Alzheimer's
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Associations of metabolic heterogeneity of obesity with the risk of dementia in middle-aged adults: three prospective studies

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Abstract

Background The associations of different obesity and metabolic phenotypes during midlife with the risk of incident dementia remain unclear. This study aimed to investigate the associations between metabolic heterogeneity of obesity and long-term risk of dementia.

Methods We conducted prospective analyses from three cohorts, including the UK Biobank (UKB), Atherosclerosis Risk in Communities (ARIC) study, and Framingham Offspring Study (FOS). Eligible participants were those aged 45–65 years with valid assessments of body mass index (BMI) and metabolic status at the study baseline. Obesity was defined as a BMI of ≥ 30.0 kg/m^2, while metabolic abnormality was defined as meeting ≥ 2 of the National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATP III) criteria. Metabolic heterogeneity of obesity was evaluated based on obesity and metabolic phenotypes and grouped as metabolically normal non-obesity (MNNO), metabolically abnormal non-obesity (MANO), metabolically normal obesity (MNO), and metabolically abnormal obesity (MAO).

Results Included in this study were 295,823 participants aged 56.3 ± 5.9 years from the UKB, 12,547 participants aged 54.0 ± 5.7 years from the ARIC, and 2,004 participants aged 53.9 ± 5.9 years from the FOS. Over 4,348,208 person-years, a total of 6,190 participants (3,601 in the UKB, 2,405 in the ARIC, and 184 in the FOS) developed incident dementia. In the pooled analysis of three cohorts, metabolic abnormality was associated with a hazard ratio (HR) of 1.41 (95% confidence interval [CI]: 1.10–1.80) for dementia, while obesity was associated with an HR of 1.20 (1.03–1.41). Compared with MNNO, individuals with MANO and MAO had increased risks of dementia (pooled HR: 1.33, 95% CI: 1.04–1.71 for MANO and 1.48, 1.16–1.89 for MAO). However, there was no significant difference in the risk of dementia among MNO (pooled HR: 1.10, 95% CI: 0.98–1.24). In addition, participants who recovered from MANO to MNNO had a lower risk of dementia (pooled HR: 0.79, 95% CI: 0.64–0.97), as compared with stable MANO.

Conclusions Metabolic abnormality has a stronger association with dementia than obesity. Metabolically abnormal non-obesity and obesity, but not metabolically normal obesity, are associated with higher risks of incident dementia as compared with metabolically normal non-obesity. Recovering from an abnormal metabolic status to normal reduces the risk of dementia in populations without obesity. Our findings highlight the important role of metabolic

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status in the development of dementia and recommend the stratified management of obesity based on metabolic status.

Keywords Obesity, Metabolic status, Heterogeneity, Transition, Dementia

Introduction

Between 1990 and 2022, the prevalence of obesity increased from 8.8% to 18.5% in adult women and from 4.8% to 14.0% in adult men worldwide [1, 2]. Although obesity has been linked to adverse health effects [3], there exists considerable heterogeneity among individuals with obesity. Previous research has revealed that approximately one-third of obese individuals present normal metabolic profiles [4]. These individuals were classified as metabolically normal obesity (MNO), whereas the others as metabolically abnormal obesity (MAO) [5].

Epidemiological studies have explored the associations of metabolic diversity observed in obesity with frailty, diabetes, cardiovascular disease (CVD), and other adverse health outcomes [6–9]. However, only a few studies have examined the associations of obesity and metabolic phenotypes with dementia or Alzheimer's disease (AD), and the results remained inconclusive [10–13]. For example, findings from a prospective cohort study conducted within the Whitehall II suggested that MNO was associated with a higher risk of dementia [10], while other studies revealed inverse associations of MNO with all-cause dementia or AD [11–13]. Differences in study designs, population characteristics, and duration of follow-up may contribute to the inconsistency across studies. In addition, most studies in this area have focused on older adults [11–13], neglecting to fully acknowledge the associations between metabolic heterogeneity of obesity and dementia in middle-aged adults. Furthermore, metabolic status is inherently dynamic and changes over time [14, 15]. Consequently, the impact of transitions in metabolic status on the onset of dementia warrants further investigation.

To address these research gaps, our study evaluated the associations of metabolic heterogeneity of obesity with incident all-cause dementia among participants aged 45–65 years in three cohort studies [16–18], including the UK Biobank (UKB), the Atherosclerosis Risk in Communities (ARIC) study, and the Framingham Offspring Study (FOS). Further, we explored the role of metabolic status transitions on dementia risk.

Methods

Study participants

We included individual-level data from three prospective cohorts [16–18]. The UKB comprises data from a population-based cohort study that recruited more than 500,000 participants who attended 1 of the 22 assessment centers across the UK between 2006 and 2010 [16]. In 1987–1989, the prospective cohort ARIC recruited 15,792 participants from ARIC field centers in 4 US communities [17], with on-going follow-up for adjudicated dementia outcomes thereafter. The Framingham Heart Study is a community-based cohort study that commenced in 1948 [19]. In 1971, children of the original cohort and their spouses formed the Offspring (FOS) cohort and underwent continuous surveillance for dementia through 2018 [18]. All participants provided informed consent before data collection. The UKB received ethical approval from the National Health Service North West Multicenter Research Ethics Committee, the ARIC was approved by each site's (at Johns Hopkins University, Wake Forest University, University of Mississippi Medical Center, and University of Minnesota) institutional review board (IRB), and the FOS was approved by the Boston University Medical Center IRB.

