Type 2 Diabetes as a Risk Factor for Alzheimer’s Disease: The Confounders, Interactions, and Neuropathology Associated With This Relationship

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We performed a systematic review and meta-analysis to explore whether type 2 diabetes mellitus (T2DM) increases the risk of Alzheimer’s disease (AD). We also reviewed interactions with smoking, hypertension, and apolipoprotein E ε4. Using a series of databases (MEDLINE, EMBASE, PubMed, Current Contents Connect, and Google Scholar), we identified a total of 15 epidemiologic studies. Fourteen studies reported positive associations, of which 9 were statistically significant. Risk estimates ranged from 0.83 to 2.45. The pooled adjusted risk ratio was 1.57 (95% confidence interval: 1.41, 1.75), with a population-attributable risk of 8%. Smoking and hypertension, when comorbid with T2DM, had odds of 14 and 3, respectively. Of the 5 studies that investigated the interaction between T2DM and apolipoprotein E ε4, 4 showed positive associations, of which 3 were significant, with odds ranging from 2.4 to 4.99. The pooled adjusted risk ratio was 2.91 (95% confidence interval: 1.51, 5.61). Risk estimates were presented in the context of a key confounder—cerebral infarcts— which are more common in those with T2DM and might contribute to the manifestation of clinical AD. We provide evidence from clinico-neuropathologic studies that demonstrates the following: First, cerebral infarcts are more common than AD-type pathology in those with T2DM and dementia. Second, those with dementia at postmortem are more likely to have both AD-type and cerebrovascular pathologies. Finally, cerebral infarcts reduce the number of AD lesions required for the manifestation of clinical dementia, but they do not appear to interact synergistically with AD-type pathology. Therefore, the increased risk of clinically diagnosed AD seems to be mediated through cerebrovascular pathology.

Alzheimer disease; apolipoprotein E; dementia; risk factors; type 2 diabetes mellitus

Abbreviations: AD, Alzheimer’s disease; ApoE, apolipoprotein E; CI, confidence interval; T2DM, type 2 diabetes mellitus.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) long has been suspected as a risk factor for Alzheimer’s disease (AD). Epidemiologic studies, however, have had conflicting results. In 2010, a conference held by the US National Institutes of Health assessed the evidence linking T2DM and other potential risk factors with AD. On the basis of a comprehensive review of the literature, the panel determined that although available data were limited and the quality of evidence generally weak, T2DM was associated with an increased risk of developing AD (1). Other risk factors found by the National Institutes of Health to increase the risk of AD included apolipoprotein E gene (ApoE) variation, current smoking, and depression.

T2DM and AD are diseases of epidemic proportions. In 2011, the worldwide prevalence of AD was 24 million (2), and in 2010, that of T2DM was 285 million, or 6.4% of the population (3). Both AD and T2DM are projected to increase. By 2050, AD prevalence is estimated to quadruple (4), and by 2030, T2DM prevalence is estimated to rise to 439 million, or 7.7% of the world population (3). The cost of managing patients with dementia exceeds that for age-matched controls without dementia by 50% (5, 6). Similarly, the cost of care for patients with T2DM is 2.5 to 4 times greater than that of controls without T2DM (7, 8). Dramatic increases in prevalence combined with comparatively high financial costs of care represent a significant challenge to already strained health care systems.

In the present review, we aim to improve on related publications by addressing key confounders and methodological differences among studies. In doing so, we present results from this meta-analysis in a relevant context. Furthermore,
by reviewing neuropathologic data, which have contradict-
ed that obtained from epidemiologic studies, the reader will obtain a current and complete perspective on how T2DM is linked to the development of AD. We also summarize the interaction of T2DM with other vascular risk factors and provide the first pooled risk estimate of the interactions among T2DM, ApoE ε4, and AD.

