Type 2 diabetes mellitus accelerates brain aging and cognitive decline: complementary findings from UK Biobank and meta-analyses.

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Abstract

**Background:** Type 2 diabetes mellitus is known to be associated with cognitive deficits; however, their extent, overlap with aging effects, and neurobiological correlates are currently unknown.

**Methods:** We characterized neurocognitive effects in T2DM in a large cohort complemented by meta-analysis of the published literature. Meta-analyses included all published reports through August 28, 2020 with cognitive or neuroimaging measures for T2DM and healthy controls (HC), and included only observational studies with no intervention. For the UK Biobank analyses, T2DM and aging effects were identified and compared using multivariable linear regression. Random-effects meta-analyses were performed to confirm UK Biobank results. All analyses were Bonferroni corrected.

**Findings:** The UK Biobank dataset included cognitive and neuroimaging data (N=26,125) including 1,270 T2DM and 24,855 HC. Duration of T2DM ranged from 0–45 years (mean 9.7±7.9 years); 559 were treated with metformin alone, while 473 were unmedicated. Our meta-analysis evaluated 34 cognitive studies (N=22,231) and 60 neuroimaging studies: 30 of T2DM (N=866) and 30 of aging (N=1088). As compared to age, sex, and education-matched HC, T2DM was associated with marked cognitive deficits, particularly in executive functioning and processing speed. Likewise, we found that the diagnosis of T2DM was significantly associated with gray matter atrophy, primarily within the ventral striatum, cerebellum, and putamen, with reorganization of brain activity (decreased in the caudate, frontal eye fields, and premotor cortex and increased in the subgenual area, thalamus, brainstem and posterior cingulate cortex). The structural and functional changes associated with T2DM show marked overlap with the effects of aging but appear earlier, with disease duration linked to more severe neurodegeneration.

**Interpretation:** The neurocognitive impact of T2DM suggests marked acceleration of normal brain aging, by approximately 24%, made worse with chronicity. As such, neuroimaging-based biomarkers may provide a valuable adjunctive measure of T2DM progression and treatment efficacy based on neurological outcomes.
Introduction

In 2018, ~6.6% of the population carried a diagnosis of Type 2 diabetes mellitus (T2DM) \(^1\). Patients with T2DM are at greater risk for developing dementia and Alzheimer’s disease (AD) and have been reported to exhibit inferior cognitive performance when compared to age-matched healthy controls (HC) \(^2\). Several human neuroimaging studies have linked T2DM with brain atrophy and cognition \(^2\)-\(^6\); recent research suggested that T2DM resulted in a more rapid rate of cognitive decline than typically associated with natural aging \(^7\)-\(^9\).

Despite strong preliminary evidence linking T2DM to neurological and cognitive decline, few patients with T2DM undergo a comprehensive neurocognitive evaluation as part of their clinical care \(^8\), \(^10\), \(^11\). This may reflect the fact that T2DM diagnosis often occurs in middle age, hindering dissociation of patients’ cognitive changes from normal aging. Several studies published to date focused on the neurocognitive effects of T2DM include age-matched participants. However, because none has compared lifespan neurological changes to those experienced by equivalently aged patients with T2DM, it is currently unknown whether neurocognitive effects represent a T2DM-specific neurodegenerative pathway or the acceleration of typical brain aging. Moreover, there remain limited data\(^12\) evaluating the impact of chronicity or role of effective treatment in the progression of cognitive and neurological decline.

Routine clinical protocols typically focus on peripheral biomarkers (e.g., blood glucose and insulin levels, body fat percentage) as diagnostic modalities for T2DM. However, the neurological effects of T2DM may be apparent for many years before they can be detected by peripheral markers \(^3\), \(^8\). As such, by the time T2DM is diagnosed and treated by standard measures, patients may have already sustained irreversible brain damage. There is an urgent need to define the neurocognitive impact of T2DM and to determine how these negative sequelae might be prevented or treated \(^1\).