In the current study, we included participants aged 45–65 years who attended the blood test at baseline survey. Participants were excluded if they lacked valid data on body mass index (BMI), had a BMI < 18.5 kg/m^2, or failed to identify their metabolic status. We then excluded participants with CVD (defined as a history of stroke, coronary heart disease, or heart failure) or dementia at baseline, or developed dementia in the first 2 years of follow-up, or without any information on dementia diagnosis during the follow-up period (Fig. 1 & Fig. S1). We reported findings according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline [20].

Definitions of obesity, metabolic syndrome criteria, and metabolic status

BMI was calculated as measured weight (in kilograms) divided by measured height (in meters) squared. According to the World Health Organization [21], participants were classified as non-obesity or obesity based on a BMI cutoff of 30 kg/m^2 (BMI < 30.0 kg/m^2 for non-obesity and BMI ≥ 30.0 kg/m^2 for obesity). We assessed metabolic status using the updated National Cholesterol Education Program-Adult Treatment Panel III criteria (NCEP-ATP III criteria) for metabolic syndrome (MetS) [22], which were the most frequently used criteria in prior investigations [10–13, 23, 24]. Participants who met ≥ 2 of the following 4 criteria were classified as metabolically

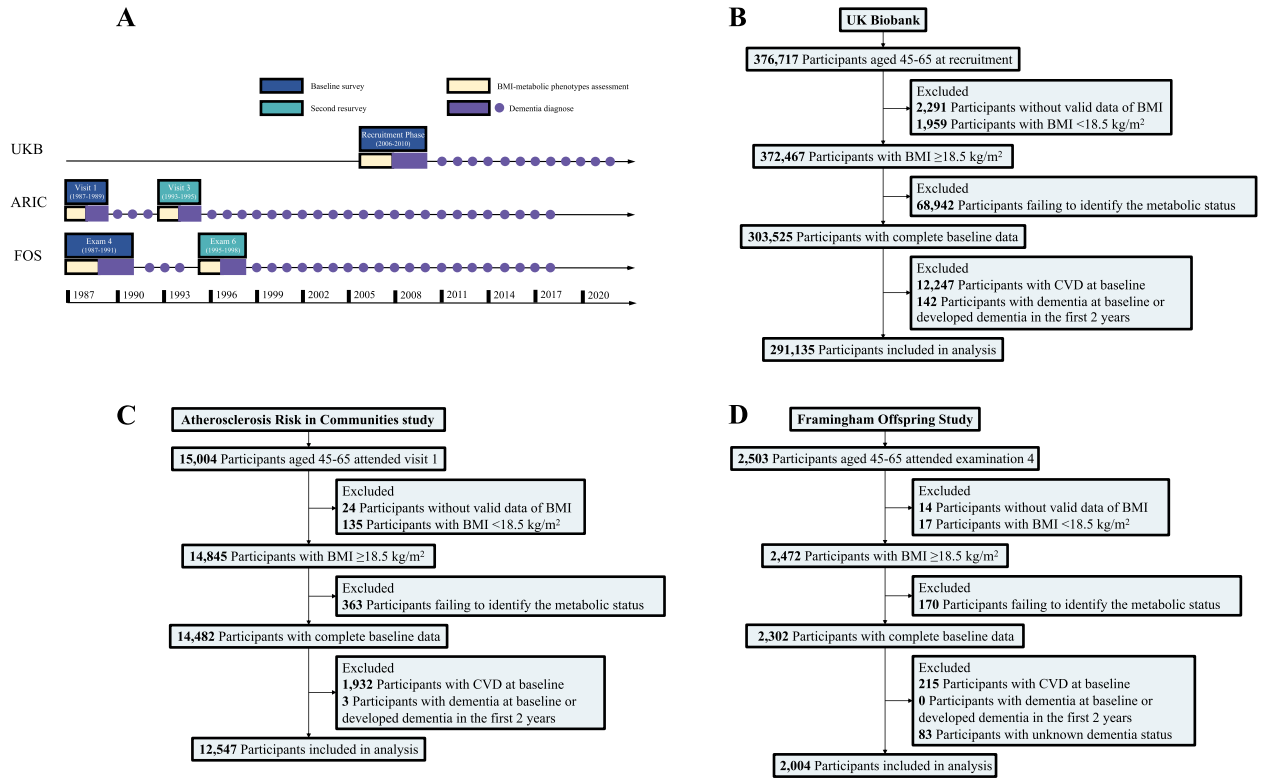

Fig. 1 The study baseline and follow-up scheme of three cohort studies (**A**), and participant inclusion flowchart for main analyses (**B-D**). Abbreviations: UKB, UK Biobank; ARIC, Atherosclerosis Risk in Communities; FOS, Framingham Offspring Study; BMI, body mass index; CVD, cardiovascular disease

