Midlife lipid and glucose levels are associated with Alzheimer’s disease

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Abstract

Introduction: It is unknown whether vascular and metabolic diseases assessed in early adulthood are associated with Alzheimer’s disease (AD) later in life.

Methods: Association of AD with lipid fractions, glucose, blood pressure, body mass index (BMI), and smoking obtained prospectively from 4932 Framingham Heart Study (FHS) participants across nine quadrennial examinations was evaluated using Cox proportional hazard and Kaplan-Meier models. Age-, sex-, and education-adjusted models were tested for each factor measured at each exam and within three adult age groups (early = 35-50, middle = 51-60, and late = 61-70).

Results: A 15 mg/dL increase in high density lipoprotein (HDL) cholesterol was associated with decreased AD risk during early (15.4%, P = 0.041) and middle (17.9%, P = 0.014) adulthood. A 15 mg/dL increase in glucose measured during middle adulthood was associated with 14.5% increased AD risk (P = 0.00029). These findings remained significant after adjusting for treatment.

Discussion: Our findings suggest that careful management of cholesterol and glucose beginning in early adulthood can lower AD risk.
INTRODUCTION

Alzheimer's disease (AD) is the fifth leading cause of death among Americans 65 years of age or older, with a prevalence of 5.8 million cases. This number is projected to nearly triple to 14 million people by 2060. To date, there are no proven effective disease-modifying therapies to prevent or slow cognitive decline from AD and related diseases. Early identification and treatment of individuals at risk for the common form of AD occurring after age 65 have been recognized as an important contributor to reductions in AD mortality and delaying the symptoms of the disease.

Individuals with AD commonly exhibit features of cerebrovascular disease in combination with amyloid beta (Aβ) and tau neuropathology. Genetic studies of AD have identified common and rare variants associated with AD in genes involved in lipoprotein metabolism and processing related to AD. Historically, cerebrovascular diseases including stroke were exclusionary factors for an AD diagnosis because of their role in vascular dementia. However, pathological and epidemiological studies suggest that potentially modifiable cerebrovascular risk factors including obesity, diabetes, and high cholesterol contribute to the development of late-life cognitive impairment and AD, but not all studies agree. Although vascular risk burden measured in mid- to late-life (ie, ≥55 years if age) is a predictor of dementia including AD, less is known about whether AD risk is associated with exposure to vascular factors in early adulthood. Addressing this question has added importance in light of the growing recognition that AD is a life-course disease.

In this study, we investigated the influence of vascular risk factors measured longitudinally for an average period of more than 30 years on incident AD in the Framingham Heart Study (FHS) Offspring Cohort participants. This allowed us to evaluate the effect of vascular risk exposure on incident AD based on single time-point measurements from early, middle, and late adulthood with a goal of exploring the appropriate timing of vascular screening and interventions necessary to maximize benefits to cognitive and brain health.

METHODS

2.1 Study design and participants

The present study was designed to assess the association of modifiable vascular risk factors measured at time points throughout adulthood with future risk of AD among participants of the FHS, a single-site, multigeneration, community-based, prospective cohort study of health in Framingham, Massachusetts (Figure 1). This design addresses the question of future AD risk assessed at multiple starting points and assuming a constant exposure from that point forward. This study focused on the FHS Offspring cohort (Generation 2) participants for whom multiple longitudinal measures of vascular risk factors were available and who have been rigorously evaluated for cognitive decline and dementia since 1979. Ascertenments and other details of this cohort have been described previously. Briefly, at baseline, the cohort included 5124 participants who were 5- to 70-years-old (mean age of 36 years) at the first health examination (1971-1975). These participants have been examined longitudinally every 4 years on average from 1971 until the present, with a total of 10 exams. There is minimal loss to follow-up for FHS participants, some of whom have moved to other regions in New England and are examined in their home. All enrolled participants are tracked until death, at which time all medical and nursing home records are requested for a final review of cardiovascular and other related health events. Participant data included in this study were collected through the period ending in 2016. Physical and cognitive examinations, interviews to obtain information about general health and exposures, and collection of blood samples for blood chemistry and molecular analyses were administered at each exam cycle. Written informed consent was obtained from all study participants. The study protocol was approved by the Boston University Institutional Review Board, followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline, and was monitored by a National Heart, Lung, and Blood Institute Observational Study Monitoring Board.