METHODS
Study protocol
We followed the Preferred Reporting Items for System-
atic Reviews (9) and Meta-Analysis of Observational
Studies in Epidemiology guidelines (10) where possible in performing our systematic review and meta-analysis. One author (N. T. V.) performed a systematic search through MEDLINE (from 1950), PubMed (from 1946), EMBASE (from 1949), Google Scholar (from 1993), and Current Contents Connect (from 1998) through to January 8, 2013, to identify relevant articles. The search used the terms “alzheimer × disease” or “alzheimer × dementia” or “alzheimer disease” and “diabetes mellitus” and “pathology” or “neu-
ropathology” or “autopsy”, which were searched as text words and as exploded Medical Subject Headings where possible. The reference lists of relevant articles also were searched for appropriate studies. No language restrictions were used in either the search or study selection. A search for unpublished literature was not performed.

Study selection
We included studies that met the following inclusion criteria: 1) The study was of a longitudinal design, and 2) the study included an original cohort. If a study population appeared in multiple publications, data from the most recent study were included. We excluded studies that did not meet the inclusion criteria.

Data extraction
One author (N. T. V.) performed the data extraction via a standardized data extraction form. Information was collect-
ed on the publication year, study design, country, continent, total sample size, number of subjects excluded for analysis, number of AD cases, number of T2DM cases, diagnostic criteria for both AD and T2DM, participant characteristics, mean age, average length of follow-up, adjusted variables, and risk estimates.

Statistical analysis
Pooled risk ratios and 95% confidence intervals were calculated with a random effects model for the effect of T2DM on the risk of developing AD (11). We tested heterogeneity with Cochran’s Q statistic, with P < 0.10 indicating heterogeneity, and quantified the degree of heterogeneity with the I² statistic, which represents the percentage of the total variability across studies that is due to heterogeneity. I² values of 25%, 50%, and 75% corresponded to low, moderate, and high degrees of heterogene-
ity, respectively (12). We quantified publication bias by using the Egger’s regression model (13), with the effect of bias assessed by the fail-safe number method. The fail-safe number was the number of studies that we would need to have missed for our observed result to be nullified to stat-
tical nonsignificance at the P < 0.05 level. Publication bias is generally regarded as a concern if the fail-safe number is <5n + 10, with n being the number of studies included in the meta-analysis (14). All analyses were performed with Comprehensive Meta-analysis (version 2.0, 2005; Biostat, Englewood, New Jersey).

RESULTS
Strength of association
This systematic review and meta-analysis identified 15 different study populations. Details about individual studies can be found in Table 1. A total of 14 cohorts reported a positive association between T2DM and probable AD, a clinical diagnosis that confers the highest level of certainty that a subject’s cognitive impairment is attributable to AD-
type neuropathology (2). Risk estimates ranged from 0.83 to 2.45. In a sensitivity analysis, we analyzed 2 groups separ-
ately. The first group contained all 15 studies, and the second group excluded 2 studies that had relatively small samples of patients with T2DM (<35 subjects). Results of the sensitivity analysis failed to demonstrate a substantial difference between these groups; however, because of questions of validity with regard to studies that had few subjects with T2DM, pooled data from the second group have been presented in the present review (Figure 1). The pooled ad-
justed risk ratio was 1.57 (95% confidence interval (CI): 1.41, 1.75), and the heterogeneity was 38.68% (P = 0.07), which suggests a moderate degree of heterogeneity. Finally, Egger’s regression showed no publication bias (P = 0.22) (Figure 2). The Levin formula, the pooled risk ratio, and recent prevalence data from the 2011 National Health Inter-
view Survey (15) were used to determine that the population-
attributable risk for T2DM was roughly 8%. This value corresponds to 432,000 cases of AD out of a total of 5.4 million Americans currently living with this disease (16).

Globally, the population-attributable risk is approximately 6%, corresponding to 1,440,000 cases of AD.