Given these unknowns and their clinical importance, here we focus on addressing three questions. First, we establish T2DM neurocognitive effects, as compared to age, sex, and education-matched healthy controls (HC). To do so, we leverage the robust statistical power made possible by UK Biobank \(^13\), the
largest (N=26,125) neurocognitive lifespan dataset to date, with UK Biobank results then compared to a meta-analysis of the published literature (34 cognitive studies, 60 neuroimaging studies) to assess convergence. Second, we ask whether changes in the brain observed in T2DM represent normal aging, accelerated aging, or a non-aging-related degenerative pathway specific to T2DM. Third, we test whether T2DM chronicity and medication status respectively exacerbate and ameliorate the progression of neurocognitive effects.

Methods

Analysis of UK Biobank Dataset (N=26,113)

General Overview: UK Biobank data were analyzed with linear regression models for both cognitive and neuroimaging data (SI Table 1). The primary factor of interest was T2DM, which we dissociated from aging effects by age matching T2DM and HC. To permit comparison of T2DM-specific effects to aging-specific effects, we also assessed the same neurocognitive variables with age as a factor of interest from samples that excluded patients diagnosed with T2DM. To determine whether T2DM neurocognitive effects suggested non-aging-related degenerative pathways specific to T2DM, versus accelerated typical aging, we compared the progression of neurodegeneration seen in T2DM to that seen in aging using Pearson correlations. To evaluate the impact of chronicity, we analyzed neurocognitive variables with time since T2DM diagnosis as a regressor. To evaluate the impact of metformin treatment, we compared medicated T2DM patients on metformin only, to unmedicated T2DM patients matched for disease duration, and controlled for body mass index (BMI)—a proxy measure for disease severity.\textsuperscript{14,15}

To mitigate potential confounders, T2DM and HC were matched for not only age, but also sex and education. To ensure that all individuals in our T2DM sample had type 2, rather than type 1 diabetes we excluded individuals with an age of onset <20 years. For all analyses, we applied Bonferroni correction to
account for multiple comparisons; $p$ values were adjusted accordingly. Regression models were fit using the Statsmodels Python library$^{16}$.

**Cognition:** Data on five cognitive domains for 24,300 participants (T2DM: $N=1,152$, HC: $N=23,148$) were extracted from the UK Biobank dataset, including *abstract reasoning*, *executive function*, *processing speed*, *reaction time*, and *short-term memory*. Exact sample sizes varied across cognitive domains based on data availability, and therefore are noted separately for each result. We used linear regression to estimate the impact of age and T2DM on a combined cognitive performance metric as well as separately on each of the five domains. The combined cognitive performance metric was derived from $z$-transformed task performance scores averaged across the individual domains for each subject. Effect sizes in cognition were quantified as percentages by dividing the beta coefficient and 95% CI of the factor of interest with the average performance of HC.

**Brain Structure:** Using structural MRI data from the UK Biobank dataset, we assessed the effects of T2DM (T2DM: $N=982$, HC: $N=982$) as compared to non-T2DM-specific aging effects ($N=14,836$) on atrophy of gray matter volume; these findings were available as voxel counts for the whole brain and also for 139 anatomical regions. For region-specific analyses, we coarse-grained the default unilateral parcellation provided by UK Biobank into 45 bilateral regions and corrected gray matter volumes for head size. We applied linear regression and quantified atrophy in each anatomical region as a relative percentage change in average gray matter volume by dividing beta coefficients and 95% confidence intervals (CIs) corresponding to the factor of interest with the average gray matter volume of HC. Statistical evaluation of the beta coefficients was Bonferroni corrected to adjust for multiple comparisons.