2.2 Risk factor assessment

A variety of vascular, metabolic, and physical exam measurements were obtained at each examination including blood lipid fractions (high-density and low-density lipoprotein cholesterol [HDL-C and LDL-C] total cholesterol [TC], and triglyceride [TG]), blood glucose (BG), body mass index (BMI), systolic and diastolic blood pressure (SBP and DBP), and number of cigarettes smoked per day. Protocols for variable measurement and data processing including quality control procedures have been described previously. Of note, plasma LDL-C concentration at each exam was calculated using the Friedewald formula:

\[ \text{LDL-C} = \text{TC} - \text{HDL-C} - \frac{\text{TG}}{5} \]

If TG values were >400 mg/dL, LDL-C was set to missing. Lipids and glucose measured at exams 1 and 2 were non-fasting (ie, before the time participants were requested to fast before blood samples were collected), and these measurements were obtained under fasting conditions for ≈98% of participants at subsequent exams. Age and treatment history (yes or no) for hypertension, hypercholesterolemia, and diabetes at the time closest to, but not after, risk factor assessment was included in the statistical analyses. This study focused on quantitative measures rather than...
vascular-related disease end points in order to capture the potential
effect of modifiable processes underlying these disorders on the develop-
ment of AD later in life. Apolipoprotein E (APOE) genotype informa-
tion was unavailable for 941 FHS Offspring participants (18.4%), most
of whom were evaluated at exams 1 and 2 only before biospecimens
were collected for genetic analysis.

2.3 | Cognitive assessment and dementia diagnosis

Surveillance of cognitive impairment and incident dementia in the Off-
spring cohort began in 1979 at the second health examination when
the cohort was still relatively young (mean age = 44 years) to establish
a dementia-free cohort. The Mini–Mental State Examination (MMSE)
was administered starting at the fifth health examination (ie, 1991-
1995) to monitor change in cognitive status. Beginning in 1999, all sur-
viving Generation 2 participants were invited for an in-depth cogni-
tive examination. Change in cognitive status or performance, report by
the participant or a family member of subjective cognitive complaints,
referral by a physician or by ancillary investigators of the FHS, or out-
side medical records indicative of cognitive complaints triggered refer-
ral to a dementia diagnostic panel consisting of at least one neurologist
and one neuropsychologist. Surveillance details and consensus diag-
nostic procedures have been described previously.24,25 Among 989
participants who were underwent a dementia diagnosis panel review
(Table S1 in supporting information), 271 participants (167 female, 104
male) diagnosed with AD dementia (AD without stroke: n = 225; AD
with stroke: n = 22; mixed dementia AD + vascular dementia: n = 24)
were included in the analysis as cases. Participants judged to be cogni-
tively normal after dementia review (n = 366, a number consistent with
the low threshold needed to be flagged for dementia review) or who
were not flagged for dementia review (n = 4,501) were eligible as con-
trols. Participants who were assigned a diagnosis of non-AD dementia
(n = 106), uncertain dementia (n = 13), or who had an unknown diag-
nosis (n = 45), were excluded from the analyses of AD. Age at AD onset
was defined as the earliest recorded date of cognitive impairment. AD
cases without a recorded age at onset or diagnosis date (n = 6) or with
a diagnosis after 2016 (n = 4) were removed.

FIGURE 1 Study design
Statistical analysis

Individuals with prevalent dementia at the time of risk factor measurement were excluded from analyses. AD cases were followed until the date of AD diagnosis before December 31, 2016. Participants who were judged to be unimpaired by cognitive screening tests or to have mild cognitive impairment that did not progress to AD during the follow-up period were censored at either the date of death or the end date of the most recent exam before December 31, 2016. The follow-up time for censored participants was measured in days from the date of the exam at which a blood sample was obtained for risk factor measurement to the censoring date.