To elucidate methodological factors that might modify the strength of the association, several subgroup analyses were performed. Two such analyses yielded notable find-
ings. First, a comparison was made between studies that diagnosed T2DM by self-reporting and those that required blood sampling (e.g., random blood glucose measure-
ments). The pooled adjusted risk ratio for studies that used self-reporting was 1.98 (95% CI: 1.64, 2.40), compared with a value of 1.46 (95% CI: 1.30, 1.64) for those that used blood glucose measurements. The heterogeneity was low in both subgroups. A comparison was then made with regard to adjustments for covariates, where studies adjusting for age and sex were compared with those that, in addition to age and sex, adjusted for cardiovascular risk factors.
<table>
<thead>
<tr>
<th>First Author, Year (Reference No.)</th>
<th>Cohort</th>
<th>Country</th>
<th>No. of Patients</th>
<th>Mean Age, years</th>
<th>Assessment of T2DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brayne, 1998 (75)</td>
<td>Population-based Cambridge City over-75s Cohort</td>
<td>United Kingdom</td>
<td>18</td>
<td>N/A</td>
<td>2,609</td>
</tr>
<tr>
<td>Ott, 1999 (46)</td>
<td>Rotterdam Study</td>
<td>The Netherlands</td>
<td>89</td>
<td>692</td>
<td>7,983</td>
</tr>
<tr>
<td>MacKnight, 2002 (76)</td>
<td>Canadian Study of Health and Aging</td>
<td>Canada</td>
<td>267</td>
<td>503</td>
<td>10,263</td>
</tr>
<tr>
<td>Hassing, 2002 (44)</td>
<td>OCTO-Twin Study</td>
<td>Sweden</td>
<td>107</td>
<td>31</td>
<td>702</td>
</tr>
<tr>
<td>Peila, 2002 (21)</td>
<td>Honolulu-Asia Aging Study</td>
<td>United States</td>
<td>76</td>
<td>900</td>
<td>3,374</td>
</tr>
<tr>
<td>Arvanitakis, 2004 (50)</td>
<td>Religious Order Study</td>
<td>United States</td>
<td>151</td>
<td>127</td>
<td>911</td>
</tr>
<tr>
<td>Xu, 2004 (18)</td>
<td>Kungsholmen Study</td>
<td>Sweden</td>
<td>260</td>
<td>114</td>
<td>1,810</td>
</tr>
<tr>
<td>Luchsinger, 2005 (17)</td>
<td>Medicare recipients, northern Manhattan, New York</td>
<td>United States</td>
<td>246</td>
<td>230</td>
<td>2,126</td>
</tr>
<tr>
<td>Akomolafe, 2006 (22)</td>
<td>Framingham Study</td>
<td>United States</td>
<td>237</td>
<td>202</td>
<td>2,210</td>
</tr>
<tr>
<td>Raffaitin, 2009 (74)</td>
<td>Three-City Study</td>
<td>France</td>
<td>134</td>
<td>538</td>
<td>9,295</td>
</tr>
<tr>
<td>Al-Emam, 2010 (78)</td>
<td>Patients referred to neuropsychology department</td>
<td>Egypt</td>
<td>137</td>
<td>106</td>
<td>876</td>
</tr>
<tr>
<td>Kimm², 2011 (77)</td>
<td>Data from National Health Insurance Corporation</td>
<td>South Korea</td>
<td>821</td>
<td>33,350</td>
<td>490,445</td>
</tr>
<tr>
<td>Kimm³, 2011 (77)</td>
<td>National Health Insurance Corporation evaluations</td>
<td>South Korea</td>
<td>1,030</td>
<td>18,261</td>
<td>358,060</td>
</tr>
<tr>
<td>Ahtiluoto, 2010 (23)</td>
<td>Vantaa 85+ Study</td>
<td>Finland</td>
<td>155</td>
<td>131</td>
<td>588</td>
</tr>
<tr>
<td>Ohara, 2011 (24)</td>
<td>Hisayama Study</td>
<td>Japan</td>
<td>105</td>
<td>150</td>
<td>1,228</td>
</tr>
<tr>
<td>Wang, 2012 (43)</td>
<td>Data from Bureau of National Health Insurance</td>
<td>Taiwan</td>
<td>8,488</td>
<td>615,532</td>
<td>1,230,403</td>
</tr>
</tbody>
</table>

Abbreviations: BGL, blood glucose level; FPG, fasting plasma glucose; N/A, not available; OGTT, oral glucose tolerance test; type 2 diabetes mellitus.