abnormal: (1) elevated blood pressure, systolic blood pressure (SBP) ≥ 130 mmHg or diastolic blood pressure (DBP) ≥ 85 mmHg or on antihypertensive treatment; (2) impaired glycemic control, fasting blood glucose (FBG) ≥ 100 mg/dL [5.6 mmol/L] or on antidiabetic treatment; (3) elevated triglyceride (TG), TG ≥ 150 mg/dL[1.69 mmol/L] or use of lipid-modifying drugs; (4) reduced high-density lipoprotein cholesterol (HDL-C), men with HDL-C < 40 mg/dL [1.03 mmol/L] or women with HDL-C < 50 mg/dL [1.29 mmol/L] or use of lipid-modifying drugs. Data on circulating glucose levels in the UKB were obtained predominantly from non-fasting blood samples, which are more likely to be affected by recent food intake (compared to fasting samples), leading to high variability in glucose measurements. Therefore, we used glycated hemoglobin (HbA1c) as a proxy measure of glucose, based on the recommendations of the American Diabetes Association [25], with a cut point of HbA1c ≥ 32.4 mmol/mol (corresponds to a glucose value of 100 mg/dL) to represent impaired glycemic control.

Based on obesity and metabolic status, participants were divided into 4 BMI-metabolic phenotypes: metabolically normal non-obesity (MNNO), metabolically abnormal non-obesity (MANO), metabolically normal obesity (MNO), and metabolically abnormal obesity (MAO).

Ascertainment of dementia

The outcome was all-cause dementia, with varied criteria of diagnosis being applied in different cohorts. Briefly, the UKB ascertained dementia using linkage to health care systems [26]. In the ARIC, dementia was ascertained from in-person or telephone cognitive assessments, informant interviews, or hospitalization codes or death certificates [27]. In the FOS, dementia was ascertained by a team of clinicians led by a neurologist based on a structured medical history, neurologic examination, and a battery of several cognitive tests [28]. Details are described in Supplement Methods.

Covariates

Covariates consisted of sociodemographic and lifestyle factors, which were selected based on previous literature [1, 29, 30]. We used questionnaires completed at baseline to collect the information on age, sex (male or female), race and ethnicity (White or non-White),

education level (below college or college and above), area-based Townsend deprivation index (TDI, as quartiles, available in the UKB), household income (< 25,000, 25,000–49,999, and ≥ 50,000 US $/year, available in the ARIC and FOS), smoking status (current, former, or never smokers), and alcohol intake (units per week). The TDI score was used as a proxy for material socioeconomic deprivation and was assigned to each study participant using their residential postal code at baseline in the UKB [31].

Statistical analysis

The missing data of covariates were imputed using the multiple imputations with chained equation [32]. The missing rates of covariates were summarized in Supplement Table S1. For descriptive statistics, continuous variables were presented as mean (standard deviation, SD), and categorical variables as number (percentage). Multivariable Cox proportional hazard models using age as the time variable were performed to examine the associations of obesity, metabolic status, and metabolic heterogeneity of obesity with incident all-cause dementia. Survival time for each observation was calculated from the baseline of each cohort to the date of incident dementia, loss to follow-up, or the end of follow-up, whichever occurred first. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated with adjustments for sex, race, education level, TDI (only in the UKB), household income (only in the ARIC and FOS), smoking status, and alcohol intake. The proportional hazard assumption was tested and verified using Schoenfeld's residual methods, and the results showed no violation in the analyses. Using similar methods, we also examined the associations of metabolic status transitions with incident dementia in the ARIC and FOS. We chose the second resurvey (visit 3 in the ARIC and exam 6 in the FOS) for the transition analyses to ensure that a sufficient number of individuals had experienced a change in metabolic status. Participants were grouped according to all possible changes, and the survival time for each observation was calculated from date of the second resurvey. We analyzed each cohort separately and pooled the estimates from all cohorts using random-effects models [33].

We conducted several sensitivity analyses to test the robustness of our primary findings. First, we used MetS criteria [34] to define the metabolic status. Second, we excluded participants who developed dementia in the first 5 years of follow-up to further reduce reverse causation. Third, we excluded cases of dementia occurring < 65 years, as the mechanisms leading to early-onset dementia may be different from late-onset cases. Fourth, we restricted our analyses to only "White" participants due to potential variations in obesity thresholds among different ethnicities [21]; the sample size of non-White individuals was insufficient for additional evaluations in this subgroup. Fifth, considering the competing risk between mortality and incident dementia, we repeated the main analyses using the competing risk model [35]. Sixth, we repeated the main analyses by excluding participants with missing data on covariates to explore the influence of multiple imputations on these covariates. Seventh, we performed the transition analyses using data from the first resurvey (visit 2 in the ARIC and exam 5 in the FOS) to further investigate the associations of metabolic status transitions with incident dementia.

All statistical analyses were performed using R 4.3.0. All *P*-values were two-sided, and $P < 0.05$ was considered statistically significant.

Results

Baseline characteristics of the study population

A total of 295,823 participants (mean [SD] age, 56.3 [5.9] years; 163,675 female [55.3%]) from the UKB, 12,547 participants (mean [SD] age, 54.0 [5.7] years; 6,831 female [54.4%]) from the ARIC, and 2,004 participants (mean [SD] age, 53.9 [5.9] years; 1,056 female [52.7%]) from the FOS were included at the study baseline (Table 1). In three cohorts, individuals in the MAO subgroup had higher BMI, waist circumference, SBP, DBP, FBG, HbA1c, TG, and lower HDL-C (Supplement Tables S2-S4).