The association of vascular risk factors with incident AD was evaluated using two analytical designs. In one approach, Cox proportional hazards regression models were used to assess the association of each risk factor measurement separately with incident AD. For each risk factor, these analyses were carried out separately for the exam 1 to 2, 2 to 4, and 4 to 6 for the earliest of exams 1 to 2, 2 to 4, and 4 to 6 for each risk factor at one or more of the nine examinations were available for risk factor at one or more of the nine examinations were available for each age group, we selected participants’ risk factor data that were available from the earliest of exams 1 to 2, 2 to 4, and 4 to 6 for the early adulthood, middle adulthood, and late adulthood groups, respectively (Table S2). Participants were included in each age group for which they were examined during the corresponding baseline period. The association of each risk factor with AD incidence was evaluated using Cox proportional-hazards regression analyses and tested a similar set of models as described earlier. Analyses within age groups and for each exam were repeated for the outcome of all cause dementia, including 271 AD cases and 106 participants with a diagnosis of non-AD dementia (Table S1).

Kaplan-Meier survival curves were generated for each age group to compare the onset of AD symptoms among three groups defined by clinically meaningful cutoffs for risk factors showing significant associations with AD in the age group analyses. The groupings for the risk factors evaluated in this manner are as follows: HDL-C (<45 mg/dL, 45-64 mg/dL, ≥65 mg/dL), LDL-C (<130 mg/dL, 130-169 mg/dL, ≥170 mg/dL), TG (<150 mg/dL, 150-199 mg/dL, ≥200 mg/dL), BG (<100 mg/dL, 100-125 mg/dL, and ≥126 mg/dL), and DBP (<80 mm, 80-89 mm, and ≥90 mm).27–30 All statistical analyses were performed using R version 3.6.3.

RESULTS

Characteristics of subjects included in analyses

Among 5124 subjects in the FHS offspring cohort enrolled at the first examination, measurement data for at least one vascular risk factor at one or more of the nine examinations were available for 4932 subjects who were followed for a total of 186,537 person-years (mean = 37.6 years). The numbers of participants and incident AD cases in each exam for each age group are shown in Table S2. The mean follow-up period for participants in the early, middle, and late adulthood age groups was 35.2 years, 25.8 years, and 18.5 years, respectively (Table 2). As participants grew older, they tended to have higher...
### TABLE 2  Characteristics of study participants at baseline

<table>
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<th>Late adulthood (61–70)</th>
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<td>41.0 (4.3)</td>
<td>54.0 (2.5)</td>
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<td>Female, No. (%</td>
<td>1,683 (52.2)</td>
<td>995 (51.2)</td>
<td>812 (51.5)</td>
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</table>

**Period of baseline risk factor measurement**

- Early adulthood
- Middle adulthood
- Late adulthood

**Follow-up time, mean (SD), y**

- Early adulthood: 35.2 (8.9)
- Middle adulthood: 25.8 (8.2)
- Late adulthood: 18.5 (6.8)

**AD incident, No. (%)**

- Early adulthood: 177 (5.5)
- Middle adulthood: 172 (8.8)
- Late adulthood: 192 (12.2)

**Male**

- Early adulthood: 64 (4.2)
- Middle adulthood: 60 (6.3)
- Late adulthood: 68 (8.9)

**Female**

- Early adulthood: 113 (6.7)
- Middle adulthood: 112 (11.3)
- Late adulthood: 124 (15.3)