* This study was stratified by male sex.
* This study was stratified by female sex.
The latter group had a pooled adjusted risk ratio of 1.66 (95% CI: 1.31, 2.10), whereas those that adjusted for age and sex alone had a value of 1.51 (95% CI: 1.34, 1.70). The heterogeneity was higher in the group that adjusted for cardiovascular risk factors ($I^2 = 60.64$ ($P = 0.04$) compared with $I^2 = 0.00$ ($P = 0.47$)).

**Interactions of T2DM with other AD risk factors**

Several vascular risk factors have been shown to interact with T2DM to modify the risk of developing AD. Of the covariates investigated, smoking demonstrated the largest interaction (17). Independently, the odds of developing AD in persons with T2DM and smokers were 3.6 and 2.2, respectively; however, the odds increased to nearly 14 in persons who smoke and have T2DM (17). Xu et al. (18) reported that neither T2DM nor a systolic blood pressure greater than 180 mm Hg independently increased the risk of developing AD. However, when both risk factors were present, the odds increased to 2.8.

The interaction between T2DM and ApoE ε4 was assessed in 5 studies (Table 2), 2 of which stratified their...
analyses with regard to ApoE ε4 status and did not provide a risk estimate for T2DM as an independent risk factor for AD (19, 20). As a result, details from these studies are not found in Table 1. All but 1 study showed an increased risk of developing AD (18, 20–22). Two reported that the interaction was synergistic (20, 21). The pooled adjusted risk ratio was 2.29 (95% CI: 1.12, 4.67), which indicates that the risk increased more than 2-fold in those with T2DM and ApoE ε4. However, the I² value was 74.85% (P = 0.003), which suggests a high degree of heterogeneity. Only 1 study showed that T2DM was protective in those with ApoE ε4 (19). However, because ApoE ε4 status was available for only 51% of the cohort, there was concern about the validity. Although excluding this study by way of a sensitivity analysis increased the overall risk, the risk ratio was still nonsignificant with regard to heterogeneity (Figure 3).

**Findings from neuropathologic studies**

Several epidemiologic studies examined a proportion of subjects at postmortem to further evaluate the association between T2DM and AD (21, 23, 24). In the Hisayama Study (24), half of the subjects with dementia were autopsied (n = 118). The association between T2DM and AD remained significant only when cases of AD confirmed by autopsy were included in the analysis. In a follow-up neuropathologic study on this cohort, 74% of those who died within a 5-year period were autopsied (n = 214), which showed that neuritic plaques, a pathologic hallmark of AD, were associated with T2DM (25). The Honolulu-Asian Aging Study autopsied 8% of the cohort (n = 291) and demonstrated good agreement between clinical and pathologic diagnoses (21). However, in the Honolulu-Asian Aging Study cohort, T2DM was associated with more cerebral infarcts than AD pathology. Interestingly, subjects with T2DM and ApoE ε4 had comparatively more hippocampal neuritic plaques, neurofibrillary tangles, and cerebral amyloid angiopathy (21). However, these findings have not been duplicated in similar neuropathologic studies (23, 26). The Vantaa 85+ study showed that subjects with T2DM had a 2-fold risk of developing probable AD; however, autopsy data from 50% of the cohort (n = 291) failed to

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**Table 2. Summary of Studies Evaluating the Interaction Between Type 2 Diabetes Mellitus and Apolipoprotein E ε4**