In the primary analyses, the median (interquartile range, IQR) follow-up periods were 13.9 (13.1, 14.6) years in the UKB, 26.0 (19.1, 30.0) years in the ARIC, and 23.5 (17.6, 27.8) years in the FOS. A total of 6,190 participants (3,601 from the UKB, 2,405 from the ARIC, and 184 from the FOS) developed incident all-cause dementia. In the analyses of metabolic status transition (median [IQR] follow-up duration: 21.9 [15.5, 24.1] years in the ARIC and 16.6 [11.9, 20.9] years in the FOS), 1,866 participants from the ARIC and 196 participants from the FOS developed dementia.

Associations of baseline obesity and metabolic status with incident dementia

In the multivariable-adjusted Cox proportional hazard model, metabolic abnormality was associated with a higher risk of incident dementia, with HRs of 1.19 (95% CI: 1.11–1.28) in the UKB, 1.36 (1.25–1.47) in the ARIC, and 1.93 (1.43–2.60) in the FOS (Fig. 2). However, significantly elevated risks of incident dementia for obesity compared with non-obesity were only found in the ARIC (HR: 1.08, 95% CI: 1.00–1.16 in the UKB; 1.33, 1.21–1.45 in the ARIC; 1.23, 0.87–1.74 in the FOS). Metabolic abnormality had a stronger association with dementia than obesity, but the difference was significant only for the UKB dataset (*P*-heterogeneity = 0.043 in the UKB;

Table 1 Baseline characteristics of participants in the UK Biobank, the Atherosclerosis Risk in Communities study, and the Framingham Offspring Study

Variable	UKB (*n* = 295,823)	ARIC (*n* = 12,547)	FOS (*n* = 2,004)
Age, y, mean (SD)	56.3 (5.9)	54.0 (5.7)	53.9 (5.9)
Female, No. (%)	163,675 (55.3)	6,831 (54.4)	1,056 (52.7)
White ethnicity, No. (%)	280,816 (95.0)	9,510 (75.8)	1,984 (99.0)
Tertiary education, No. (%)	98,528 (33.3)	5,747 (45.8)	1,204 (60.1)
TDI, No. (%)			
Quartile 1 (least deprived)	76,712 (25.9)	NA	NA
Quartile 2	74,883 (25.3)	NA	NA
Quartile 3	74,221 (25.1)	NA	NA
Quartile 4 (most deprived)	70,007 (23.7)	NA	NA
Household income, No. (%)			
< 25,000 $	NA	4,459 (35.5)	321 (16.0)
25,000–49,999 $	NA	4,782 (38.1)	1,002 (50.0)
≥ 50,000 $	NA	3,306 (26.3)	681 (34.0)
Smoking status, No. (%)			
Never smokers	30,919 (10.5)	5,332 (42.5)	677 (33.8)
Former smokers	100,541 (34.0)	4,021 (32.0)	871 (43.5)
Current smokers	164,363 (55.6)	3,194 (25.5)	456 (22.8)
Alcohol intake, units/week, mean (SD)	3.0 (3.3)	3.2 (7.1)	3.4 (5.0)
BMI, kg/m^2, mean (SD)	27.5 (4.8)	27.5 (5.1)	27.1 (4.6)
WC, cm, mean (SD)	90.2 (13.4)	96.6 (13.5)	90.2 (14.3)
SBP, mmHg, mean (SD)	139.7 (19.2)	120.8 (18.5)	128.4 (17.5)
DBP, mmHg, mean (SD)	82.8 (10.6)	73.6 (11.1)	80.1 (9.6)
HbA1c, mmol/mol, mean (SD)	36.1 (6.6)	NA	NA
FBG, mg/dL, mean (SD)	NA	105.6 (32.5)	96.4 (25.9)
TG, mg/dL, mean (SD)	155.9 (91.4)	129.6 (88.7)	129.5 (105.8)
HDL-C, mg/dL, mean (SD)	56.7 (14.8)	51.9 (17.0)	50.3 (15.4)

Abbreviations: *UKB* UK Biobank, *ARIC* Atherosclerosis Risk in Communities, *FOS* Framingham Offspring Study, *TDI* Townsend deprivation index, *BMI* Body mass index, *WC* Waist circumference, *SBP* Systolic blood pressure, *DBP* Diastolic blood pressure, *HbA1c* Glycated hemoglobin, *FBG* Fasting blood glucose, *TG* Triglyceride, *HDL-C* High-density lipoprotein cholesterol, *NA* Not applicable, *SD* Standard deviation

P-heterogeneity = 0.719 in the ARIC; *P*-heterogeneity = 0.054 in the FOS).

