, given the limitation that using a self-administered instrument is subject to bias, findings from this study call for further studies with detailed clinical measures and evaluations. Third, in the analysis, CMS was included for the purpose of examining the associations of CMS and its components with risk of AD. We had to estimate missing values of TG and HDL using their corresponding surrogates. These estimations may lead to under- or overestimate of their true values, which would introduce bias. Nevertheless, as consistent findings of CMS and DM were observed in the study and compared with the others, we would say that the bias due to the estimated approach is minimized. Finally, residual confounding cannot be completely eliminated from epidemiological studies, which could be attributable to the factors that the survey did not include.

Our study also has several strengths. First, the WHIOS is one of the largest observational prospective study among postmenopausal women. With an increase in life expectancy in the nation and worldwide, findings from the study add important evidence to the research literature. Second, of all reported studies related to DM and AD risk, the WHIOS has the longest duration of follow-up, which offers an unique opportunity to test the long-term effect of DM and CMS on the risk of AD. Third, a significantly higher relative risk of AD in younger women with DM or CMS *vs* those without DM or CMS than that in the older age group not only calls for further etiological studies, but also adds evidence to the prevention of AD risk in younger adults with DM or CMS.

## CONCLUSION

During a median follow-up of 20 years, DM and CMS were significantly associated with the risk of AD among postmenopausal women. More specifically, women aged 50-69 with DM or CMS *vs* those without these conditions had significantly higher relative risks of AD than the relative risks of AD in those aged 70-79 with DM or CMS *vs* those without DM or CMS.

## ARTICLE HIGHLIGHTS

### **Research background**

In spite of an increase in the incidence and prevalence of diabetes mellitus (DM) and Alzheimer's disease (AD) in the aging population, limited attention has been paid to investigate their associations.

### **Research motivation**

To investigate the association of DM and cardiometabolic syndrome with risk of AD among the United States older adults.

### **Research objectives**

To examine the association of DM and cardiometabolic syndrome (CMS, a precursor to DM) with risk of incident AD among postmenopausal women.

### **Research methods**

Postmenopausal women aged 50-79 ( $n = 63117$ ) who participated in the U.S. Women's Health Initiative Observational Study (WHIOS), recruited in 1993-1998 without baseline AD and followed up through March 1, 2019 were analyzed. AD was classified by participants-reported history of doctor-diagnosis of first-listed AD. DM was defined by participant-report or serum glucose concentrations or those anti-diabetic medication use. CMS was defined as having  $\geq 3$  of five CMS components: large waist circumference, high blood pressure, elevated triglycerides, elevated glucose, and low high-density lipoprotein cholesterol. The associations of DM and CMS with AD were analyzed using Cox's proportional hazards regression analysis.

### Research results

Within a median follow-up of 20 years (range: 3.36 to 23.36 years), of 63117 participants, 8340 had incident AD. Women with DM had significantly higher incidence of AD [8.5, 95% confidence interval (CI): 8.0-9.0 per 1000 person-years (PY)] than those without DM (7.1, 95%CI: 6.9-7.2 per 1000 PY). Multivariate Cox's regression analysis indicates that women with DM or CMS had significantly higher risk of AD than those without DM or CMS. The corresponding hazard ratios [HR (95%CI)] were 1.22 (1.13-1.31,  $P < 0.001$ ) in subjects with DM, and 1.18 (1.09-1.27,  $P < 0.001$ ) in subjects with CMS. The HRs of AD in those with DM or MS *vs* those without DM or CMS diminished with age and became non-significant in the oldest age group.

### Research conclusions

Diabetes and cardiometabolic syndrome were significantly associated with risk of Alzheimer's disease.

### Research perspectives

Further studies are needed to investigate the mechanisms by which DM and CMS may cause the development of AD.

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