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients</th>
<th>95% Confidence Interval</th>
<th>Risk Estimate</th>
<th>Observed Relationship</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peila, 2002 (21)</td>
<td>Peila, 2002</td>
<td>4.4a</td>
<td>N/A</td>
<td>Synergistic relationship</td>
</tr>
<tr>
<td>Xu, 2004 (18)</td>
<td>Xu, 2004</td>
<td>2.4</td>
<td>95% CI: 1.12, 4.67</td>
<td>Positive association</td>
</tr>
<tr>
<td>Borenstein, 2005 (19)</td>
<td>Borenstein, 2005</td>
<td>0.45c</td>
<td>95% CI: 0.11, 1.96</td>
<td>Negative association</td>
</tr>
<tr>
<td>Akomolafe, 2006 (22)</td>
<td>Akomolafe, 2006</td>
<td>1.44</td>
<td>95% CI: 0.52, 2.51</td>
<td>Positive association</td>
</tr>
<tr>
<td>Irie, 2008 (20)</td>
<td>Irie, 2008</td>
<td>4.99c</td>
<td>95% CI: 2.7, 9.2</td>
<td>Synergistic relationship</td>
</tr>
</tbody>
</table>

**Abbreviations:** AD, Alzheimer’s disease; ApoE, apolipoprotein E; N/A, not available; T2DM, type 2 diabetes mellitus.

a Risk estimate did not exclude subjects with concomitant cerebrovascular disease (see Assessment of AD in the results section of the article by Peila et al.).
b ApoE ε4 data were missing for 316 subjects, although distribution was roughly equal among people with and without diabetes.
c All participants were stratified on the basis of ApoE ε4 status, and diabetes mellitus was not assessed as an independent variable.
d ApoE ε4 was available for only 51% of the cohort.

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**Figure 3.** Effect of interaction between type 2 diabetes mellitus and apolipoprotein E ε4 on the risk of Alzheimer’s disease. CI, confidence interval; OR odds ratio.
show agreement and showed that those with T2DM were more likely to have cerebral infarcts at postmortem (23). Similarly, a follow-up of the Religious Order Study, in which 94% of individuals who died within a 12-year period were autopsied (n = 325), demonstrated that those with T2DM were more likely to have cerebral infarcts than AD-type pathology (27). Additionally, several community-based neuropathologic studies support this finding, concluding that subjects with T2DM and dementia have less AD-type pathology than do controls with dementia but without T2DM (26, 28–31).

**Confounding of the association**

The diagnosis of AD is made according to criteria of the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer’s Disease and Related Disorders Association, which classifies the diagnosis into possible, probable, and definite AD (32). Although the latter diagnosis is made only upon neuropathologic examination, the diagnosis of probable AD is made clinically according to specific diagnostic criteria. Probable AD achieves the maximum level of certainty that can be obtained without autopsy (2). The diagnosis of possible AD, however, is designated to patients with clinical features not typically seen in AD or when coexisting disorders potentially could account for the presence of dementia (2). The diagnostic specificity ranges from 23% to 88% when National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer’s Disease and Related Disorders Association criteria are used (33). These figures indicate the potential for other dementia subtypes to confound the association between T2DM and AD. This potential has been substantiated by studies that have demonstrated that the majority of cases of clinical dementia have mixed AD-type and vascular pathology at postmortem (34–36). Additionally, a retrospective study has shown that macroscopic infarcts increased the odds of a diagnosis of probable AD by a factor of 1.64 (37). This suggests that patients with dementia who have cerebral infarcts are more likely to be diagnosed with probable AD. The potential for misdiagnosis could be explained partially by infarcts occurring in brain regions responsible for episodic memory, the loss of which is a hallmark of AD (37).

Cardiovascular risk factors such as smoking (38), hypertension (39), hyperlipidemia (40), and obesity (41) have been associated with AD previously. Clustering of hyperglycemia, hypertension, hyperlipidemia, and obesity comprises the metabolic syndrome, a condition found in more than 20% of the American population (42). Because of the independent association of these risk factors with AD and their tendency to occur in clusters, studies that have not properly adjusted for these covariates are highly susceptible to confounding. Although most studies adjusted for age and sex, less than half adjusted for vascular risk factors (18, 21, 22, 24, 43). Interestingly, results from our subgroup analysis demonstrated that adjusting for cardiovascular risk factors increased the risk estimate. This suggests that T2DM is more likely to be involved in the pathogenesis of AD than associated through a spurious relationship.