Associations of baseline BMI-metabolic phenotypes with incident dementia

Table 2 shows the associations of baseline BMI-metabolic phenotypes with the risk of dementia among three cohorts. Compared with MNNO, the risk of dementia was higher for individuals with MANO (pooled HR: 1.33, 95% CI: 1.04–1.71) and MAO (1.48, 1.16–1.89). However, MNO was not significantly related to the risk of incident all-cause dementia (1.10, 0.98–1.24). We also constructed Kaplan–Meier curves (Supplement Fig. S2) to compare the cumulative incidence of all-cause dementia across different BMI-metabolic phenotypes. The results showed that for individuals from three cohorts, participants with MAO had the highest incidence of dementia, and participants with MANO came second. On the contrary, no significant difference in the cumulative incidence of dementia was found between obese and non-obese groups with normal metabolic status. In the stratified analyses, similar results were observed in males and females (Supplement Tables S5). However, the associations of MANO and MAO with dementia were stronger in females in the UKB (*P*-interaction = 0.007 in the UKB, 0.715 in the ARIC, and 0.765 in the FOS).

Associations of changes in metabolic status with incident dementia

Since the metabolic status changed over time (Supplement Table S6), we estimated the effect of these changes on the incidence of dementia. Given the small number of individuals experienced weight changes after 4-6 years of follow-up in both cohorts, we investigated the associations of metabolic status transitions with

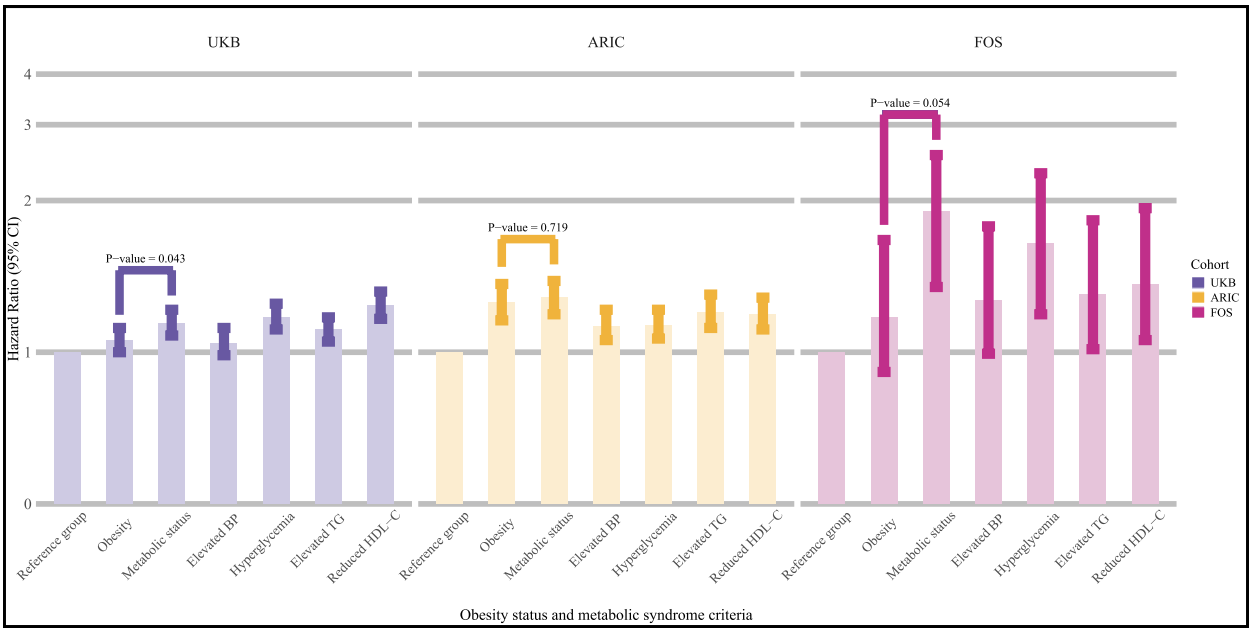

Fig. 2 Multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for incident dementia according to obesity status and metabolic syndrome criteria. Abbreviations: UKB, UK Biobank; ARIC, Atherosclerosis Risk in Communities; FOS, Framingham Offspring Study; BMI, body mass index; BP, blood pressure; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol. The Cox proportional hazard models using age as the time variable were adjusted for sex (male or female), race (White or non-White), education (below college or college and above), Townsend deprivation index (as quintiles, only in the UK Biobank), household income (< 25 000, 25 000–49,999, and ≥ 50,000 US $/year, only in the ARIC and FOS), smoking status (current, former, or never smokers), and alcohol intake (units per week)

dementia only in populations with consistent weight status between two waves. Table 3 shows the associations between changes in metabolic status and the risk of incident dementia. When compared with the stable normal metabolic status counterparts, participants who transitioned to abnormal metabolic status (MNNO to MANO and MNO to MAO) presented the accelerated progression of dementia, although they did not reach statistical significance in both cohorts. In contrast, a significantly decreased risk of incident dementia was observed in participants with non-obesity who recovered to normal metabolic status when compared with stable metabolically abnormal (pooled HR: 0.79, 95% CI: 0.64–0.97). Participants with MAO who recovered to MNO also presented a decreased risk of incident dementia, but did not reach statistical significance. For the intergroup comparisons (Supplement Table S7), when compared with the stable MNNO, participants with stable abnormal metabolic status (stable MANO and stable MAO) presented accelerated dementia development.