**Brain Function:** Using functional MRI data from the UK Biobank dataset, we assessed the effects of T2DM (T2DM: $N=712$; HC: $N=712$) as compared to non-T2DM-specific aging effects ($N=3,660$) on resting-state brain activity. Data were accessed already preprocessed by UK Biobank according to their standard pipelines$^{17}$. After transforming functional images to Montreal Neurological Institute (MNI) space, we performed spatial smoothing with a full width at half maximum (FWHM) of 5 mm, then quantified brain activity using the amplitude of low-frequency fluctuation$^{18}$ (ALFF). We used the program 3dRSFC,
which is a component of Analysis of Functional NeuroImages\textsuperscript{19, 20} (AFNI), to compute ALFF in voxel space. ALFF was computed from the 0.01–0.08 Hz frequency band, within a gray matter only brain mask. Computed voxel space ALFF values were normalized to the global mean of each individual subject. Statistical analyses were performed in voxel space using the Nistats Python library. We used a significance threshold of $p < 0.05$ and a minimum cluster size of 12 voxels ($\sim 100 \text{ mm}^3$) and controlled for multiple comparisons using false discovery rate (FDR).

*Impact of T2DM Duration:* To evaluate the impact of chronicity, we analyzed neurocognitive variables with (self-reported) time since T2DM diagnosis as a regressor.

*Impact of Metformin Treatment:* Focusing solely on patients with T2DM we evaluated whether metformin, the first-line medication for the treatment of T2DM, was associated with improved outcomes in terms of cognition, atrophy and brain activity. We compared subjects who reported not taking any medications to treat T2DM, to subjects who reported taking metformin but no other medications. For these comparisons, we matched subjects for age, sex, education and T2DM disease duration, and controlled for BMI—a proxy measure for disease severity\textsuperscript{14, 15}—since HbA1c levels were not measured by UK Biobank.

**Meta-Analysis of Published Literature (N=24,185)**

*Search strategy and selection criteria (cognition):* We conducted a literature search for peer-reviewed articles published up to August 28, 2020 from PubMed/Medline using the following search terms: “type-2-diabetes,” “diabetes mellitus, type 2,” “insulin-resistance,” <AND> “cognition,” “cognitive-function,” “cognitive-dysfunction,” “cognitive-performance,” and “neuropsychological tests.” Search results were filtered to include manuscripts that had undergone peer-review, were published in English with full-text availability, and reported relevant results. Both meta-analyses adhered to PRISMA guidelines [citation needed].

We excluded studies that (a) included participants with neurological or psychiatric diagnoses, (b) utilized treatment interventions without first obtaining baseline cognitive measurements, and (c) included only diagnostic threshold instruments for dementia (e.g., the Mini-Mental State Examination, or MMSE),
(d) included a novel cognitive test without adequate explanation of the scoring procedures, (e) did not perform age and education-matching of the participants diagnosed with T2DM to their HC, or (f) failed to provide summary statistics needed to calculate effect sizes. In the latter case, the authors were contacted to obtain relevant data.

Our literature search yielded 219 articles; relevant reviews were also screened for eligible studies. Seventy-five articles were identified for full-text evaluation; 34 studies were eligible for inclusion. Among the studies that were excluded, eight featured inadequate testing or scoring procedures, 14 included secondary analyses of the same patient sample that was used in previous publications, and five failed to perform appropriate education-matching of the study groups. Furthermore, one longitudinal study did not report baseline scores and another reported inconsistent sample sizes. Fifteen authors were contacted to obtain data not provided in the text; three authors provided the data requested, and the remaining 12 studies were excluded. Eligible studies included a total of 4,735 subjects diagnosed with T2DM and 17,496 HC.

Data analysis (cognition): We extracted data including publication year, authors, sample demographics, and cognition from all included studies. We extracted baseline data only from longitudinal studies to avoid practice effects. We sorted individual cognitive tests into several domains, including abstract reasoning, verbal memory, visual memory, working memory, information processing speed, executive function, short-term memory, verbal fluency, visuospatial construction, and motor speed (SI Table 2).