**DISCUSSION**

Epidemiologic evidence supports a provisional conclusion that T2DM is a risk factor for probable AD. Our pooled risk ratio of 1.57 (95% CI: 1.41, 1.75) corresponds roughly to a 60% increase in the risk of developing probable AD, which, because of the high prevalence of T2DM, represents a substantial effect size. All but 1 study showed a general trend toward an increased risk of AD in those with T2DM. Results from the outlier, a Swedish cohort that had relatively few subjects with T2DM, could be explained by reduced statistical power (44). Additionally, during the time of that study in Sweden, patients with T2DM had a 4-fold increase in mortality rate, with a median age at death of 80 years (45); however, the mean age at baseline for participants in the outlier study was 84 (44). Therefore, low statistical power and a potential for survival bias could account for the negative association found in that study. Despite the potential for survival bias and low statistical power to modify the results from other epidemiologic studies, there was an insufficient total number of studies to carry out a meta-regression analysis and thus to quantify the effect of age at baseline and the number of subjects with T2DM.

The assertion that T2DM is a risk factor for probable AD has been contested largely as a result of the inconsistency of findings across epidemiologic studies. This inconsistency, as well as the moderate degree of heterogeneity generated in our pooled risk ratio estimate, could potentially be explained by key methodological differences. Of particular importance is the variation in methods by which T2DM has been diagnosed across studies. Several studies have used the oral glucose tolerance test (21, 24, 46), a technique recommended by the World Health Organization for use in epidemiologic studies (47). However, use of the oral glucose tolerance test in large, community-based population studies can be challenging because it is time consuming, requires overnight fasting, and is susceptible to acute perturbations in plasma glucose. Because of the impracticality of this technique, sampling bias could generate a nonrepresentative study population. This might be reflected by our subgroup analysis, which demonstrated that populations evaluated by self-reporting were at increased risk compared with studies that used techniques requiring blood samples. Because 30% of T2DM is undiagnosed in the community (48), assessment of T2DM status by self-reporting, medication history, or medical records would correspond to an underestimation of the number of subjects with T2DM in the study population. Although self-reporting is less accurate than objective blood glucose measurements, it is less labor intensive and more conducive to large population studies. Importantly, systematic error generated by using less accurate techniques could be minimized by multiple assessments of T2DM status over the course of the study (49). The benefit of multiple assessments of exposure might be evident in the studies that showed statistically significant findings after using a combination of self-reporting, medication history, and information from medical records at multiple follow-up evaluations (17, 23, 50).

The mechanism by which T2DM interacts with vascular risk factors to modify the risk of developing AD likely
involves cerebrovascular pathology. This is supported by studies that have demonstrated that cerebral infarcts lower the threshold for the clinical manifestation of AD (51–53). Although it is controversial whether smoking and hypertension are risk factors in AD (17, 18, 38, 39, 54), both are well-known risk factors for cerebrovascular disease and therefore can interact with T2DM by increasing the propensity to form cerebral infarcts. Additionally, hypertension is associated with cerebral amyloid angiopathy (55), a histopathologic feature of AD and an independent risk factor for cognitive impairment (28, 56–59). Cerebral amyloid angiopathy has been shown to interact with neuritic plaques and neurofibrillary tangles and to increase the severity of cognitive impairment beyond that seen in persons with neuritic plaques and neurofibrillary tangles alone (60, 61).