**APOE genotype (N)**

- Early adulthood: 2,761
- Middle adulthood: 1,799
- Late adulthood: 1,518

**Cerebrovascular risk factors**

| LDL cholesterol, mean (SD), mg/dL       | 133.3 (36.0)            | 146.0 (36.5)             | 134.0 (33.8)           |
| HDL cholesterol, mean (SD), mg/dL      | 51.1 (16.0)             | 49.5 (15.3)              | 49.4 (15.7)            |
| Triglycerides, mean (SD), mg/dL        | 109.0 (82.5)            | 133.2 (107.1)            | 153.0 (109.5)          |
| Total cholesterol, mean (SD), mg/dL    | 205.6 (37.7)            | 225.3 (37.8)             | 213.2 (38.8)           |
| Blood glucose, mean (SD), mg/dL       | 101.3 (15.4)            | 100.8 (26.5)             | 105.3 (33.7)           |
| Systolic blood pressure, mean (SD), mm Hg | 123.9 (16.0)        | 129.1 (17.2)             | 134.9 (19.2)           |
| Diastolic blood pressure, mean (SD), mm Hg | 79.5 (10.5)          | 81.1 (9.3)               | 77.5 (9.7)             |

**Treatment**

- Treated for diabetes, No. (%)
- Early adulthood: 25 (0.8)
- Middle adulthood: 52 (2.7)
- Late adulthood: 98 (6.2)

- Treated for hypertension, No. (%)
- Early adulthood: 153 (4.7)
- Middle adulthood: 401 (20.6)
- Late adulthood: 538 (34.1)

- Treated for dyslipidemia, No. (%)
- Early adulthood: 17 (0.5)
- Middle adulthood: 42 (2.2)
- Late adulthood: 171 (10.8)

*Participants are included in each age group for which they were examined during the corresponding baseline period as defined in Table S1.*

triglyceride and glucose levels, higher systolic and diastolic blood pressure, and lower HDL-C levels, as well were more likely to be treated for diabetes, hypertension, and dyslipidemia. The number of lifetime incident AD cases was similar among participants assessed in early adulthood (n = 177), middle adulthood (n = 172), and late adulthood (n = 192), which is expected because of the high overlap of subjects across age groups, despite the decreasing mean follow-up time.

### 3.2 Association of AD with risk factors by exam

AD risk was inversely associated with HDL-C level measured at the first (hazard ratio [HR] = 0.87 [0.76–1.00], P = 0.045), second (HR = 0.83 [0.72–0.97], P = 0.016), sixth (HR = 0.82 [0.72–0.93], P = 0.0021), and seventh (HR = 0.79 [0.68–0.92], P = 0.0024) examinations at which the mean age was 36, 44, 59, and 62, respectively (Table 3). The associations at these four exams remained significant after adjusting for dyslipidemia treatment (Table S3 in supporting information). Similarly, AD risk was associated with triglyceride levels measured at the first (HR = 1.34 [1.12–1.59], P = 0.0010), second (HR = 1.27 [1.10–1.47], P = 0.0041), fifth (HR = 1.19 [1.23–1.39], P = 0.024), sixth (HR = 1.20 [1.03–1.40], P = 0.022) and seventh (HR = 1.33 [1.10–1.59], P = 0.0027) examinations and these findings were not meaningfully altered after adjusting for dyslipidemia treatment. BG was significantly associated with AD incidence at every exam it was measured (Exam1: HR = 1.12 [1.01–1.26], P = 0.041; Exam2: HR = 1.12 [1.04–1.20], P = 0.0020; Exam3: HR = 1.09 [1.01–1.16], P = 0.022; Exam4: HR = 1.11 [1.05–1.17], P = 0.0040; Exam5: HR = 1.07 [1.01–1.13], P = 0.020; Exam6: HR = 1.09 [1.03–1.15], P = 0.0041; Exam7: HR = 1.13 [1.05–1.12], P = 0.0006; Exam8: HR = 1.14 [1.04–1.26], P = 0.0058; Exam9: HR = 1.39 [1.06–1.82], P = 0.017) (Table 3). In general, these results were attenuated after
Association of plasma HDL-C, triglyceride, LDL-C, and glucose measured at each longitudinal exam with incident AD adjusted for age and sex

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<th>Beta</th>
<th>HR&lt;sup&gt;c&lt;/sup&gt;</th>
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<sup>a</sup>Maximum number incident AD cases shown among subjects with for diastolic blood pressure measurements; numbers may be slightly less for other factors (see Table S3).