Table 2 Multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for incident dementia according to BMI-metabolic phenotypes

BMI-metabolic phenotypes	UKB		ARIC		FOS		Pooled[b]
	Cases/N	HR (95% CI)[a]	Cases/N	HR (95% CI)[a]	Cases/N	HR (95% CI)[a]	HR (95% CI)[a]
MNNO	1,056/121,593	1 (Reference)	944/5,631	1 (Reference)	67/994	1 (Reference)	1 (Reference)
MANO	1,572/101,671	**1.18 (1.09, 1.28)**	783/3,677	**1.21 (1.10, 1.33)**	74/573	**1.91 (1.36, 2.68)**	**1.33 (1.04, 1.71)**
MNO	154/16,941	1.04 (0.88, 1.24)	196/1,008	1.17 (0.99, 1.37)	8/146	1.00 (0.48, 2.09)	1.10 (0.98, 1.24)
MAO	819/55,618	**1.22 (1.11, 1.34)**	482/2,231	**1.58 (1.41, 1.77)**	35/291	**1.96 (1.29, 2.97)**	**1.48 (1.16, 1.89)**

Abbreviations: *ARIC* Atherosclerosis Risk in Communities, *FOS* Framingham Offspring Study, *BMI* Body mass index, *MNNO* Metabolically normal non-obesity, *MANO* Metabolically abnormal non-obesity, *MNO* Metabolically normal obesity, *MAO* Metabolically abnormal obesity

[a] The Cox proportional hazard models using age as the time variable were adjusted for sex (male or female), race (White or non-White), education (below college or college and above), Townsend deprivation index (as quintiles, only in the UK Biobank), household income (< 25 000, 25 000–49,999, and ≥ 50,000 US $/year, only in the ARIC and FOS), smoking status (current, former, or never smokers), and alcohol intake (units per week)

[b] Random-effects model was used; $I^2 = 0\%$ for the estimates from the three cohorts

Table 3 Multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for incident dementia according to intragroup comparisons of transitions of metabolic status

BMI-metabolic phenotype transitions		ARIC			FOS			Pooled[b]	
Baseline category	**Follow-up category**	**Cases/N**	**HR (95% CI)[a]**	***P*-value**	**Cases/N**	**HR (95% CI)[a]**	***P*-value**	**HR (95% CI)[a]**	***P*-value**
MNNO	**MNNO**	537/3,088	1 (Reference)		44/950	1 (Reference)		1 (Reference)	
	MANO	232/1,202	1.10 (0.94, 1.29)	0.216	28/373	1.14 (0.71, 1.85)	0.543	1.10 (0.95, 1.28)	0.197
MANO	**MANO**	479/2,032	1 (Reference)		69/463	1 (Reference)		1 (Reference)	
	MNNO	98/493	**0.79 (0.63, 0.98)**	**0.030**	12/87	0.79 (0.42, 1.45)	0.442	**0.79 (0.64, 0.97)**	**0.026**
MNO	**MNO**	85/390	1 (Reference)		1/72	1 (Reference)		1 (Reference)	
	MAO	76/391	0.92 (0.67, 1.25)	0.593	8/104	7.43 (0.93, 59.65)	0.059	2.01 (0.28, 14.56)	0.490
MAO	**MAO**	325/1,404	1 (Reference)		32/267	1 (Reference)		1 (Reference)	
	MNO	34/174	0.81 (0.57, 1.15)	0.231	2/26	1.79 (0.42, 7.56)	0.428	0.87 (0.56, 1.37)	0.553

Abbreviations: *UKB* UK Biobank, *ARIC* Atherosclerosis Risk in Communities, *FOS* Framingham Offspring Study, *BMI* Body mass index, *MNNO* Metabolically normal non-obesity, *MANO* Metabolically abnormal non-obesity, *MNO* Metabolically normal obesity, *MAO* Metabolically abnormal obesity

[a] The Cox proportional hazard models using age as the time variable were adjusted for sex (male or female), race (White or non-White), education (below college or college and above), household income (< 25 000, 25 000–49,999, and ≥ 50,000 US $/year), smoking status (current, former, or never smokers), and alcohol intake (units per week)

[b] Random-effects model was used; $I^2 = 0\%$ for the estimates from the two cohorts

Sensitivity analyses

Multiple sensitivity analyses demonstrated the robustness of our main findings regarding the associations of different BMI-metabolic phenotypes and changes in metabolic status with incident dementia. In analyses using MetS criteria to define the metabolic status, the associations were consistent with those using 4 criteria in NCEP-ATP III (Supplement Tables S8 & S9). Additional exclusion of incident dementia cases within the first 5 years of follow-up did not alter the observed associations (Supplement Tables S10 & S11). When we further excluded early-onset dementia cases, the associations did not substantially change (Supplement Tables S12 & S13). When restricted the analyses to only White participants, we observed similar associations (Supplement Tables S14 & S15). The results were consistent with the main analyses after conducting the competing risk analyses between mortality and dementia (Supplement Tables S16 & S17). When we excluded participants with missing data on covariates, the association of MANO with dementia was moderately attenuated, whereas that for MAO persisted (Supplement Table S18). When using data from the first resurvey (visit 2 in the ARIC and exam 5 in the FOS) for the transition analyses (Supplement Table S19), the association of recovery from MANO to MNNO was slightly attenuated (pooled HR: 0.75, 95% CI: 0.53–1.07), but the association of transition from MNO to MAO was stronger (pooled HR: 1.46, 95% CI: 1.08–1.97).