Statistical analyses were performed using R version 3.6.1 and the Metafor package version 2.4-0. Cognitive differences between participants diagnosed with T2DM and HC were determined by calculating standardized mean difference (SMD) effect sizes and 95% CIs for all cognitive domains. We calculated effect sizes as Cohen’s d by dividing the mean difference in group scores by the pooled standard deviation of individual domains; an SMD (Cohen’s d) of $-1.0$ was interpreted as a difference of one standard deviation in the negative direction. We used random-effects models to account for variability between samples not due to sampling error with significance at $p < 0.05$ and effect-size heterogeneity was evaluated using values for Cochran’s Q and $I^2$. Publication bias was evaluated with funnel plots.
Search strategy and selection criteria (brain): We used NeuroQuery\textsuperscript{25} to conduct a meta-analysis of all published neurobiological results associated with T2DM and aging. NeuroQuery is an automated Coordinate-Based Meta-Analysis (CBMA)\textsuperscript{26-28} tool based on a database of z-scores collected by crawling through texts and tables of published research articles by an automated algorithm\textsuperscript{29}. NeuroQuery then uses a multivariate model to predict the spatial distribution of voxel activations corresponding to a search term. The search terms we used to obtain the meta-analytic maps were: “diabetic” and “age”. These terms identified the 30 most relevant neuroimaging studies for T2DM and 30 most relevant neuroimaging studies for aging (SI Table 3). To account for any errors in the automated search results, the identified set of studies were cross-validated by an independent manual search using the same search terms for Google Scholar and PubMed to verify their relevance, as well as to confirm that they included T2DM age and sex-matched HC and T2DM (not Type 1 diabetes). In the T2DM datasets, 23 were fMRI (ALFF), two were structural (T1), three were FDG positron emission tomography (PET), and two were tractography (diffusion tensor imaging, DTI). In the aging datasets, 22 were fMRI (ALFF), three were structural (T1), and five were tractography (diffusion tensor imaging, diffusion weighted imaging).

Data analysis (brain): For region and voxel level comparisons of the meta-analytic T2DM and Aging maps from Neuroquery with their structural and functional counterparts from UK Biobank, the meta-analytic maps were transformed onto comparable coordinate space and spatial resolution. At the voxel level, the meta-analytic maps were resampled to the standard MNI affine (the transformation matrix that maps from voxel indices of the data array to actual real-world locations of the brain; no registration was required as images were already aligned). For region level comparisons, the transformed voxel maps were coarse-grained to the 45 regions of interest from UK Biobank by masking with each individual region and computing the mean activation of the masked voxels as the representative region value.
Results

Cognitive Effects of Aging and T2DM

Individuals without T2DM showed age-based cognitive effects across all domains in the UK Biobank (Fig. 1A). The strongest effects were observed in **executive function**, which showed a 2% decrease in performance per year (N=7,296, T=−30.6, p<1e−10) and **processing speed**, which showed a 1.6% decrease in performance per year (N=7,508, T=−41.0, p<1e−10). Our analyses identified further cognitive deficits associated with T2DM, beyond typical aging effects (Fig. 1B). The strongest effects were observed in **executive function**, which showed an 8.8% decrease in performance (T2DM: N=594; HC: N=594; T=−3.0, p=0.01), and **processing speed**, which showed a 6.3% decrease in performance. (T2DM: N=612; HC: N=612; T=−4.3, p=0.0001). All other domains were also significantly affected: −3% in **reaction time** (T2DM: N=1,149; HC: N=1,149; T=−4.0, p=0.0003), −4.3% in **short-term memory** (T2DM: N=647; HC: N=647; T=−4.2, p=0.0001) and −4% in **abstract reasoning** (T2DM: N=1,119; HC: N=1,119; T=−3.1, p=0.01). Our meta-analysis confirmed that individuals with T2DM exhibited markedly lower performance when compared to age, sex, and education-matched controls, over an even broader set of domains (Fig. 1C). These included **executive function** (K=18, d=−0.40, p=0.009), **short-term (~30 seconds) verbal memory** (K=23, d=−0.39, p=0.001), **verbal fluency** (K=25, d=−0.37, p=2e−8), **working memory** (K=12, d=−0.36, p=0.002), **abstract reasoning** (K=8, d=−0.36, p=1e−7), **information processing speed** (K=31, d=−0.34, p=5e−8), **visuospatial reasoning** (K=13, d=−0.32, p=4e−7), **delayed (~20 minute) verbal memory** (K=21, d=−0.21, p=0.005), and **short-term (~2-3 seconds) memory** (“attention”) (k=16, d=−0.21, p=0.05) (SI Table 4).