<sup>b</sup>Log2 transformed values for betas and HRs.

<sup>c</sup>Hazard ratio (HR) and 95% confidence interval for each 10 mm increase.

<sup>d</sup>Hazard ratio (HR) and 95% confidence interval for each 15 mg/dL increase.

### Table 3

Association of AD with risk factors by age group

### 3.3 Association of AD with risk factors by age group

Analysis by age group showed that incident AD was negatively associated with HDL-C measured in early adulthood (HR = 0.85 [0.72–0.99] per 15 mg/dL, P = 0.041) and middle adulthood (HR = 0.82 [0.70–0.96] per 15 mg/dL, P = 0.014), but the effect was attenuated in the late adulthood group (HR = 0.89 [0.77–1.02] per 15 mg/dL, P = 0.11) (Table 4). Specifically, a 15 mg/dL increase in HDL-C corresponds to a reduction in AD risk of 15.4% and 17.9% in the early and middle adulthood groups, respectively. As shown in Table S4 in the supporting information, this association remained significant with a similar effect size in the middle adulthood group when adjusted for dyslipidemia treatment (P = 0.022). BG measured in middle adulthood was significantly associated with AD at nearly the same magnitude of effect before (HR = 1.15, 1.06–1.23; P = 0.00029) and after (HR = 1.18, 1.08–1.29; P = 0.00036) adjusting for diabetes treatment (Table 4, Table S4). Among persons in this age group, for every 15 mg/dL increase in BG, risk of AD increases by 14.5%. TG level was significantly associated with AD only in the early adulthood group before (HR = 1.14, 1.06–1.23; P = 0.0013) as well as after (HR = 1.14, 1.00–1.29; P = 0.044) adjusting for treatment. AD was not associated with LDL-C, total cholesterol, BMI, smoking, and systolic blood pressure in any stage of adulthood (P > 0.05). In models adjusting for APIOE status, only glucose measured in middle adulthood (HR = 1.14, 1.06–1.23; P = 0.00034) and TG measured in early adulthood (HR = 1.21, 1.02–1.43; P = 0.030)
remained significantly associated with AD (Table S5). The association with glucose in late adulthood became significant when APOE ε4 status was added to the model (HR = 1.08, 1.01-1.15; P = 0.030).

3.4 | Association of risk factors with all-cause dementia

Risk factor analyses within age groups yielded a pattern of results for HDL-C, TG, and BG levels that was similar to those observed for AD incidence only, but they were less significant especially for both lipid measures (Table S6). The associations of all-cause dementia incidence with TG in early adulthood (HR = 1.23, 1.03-1.48; P = 0.021), BG in middle adulthood (HR = 1.13, 1.05-1.21; P = 0.00057), and DBP in late adulthood (HR = 1.15, 1.01-1.31; P = 0.038) were attenuated (Table S7). However, the incidence of all-cause dementia was not associated with HDL in any age group.

3.5 | Survival analysis results

Kaplan-Meier analysis showed that future development of AD was significantly and progressively higher and likely to occur earlier among individuals with BG in the pre-diabetic (100-126 mg/dL) and diabetic (>126 mg/dL) ranges compared to those with normal BG (<100 mg/dL) in early adulthood (P = 0.0030, Figure 2A, left panel) and middle adulthood (P = 0.04, Figure 2B, left panel), but not in late adulthood (P = 0.51, Figure 2C, left panel). The comparison was slightly more significant when combining those with prediabetic and diabetic BG levels in the early adulthood (P = 0.0012, Figure 2A, right panel) and middle adulthood (P = 0.0094, Figure 2B, right panel) groups. A similar trend for AD-free survival was also observed in the comparison of individuals with normal (<130 mg/dL), elevated (130-169 mg/dL), and clinically abnormal (≥170 mg/dL) LDL-C levels (P = 0.02) in early adulthood (Figure S2A). Similar results were observed in the same age group when comparing those with normal or elevated LDL-C to those with high LDL-C (P = 0.02, Figure S2B in supporting information). These comparisons were not significant for HDL-C (Figure S3 in supporting information) or TG (Figure S4 in supporting information) in any age group, but borderline significant for individuals with normal DSP (<80 mm) compared to those with elevated (80-89 mm) and abnormal (≥90 mm) DBP in early adulthood (Figure S5, right panel).