Discussion

In the current investigation of three cohort studies, we extend findings in previous publications exploring the associations of obesity and metabolic status with incident dementia. Our findings implicated that metabolic status had a stronger association with dementia than obesity. When compared with MNNO, MANO and MAO presented higher risks for incident dementia. However, we didn't observe evidence suggesting that the cumulative incidence of dementia in MNO group was different from MNNO. Moreover, participants with MANO who recovered to normal metabolic status showed a decreased risk of incident dementia when compared with their stable counterparts.

Previous studies showed that there were close associations of obesity and metabolic abnormality with incident dementia in middle-aged adults [23, 36–40]. A meta-analysis including 14 cohort studies found that compared to non-obesity, obesity was associated with approximately 31% higher risk of incident dementia in populations below the age of 65 years [40]. In terms of metabolic status, Qureshi et al. found a positive association between MetS and dementia in mid-life individuals [23]. In our study with three prospective cohorts, we observed consistent results for elevated risk of incident dementia in participants with obesity or abnormal metabolic status.

To date and to our knowledge, only a few cohort studies have examined the associations of metabolic

heterogeneity of obesity with incident dementia in middle-aged adults, with inconclusive findings [10, 11, 41]. In the Whitehall II (median follow-up = 20.8 years), MNO was associated with a substantially higher risk of incident dementia in individuals aged < 60 years (HR: 1.69, 95% CI: 1.16–2.45 compared with MNNO) [10]; while in another cohort study based on the National Health Insurance System of Korea (median follow-up = 5.4 years), an inverse association was observed between MNO and incident dementia (HR: 0.90, 95% CI: 0.87–0.93) [11]. Our observations in three well-characterized cohort studies suggested no significant difference in dementia risks between MNNO and MNO groups. Differences in population characteristics and methodologies for assessing obesity and metabolic status may contribute to the inconsistency across studies. For instance, the Whitehall II study primarily involved a male population [10], which was inconsistent with the three cohorts in the current study. Additionally, Wang and colleagues used blood pressure and blood-based biomarkers, including C-reactive protein (CRP), TG, low-density lipoprotein cholesterol (LDL-C), HDL-C, and HbA1c, to define metabolic status [41], which was different from the other studies [10–13]. In addition, variations in adjustments for confounding may contribute to the different associations observed across investigations. Furthermore, most previous studies were limited by small sample sizes or short-term follow-up, which may result in reverse causation induced by early physiological and biochemical changes resulting from preclinical dementia. Our study provided valuable information with relatively long-term follow-up, but future studies are still warranted to clarify the causal association between MNO and dementia.

The comparisons of the associations of obesity and abnormal metabolic status with dementia findings are novel. Participants with abnormal metabolic status had a higher HR for incident dementia than participants with higher BMI. In addition, individuals with MANO had a 33% higher risk of incident dementia, while MNO was not associated with dementia. Thus, our study provided additional evidence that metabolic abnormality had a greater impact on elevated dementia risk than obesity.

In addition to the baseline BMI-metabolic phenotypes, our study also investigated the associations of changes in metabolic status with incident dementia in populations with and without obesity, which were few examined previously [10, 13]. Machado-Fragua and colleagues constructed five trajectories to identify different transition patterns, but they failed to explore the associations of metabolic status transitions with dementia in individuals with obesity due to the absence of corresponding trajectories [10]. Cho et al. investigated the associations between BMI-metabolic phenotypes transitions and AD among participants aged > 60 years [13], which were different from current study populations. Therefore, our findings of the associations between changes in metabolic status and risk of incident dementia in middle-aged adults are unique. The findings suggested potential risks of accelerated dementia progression when metabolic status transitioned from normal to abnormal in both populations with and without obesity, although they did not reach statistical significance in the main analyses. In contrast, attenuated dementia development was observed in participants who transitioned from MANO to MNNO as compared with stable MANO.

Although the underlying biological mechanism remains unclear, insulin resistance, oxidation, and inflammation pathways could potentially explain the observed associations [42–45]. For example, both obesity and metabolic abnormality can increase the expression of proinflammatory cytokines [43, 44], which contribute to neurodegeneration and neurotoxicity, leading to the onset of dementia [46–48]. Compared with MAO group, individuals with MNO had lower oxidative stress, greater plasma adiponectin concentration, and lower skeletal muscle ceramide content. These factors may confer protection against the higher degree of insulin resistance observed in MAO group [45]. On the other hand, obesity is positively associated with the secretion of nerve growth factors, which might potentially protect against dementia by affecting the cholinergic system [49]. Consequently, the direction of the pooled effect of obesity remains uncertain, which might clarify the observations that a combination of abnormal metabolic conditions may have a greater influence on dementia development than obesity alone, and the risk of dementia for participants with MAO was higher than participants with MNO.

Our findings have several critical clinical and public health implications. First of all, our results suggested that metabolic abnormality plays a more significant role in dementia than obesity, indicating that individuals with abnormal metabolic status are crucial targets for dementia prevention. However, since obesity is a major contributor to abnormal metabolic status, a combination of effective weight management and maintaining a healthy metabolic status is essential for the prevention of dementia. Secondly, it is imperative to incorporate the assessment of metabolic status into standard clinical procedures. Individuals with MANO are frequently overlooked in health management due to their seemingly normal weight, while regular screening for metabolic status can facilitate the early identification of these at-risk individuals, enabling timely interventions that may decelerate the progression of dementia. In addition, given that abnormal metabolic status is reversible and individuals without obesity can decrease the risk of dementia by restoring normal

metabolic status, public health initiatives should focus on enhancing metabolic health education among middle-aged adults, promoting consistent metabolic screenings, and ensuring prompt interventions.