Neurobiological Effects of Aging and T2DM

*Brain Atrophy:* HC (N=14,836) showed a linear decrease in brain gray matter with age. This was most pronounced in the **ventral striatum**, which showed a 0.9% decrease per year (T=−55.4, p<1e−10) and **Heschl’s gyrus**, which also showed a 0.9% decrease per year (T=−55.1, p<1e−10) (Fig. 2A). As compared to their age-matched HC, T2DM patients showed further decreases in gray matter beyond typical aging
effects (T2DM: N=982; HC: N=982). These included both cortical and subcortical regions, with the most severe atrophy observed in the ventral striatum, which showed a 5.5% further decrease in volume per year beyond typical aging effects (T=–7.5, \( p<1\times10^{-10} \)), in the putamen with an additional 4.7% decrease in volume per year (T=–4.6, \( p=0.0002 \)), and in the cerebellum, which showed a 5% further decrease in volume per year (T=–9.8, \( p<1\times10^{-10} \)) (Fig. 2B).

**Brain Activity:** Aging was associated with functional reorganization of brain activity (ALFF), rather than global decrease or increase. Brain activation in T2DM showed similar reorganization. Normalized to whole brain activity, both aging (HC: N=3,660) and T2DM (T2DM: N=712, HC: N=712) were associated with decreased activation in the caudate, premotor cortex and frontal eye fields, with increased brain activity in the subgenual area, thalamus and brainstem (Fig. 3A). Our meta-analysis of 60 multi-modal neuroimaging studies (30 aging-specific, 30 T2DM-specific) independently identified the same regions as UK Biobank (caudate, frontal eye fields, premotor cortex, thalamus), but additionally identified clusters of decreased activity in Broca area and the superior temporal gyrus and increased activity in the posterior cingulate cortex, and angular gyrus (Fig. 3B).

**Neurocognitive Changes in T2DM and Normal Aging Overlap, Suggesting Common Pathways.**

Together, these analyses confirm that T2DM patients show evidence of neurocognitive deficits, with the most consistent and profound effects observed in structural atrophy (across all regions: T=–9.0, \( p<1\times10^{-10} \)) (SI Fig. 1B). Even after controlling for education, cognitive deficits remained statistically significant (T=–3.8, \( p=0.0001 \)) (SI Fig. 1A). Both aging and T2DM implicated the same areas of greatest vulnerability: for brain atrophy, this was the ventral striatum; for cognition, these were executive function and processing speed. When assessed across all brain regions, T2DM-related patterns in brain atrophy exhibited strong overlap with those associated with age \( (r=0.61, p=0.0002) \). Similarly, T2DM-related changes in brain activity (ALFF) also exhibited significant overlap with those associated with age \( (r=0.44, p=0.04) \). The meta-analysis, which included multi-modal neuroimaging measures (not only atrophy and brain activity,
but also glucose uptake via FDG-PET) also yielded equivalent results in terms of the overlap between neurobiological effects of T2DM and age ($r=0.58, p=0.0005$) (SI Fig. 2).

**T2DM Chronicity Exacerbates Neurocognitive Symptoms.**

Neurocognitive effects were more severe with increased disease duration, particularly for structural changes ($T= -4.8, p=0.000003$) (Fig. 4); each additional year of T2DM duration was associated with 24% acceleration of typical neurogenerative aging effects.

**T2DM Patients Treated with Metformin Do Not Demonstrate Improved Neurocognitive Symptoms.**

After matching groups for disease duration and BMI, T2DM patients who were treated with metformin alone (N=559) did not differ with respect to cognition or brain atrophy compared to T2DM patients who were unmedicated (N=473) (SI Fig. 3). Likewise, treatment status showed no significant impact on resting-state brain activity.

**Discussion**

The UK Biobank dataset confirms that T2DM patients show deficits in cognitive performance compared to HC, even after controlling for age, sex, and education, findings that were supported by meta-analysis of the published literature. These deficits in cognitive performance were accompanied by marked brain atrophy in the in T2DM sample as compared to age-matched HC. The atrophy was most severe (5% grey matter loss compared to HC) in the ventral striatum, a region critical to learning, decision making, goal-directed behavior, and cognitive control. These cognitive functions, collectively known as executive functioning, were (with processing speed) also those most affected by T2DM. Neurodegeneration for all regions was worsened with chronicity.