4 | DISCUSSION

The association of vascular and metabolic risk factors including diabetes, obesity, high blood pressure, and elevated serum cholesterol levels with cognitive decline and AD is widely reported.10-14,31 These observations contribute to the rationale for the U.S. Study to Protect Brain Health Through Lifestyle Intervention to Reduce Risk (U.S. POINTER), a 2-year clinical trial recently launched by the Alzheimer’s Association to evaluate whether healthy lifestyle interventions that
FIGURE 2  Cumulative probability of Alzheimer’s disease (AD)–free survival among individuals stratified into three (left panel) or two (right panel) clinically defined cutoffs for blood glucose (BG) concentration who were followed starting in (A) early adulthood (ages 35–50 years) (B) middle adulthood (ages 51–60 years), and (C) late adulthood (ages 61–70 years). The number of years of follow-up and number of surviving individuals in each BG level group are shown below the x-axis. Lighter shades of color indicate standard deviation of point estimates.
target risk factors can protect cognitive function in adults 60 to 79 years of age (https://alz.org/us-pointer/overview.asp). In this study, we demonstrated that HDL-C, glucose, and TG measured in early adulthood (age 35-50 years), HDL-C and glucose measured in middle adulthood (51-60 years), and diastolic blood pressure measured in late adulthood (61-70 years) are significantly associated with incident AD up to several decades later. Other vascular risk factors including BMI, LDL-C, systolic blood pressure, and smoking were not associated with AD in analyses considering measurements of the entire cohort at an individual exam or measurements of individuals within age groups. To our knowledge, this is the first report of an association of AD with HDL-C, triglyceride, and glucose levels measured in cognitively normal individuals during early to middle adulthood. These findings are consistent with a previous study showing that the cumulative number of vascular risk factors in midlife but not late life is associated with late-life brain amyloid measured by positron emission tomography (PET) imaging.32

Our findings that link cholesterol fractions and pre-diabetic glucose level in persons as young as age 35 to high AD risk decades later suggest that an intervention targeting cholesterol and glucose management starting in early adulthood can help maximize cognitive health in later life. This idea is supported by previous studies of Framingham Offspring study participants that showed that elevated coronary heart disease risk and metabolic syndrome were associated with lower cognitive performance at age 55.18,19 However, our results do not distinguish whether the influences of these risk factors on the development of AD may be particularly damaging during early adulthood and midlife or reflect longer accumulated risk exposure. Our data showing only modest attenuation of treatment on the effect of these factors on AD incidence and weaker association among persons older than 60 years are consistent with the idea that exposure earlier in life may better explain our findings; however, secular trends in treatment for managing cholesterol and glucose could also have contributed to the observed patterns.