The strengths of the current study include long-term follow-up in population-based cohort studies, which enabled us to robustly investigate the associations of obesity, metabolic status, and metabolic heterogeneity of obesity with incident dementia. Since the continuum of dementia includes a long latent phase, our study offered valuable insights into the exploration of early risk factors for incident dementia. Notably, the observed associations remained consistent after excluding individuals who developed incident dementia within five years of follow-up, suggesting that our findings are not merely cross-sectional. Furthermore, this study included three prospective cohorts from different ethnicities, all with rigorous study designs and large sample sizes, which strengthens our findings. The consistency of results across these cohorts underscores the generalizability of our conclusions, and diverse sensitivity analyses further ensured the robustness of the results.

However, our findings should be interpreted with caution due to some limitations. First, we utilized HbA1c as a substitute for fasting glucose due to the limited number of fasting samples in the UKB, which differs from the other two cohorts. Nevertheless, the American Diabetes Association recommendations support using this metric as a reliable stand-in for glucose values [25]. Second, mild dementia may go undetected, potentially resulting in misclassification bias. Notably, previous studies showed acceptable positive predictive values for the defined dementia outcome in the UKB, ARIC, and FOS [26–28]. Third, as the cohort studies mainly consisted of a Western population, the generalizability of our findings to diverse cultural and ethnic backgrounds may be limited. Fourth, we were unable to investigate the associations of weight status transitions with the risk of dementia due to the insufficient number of participants who experienced weight changes across the two waves of data collection. Longitudinal studies of a larger scale are still warranted to construct a more complex transition model and clarify the causal associations between transitions in BMI-metabolic phenotypes and dementia. Finally, given the observational design of this study, residual confounding and other non-causal explanations should be considered.

Conclusions

In conclusion, this study provides evidence that metabolic abnormality has a stronger association with dementia than obesity. MANO and MAO, but not MNO, are associated with higher risks of incident dementia in middle-aged adults. Transitioning from abnormal metabolic status to normal decelerates the development of dementia in populations without obesity. These findings highlight the important role of metabolic status in the development of dementia and recommend the stratified management of obesity based on metabolic status.

Abbreviations

AD	Alzheimer's disease
ARIC	Atherosclerosis Risk in Communities
BMI	Body mass index
CI	Confidence interval
CRP	C-reactive protein
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
FBG	Fasting blood glucose
FOS	Framingham Offspring Study
HbA1c	Glycated hemoglobin
HDL-C	High-density lipoprotein cholesterol
HR	Hazard ratio
IQR	Interquartile range
IRB	Institutional Review Board
LDL-C	Low-density lipoprotein cholesterol
MANO	Metabolically abnormal non-obesity
MAO	Metabolically abnormal obesity
MetS	Metabolic syndrome
MNNO	Metabolically normal non-obesity
MNO	Metabolically normal obesity
NCEP-ATP III	National Cholesterol Education Program-Adult Treatment Panel III
SBP	Systolic blood pressure
SD	Standard deviation
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TDI	Townsend deprivation index
TG	Triglyceride
UKB	UK Biobank

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13195-024-01581-x.

Supplementary Material 1.

Acknowledgements

We thank all of the participating individuals and staff of the UK Biobank (UKB), the Atherosclerosis Risk in Communities (ARIC) study, and the Framingham Offspring Study (FOS) who made the study possible.

Authors' contributions

D.Z., C.Y., and Y.Z. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Y.D., Y.Z., and D.Z. designed and conceptualized the study, interpreted the findings, and drafted and revised the manuscript. Y.D. and T.G. performed data analysis and D.Z. validated the analyses. J.S. and M.D. revised the manuscript. All authors were involved in writing the paper and gave final approval for the submitted and published versions.

Funding

This work was supported by Fundamental Research Funds from the Central Universities of Zhejiang University and the National Natural Sciences Foundation of China (82204118). The funding agencies had no role in study design, data collection, analysis, decision to publish, or manuscript preparation.

Data Availability

Data are available on request for bone fide investigators from managing institutions of the three cohort studies: https://www.ukbiobank.ac.uk/enable-your-research/apply-for-access for the UKB, https://aric.cscc.unc.edu/aric9/

researchers/Obtain_Submit_Data for the ARIC, and https://www.framingham-heartstudy.org/fhs-for-researchers/ for the FOS.

Declarations

Ethics approval and consent to participate

This research was conducted using the UKB (application number 55005), the ARIC, and the FOS. All participants provided written informed consent for participation in the trial. The UKB received ethical approval from the National Health Service North West Multicenter Research Ethics Committee, the ARIC was approved by each site's (Johns Hopkins University, Wake Forest University, University of Mississippi Medical Center, and University of Minnesota) institutional review board (IRB), and the FOS was approved by the Boston University Medical Center IRB.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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Received: 5 July 2024 Accepted: 25 September 2024
Published online: 11 October 2024

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