The pathologic link between T2DM, ApoE ε4, and the development of AD could involve inflammatory pathways and oxidative stress. The ApoE ε4 allele confers a reduced capacity for repair of neuronal injury (62, 63) and prevention of oxidative damage compared with other ApoE isoforms (64–66). T2DM is associated with elevated levels of interleukin-6 in the central nervous system, which suggests increased inflammation in the brains of patients with T2DM (30). Together, cerebral inflammation and oxidative stress, coupled with reduced antioxidant capacity, could result in the accumulation of oxidative damage, an outcome consistent with a theory that oxidative stress contributes to the pathogenesis of AD (67). Not all studies, however, have demonstrated a statistically significant, positive interaction between T2DM and ApoE ε4. This potentially could be explained by incomplete collection of ApoE genotype data. Both the study by Borenstein et al. (19), which reported a negative association, and the Framingham study (22), which reported a nonsignificant positive interaction, obtained ApoE genotype data for <60% of subjects. As a result, sampling bias could account for the discrepancy among studies. Although this also could account for the heterogeneity observed in our analysis, excluding the study by Borenstein et al. (19) only minimally reduced the degree of heterogeneity.

The general trend toward an increased risk of probable AD in those with T2DM is not consistently supported by neuropathologic data. Although the association in the Hisayama Study was strengthened when cases of AD confirmed by autopsy were used in the analysis, only subjects with dementia were autopsied, and thus the findings are not representative of the population (24). The follow-up study, however, was population based, and thus the positive association reported in that study is more generalizable (25). In the Honolulu-Asian Aging Study cohort, the association with definite AD was significant only when subjects had both T2DM and ApoE ε4 (21). However, additional neuropathologic studies have not been able to provide similar evidence (23, 26). Finally, autopsy data from 2 cohorts have demonstrated negative associations between T2DM and definite AD (23, 27); however, both of these studies have potential limitations. The Vantaa 85+ and Religious Order Study cohorts are supported by several large, community-based neuropathologic studies that demonstrated that those with T2DM are less likely to have AD-type pathology than are subjects with dementia without T2DM (26, 28–31) and more likely to have cerebrovascular pathology (21, 23, 29, 30).

As mentioned, fewer AD-type lesions are required for the clinical expression of AD in the presence of no cerebral infarcts (51–53, 68). Additionally, several studies have shown that most patients with dementia have a combination of AD-type and cerebrovascular pathologies (34–36). It remains somewhat controversial, however, whether the reduction in threshold of the clinical expression of dementia reflects an interaction between cerebrovascular and AD-type pathology or an independent contribution by each pathologic process. A neuroimaging study has demonstrated a synergistic interaction between medial temporal lobe atrophy, a feature seen in 71%–96% of those with AD (69), and white-matter hyperintensities, a marker for microvascular disease (70). Evidence from autopsy studies, however, has not supported this interaction, but rather supports the likelihood that cerebral infarcts have an independent role in the expression of clinical dementia (55, 71, 72). Neuropathologic data therefore suggest that T2DM increases the risk of probable AD through its association with cerebral infarcts, lesions known to contribute to the expression of vascular dementia (73).

In summary, findings from the present meta-analysis and systematic review support a role for T2DM in the clinical manifestation of AD. Results from the meta-analysis, however, are presented within the context of neuropathological evidence which demonstrates that individuals with T2DM and probable AD are more likely to have cerebral infarcts than AD-type pathology. Importantly, studies have failed to demonstrate a synergistic interaction between cerebrovascular and AD pathology (53, 71, 72), which suggests that the association between T2DM and AD may be confounded by cerebral infarcts. Further, the increased risk of developing probable AD, a clinical diagnosis, is likely mediated through the independent role of cerebrovascular pathology. ApoE ε4 and vascular risk factors such as smoking and hypertension appear to interact with T2DM to increase the risk of developing probable AD. Evidence suggests that the pathogenesis of the interaction between T2DM and other vascular risk factors is, indeed, vascular in origin and mediated by an increased load of cerebral infarcts and other vascular lesions. Despite the lack of evidence for an independent role of T2DM in the pathogenesis of AD-type pathology, neuropathologic and epidemiologic evidence supports a role for aggressive primary prevention to effectively reduce the projected increase of dementia prevalence in our growing elderly demographic.

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