Prior studies examining the relationship between HDL-C and risk of AD are inconclusive. Those with the highest baseline HDL-C in elderly individuals (≥ 65 years) had reduced AD risk,33 and higher baseline HDL-C protected against cognitive impairment and brain volume reductions 20 years later,34 but other studies found no association between HDL-C and cognitive impairment, noting that HDL was measured in subjects generally after age 65 who were followed for a period of follow-up after HDL-C was measured when the participants had a mean age of 76.1 years.22 HDL-C concentration was also not associated with risk of AD or vascular dementia after accounting for other vascular risk factors in the large community-based prospective 3C study of persons ≥65-years-old at baseline with up to 13 years of follow-up.15 These and other longitudinal studies37,40 yield inconsistent results that depend largely on the age at which cholesterol was measured and length of follow-up between cholesterol and cognitive assessments. Indeed, studies with a follow-up period ≥10 years found significant associations between HDL-C levels or apolipoprotein A1 (which is the major component of HDL particles in plasma) and AD risk.34,40 whereas studies with <10 years of follow-up did not.37,39 Furthermore, association of AD risk with HDL-C level is evident in studies with baseline measurements taken at middle age (<70 years),40−42 but not in those with HDL-C baseline measures in older subjects (≥70 years).38,39 Taken together, these studies and our findings suggest that HDL may exert its greatest influence on AD risk starting in as early as age 35.

A variety of evidence supports a mechanistic role of HDL in AD pathogenesis. A recent Mendelian randomization meta-analysis showed that reduced HDL levels might be potential causal risk factors of the development of AD,43 but other Mendelian randomization studies do not support this conclusion, but other MR studies do not support this conclusion.44,45 In vitro studies demonstrated that HDL reduces vascular Aβ accumulation46 and attenuates Aβ-induced endothelial inflammation.47 Reed et al. reported that low HDL-C and high LDL-C are associated with elevated cerebral Aβ measured using Pittsburgh compound B and PET in living non-demented individuals with a mean age of 78 years.48 Other properties of HDL that are relevant to AD include its ability to reduce accumulation and increase transport of Aβ through the vasculature, inhibit Aβ-induced endothelial activation, delay Aβ fibrillation, and induce nitric oxide (NO) production.56,67 The cerebrovascular benefits of HDL in healthy humans may partly explain our finding of a protective association of circulating HDL levels against AD risk.49 A role for HDL in AD is also supported by studies that have identified associations with genes that encode HDL biogenesis proteins and HDL protein components including APOE, ABCA1, PON1, CLU, and APOA1.7,8,50−55

The functional relationship between APOE and HDL56 likely accounts for the attenuated association of AD risk with HDL-C level in a model including APOE ε4 carrier status, and is consistent with findings showing that the effect of the APOE ε4 allele on AD risk is mediated in part through its impact on reducing HDL-C.53 However, because cholesterol levels are modifiable, understanding the mechanisms through which HDL and related proteins modulate Aβ could offer new approaches to slowing Aβ deposition and thus reduce the incidence of AD including among APOE ε4 carriers.

Although the association of AD with diabetes32,57−59 and impaired glucose levels60,61 is well established, to our knowledge this is the first evidence of the association of AD with glucose levels measured in cognitively normal individuals throughout adulthood beginning as early as age 35. Of interest, our findings are consistent with results from a prospective cross-sectional study of 799 men and women with an average age of 50 showing association of increased glucose levels with lower cognitive function.62 Schrijvers et al. observed an increased risk of AD associated with fasting glucose levels among 3319 Rotterdam Study participants within a 3-year follow-up period starting at baseline, but this association was not evident (in fact, an inverse relationship) after longer follow-up periods.63 Notably, the mean age of subjects at baseline in that study (71.8 years) was more than 25 years older than the age of FHS participants at which we observed the deleterious effects of increased glucose on cognition. By contrast, results of another study suggest that higher glucose levels may be a risk
factor for dementia, even among persons older than age 70 without diabetes.\textsuperscript{64} That study is consistent with our findings showing association of increased glucose in middle age with dementia more generally.

Peripheral glucose homeostasis has been implicated in the pathogenesis of AD.\textsuperscript{65} Longitudinal increases in fasting plasma glucose levels are associated with higher brain glucose concentrations. Higher brain glucose levels are correlated with more severe plaques and tangles in AD brains along with impaired glucose metabolism in brain due to reduced glycolytic flux.\textsuperscript{66} In addition, high blood glucose (hyperglycemia) may contribute to the increased risk of AD by exacerbating astrocyte-mediated neuroinflammation and neuronal injury caused by disease-associated agents, for example, fibrillar A\textsubscript{β}42.\textsuperscript{67} Hyperglycemia can result in the glycation of proteins and dysregulate the innate immune system through glycation and oxidation of macrophage migration inhibitory factor (MIF), a process that is accelerated in both early and late-stage AD brains.\textsuperscript{68} Furthermore, high glucose can render cells, including those in the brain, insulin resistant, which may worsen mental functioning. It is also linked to reduced insulin uptake (resulting in lowered glucose metabolism) in areas of the brain associated with AD.\textsuperscript{69} Finally, insulin has an important role in neuronal signaling, and thus insulin resistance can inhibit signaling between brain cells and affect memory.\textsuperscript{70}

This study has several notable strengths including the quaddrennial measurement of risk factors in a community-based sample of nearly 5000 participants beginning in early adulthood who were followed \( \approx 38 \) years on average. Several caveats should also be considered. First, all participants in the FHS Offspring cohort are white, which limits generalizability to other populations. Second, although we applied two approaches to estimate the association of vascular risk factors measured across adulthood with incident AD, each design has limitations. The age-stratified approach addresses the age question more directly than the exam-by-exam approach, which considers all cohort members who survived to each exam as one group. However, this approach has less power because of divided samples, as well as issues of combining risk factors measured at different exams (possible measurement bias) and introducing correlation because some individuals were included in more than one age group, although participants are independent within each age group. In the exam-by-exam approach, participants have the same follow-up time for each exam and risk factors were measured in a relatively narrow period (\( \approx 2-4 \) years) among participants at each exam. However, because the age range is relatively large among participants at each exam, our results might not accurately reflect age-specific trends, even though the age of survivors at each exam is progressively increasing. Both approaches have uneven power across exams and age groups due to a progressively smaller follow-up period, although we endeavored to balance the number of AD incident cases in the analyses within age groups. This issue may explain, for example, negative findings in previous studies and less significant results in our study for HDL in the oldest age group, which had the shortest follow-up. Despite these concerns, the overall similarity of results from both approaches suggests that our findings are relatively robust. Third, we were unable to assess the association of fasting measures of lipids and glucose in early adulthood because blood samples were not collected under fasting conditions at the first two examinations of the Offspring cohort. However, although non-fasting measurements may be slightly more abnormal, significant associations of HDL-C, triglyceride, and glucose measured at exams 1 and 2 with AD risk are unlikely spurious because the onset of AD symptoms did not occur until several decades later on average. Another limitation of our findings is that they are based on analyses of one-time measurements of risk factors. Studies that allow for time-course changes of risk factors on the AD risk in late life may better explain the dynamic relationship between vascular risk factors on cognitive and brain health in late life; however, a time-dependent Cox analysis generally requires complete data for subjects followed for a fixed period, is complicated by death which is a competing risk, only addresses relatively short-term effects, and does not adequately adjust for confounders (eg, treatment) that are measured repeatedly during follow-up.\textsuperscript{71,72} Our findings showing similar but attenuated associations of all-cause dementia with triglyceride and glucose levels, and no association with HDL-C level, should be interpreted cautiously because of the heterogeneous etiologies of dementia. Finally, although we tested models that included a term for treatment of abnormal cholesterol levels and blood pressure, and for diabetes (adjustment for which had little impact on our results), we did not distinguish specific medications or account for duration of their use.

## 5 | CONCLUSIONS

Our findings showing that HDL-C, triglyceride, and glucose levels measured in early to middle adulthood are significantly associated with incident AD several decades later, which suggests that early intervention to maintain healthy HDL, triglyceride, and glucose levels may improve cognition and lower AD risk in addition to the benefits of promoting vascular and metabolic health. The effects of these risk factors, particularly glucose level, may not be AD specific and may contribute to incidence of other forms of dementia. Studies combining multiple prospective cohorts with long follow-up periods that collectively contain much larger samples of non-AD dementias than the FHS will be necessary to address this question.

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