Our findings indicate that structural brain imaging, in particular, can provide a clinically valuable metric for identifying and monitoring neurocognitive effects associated with T2DM. Normalizing across
sample sizes to compare the measures of neurocognitive effects: structural MRI, functional MRI, and
cognitive testing, structural atrophy showed global effects that were more statistically robust ($p<2\times10^{-10}$)
than either global cognitive measures ($p=0.0001$) or global brain activity ($p=0.002$). One important
advantage of structural MRI over cognitive testing is that the former avoids confounding associated with
education and practice effects. Moreover, cognitive testing may be less interpretable in real-world clinical
settings in which such matching is not feasible. Structural MRI also showed advantages as a biomarker
over a functional MRI-derived measure of brain activation (ALFF). The reorganization of brain activity
seen with T2DM may reflect the brain’s switch to less metabolically expensive networks to conserve energy
in the face of diminishing access to glucose, a pattern previously documented in aging$^{30-33}$. Yet activation
patterns that are spatially reorganized, rather than globally increased or decreased, are less straightforward
to quantify. Moreover, functional MRI is an inherently more complex measure than structural MRI,
reflecting both neuronal and hemodynamic influences. Each of these of these influences may be
differentially affected by T2DM, further complicating its interpretation in a clinical setting.

The localization of brain atrophy in T2DM to the ventral striatum, followed by the cerebellum,
may reflect the fact that these two brain regions contain the densest concentrations of insulin-dependent
GLUT-4$^{34-37}$, as compared to non-insulin-dependent isoforms GLUT-1 and GLUT-3. The ventral striatum
functions as a critical hub within the reward circuit, integrating inputs (including external stimuli) from
both cortical and subcortical regions, and therefore is a key structure required for all learning. Rat studies
have shown modulation of nitric oxide within the ventral striatum to control release of acetylcholine$^{38}$, a
neurotransmitter severely reduced in dementia$^{39}$ and a target for its pharmaceutical treatment$^{40,41}$. Release
of nitric oxide is insulin dependent and reduced in T2DM$^{42}$. Together, these suggest a potential mechanistic
pathway between insulin resistance, atrophy of the ventral striatum, and widespread deficits with respect
to learning. In this context, memory deficits may be primarily driven by failure to encode rather than failure
to retrieve, which would be consistent with our results which did not identify the hippocampus as be one of
the regions most affected. Importantly, the structural and functional changes associated with T2DM show
marked overlap with the effects of aging but appear earlier. This suggests that neurocognitive changes
seen in T2DM may progress via a common mechanistic trajectory as normal brain aging, but which is accelerated.

Our analyses had two limitations, inherent in the datasets analyzed, which represent important directions for future research. First, our use of a lifespan dataset permitted tracking how variables change with age, but not for the same subjects. A more rigorous assessment of phase shift between trajectories of neurodegeneration for patients with T2DM and HC would be made possible only with a longitudinal study. Second, while we had access to disease duration and BMI, we did not have HbA1c measures, which would have provided a more direct measure of disease severity. While metformin was not found to be associated with better neurocognitive measures when matched to unmedicated patients with equivalent disease duration, and after controlling for BMI (a proxy measure for disease severity\textsuperscript{14, 15}), it was not possible to determine other diabetes-related characteristics. As such, our medication findings should be considered suggestive but not conclusive.

Consistent with findings from earlier studies that focused on the brain and energy metabolism\textsuperscript{43, 44}, we suggest that the T2DM and its progression may be associated with accelerated brain aging. As T2DM results in compromised energy availability, brain structure and function undergo accelerated deterioration. We consider the possibility that, by the time T2DM is formally diagnosed, neuronal insulin resistance may have already resulted in significant brain damage. As such, our findings underscore the need for additional research into brain-based biomarkers for T2DM and treatment strategies that specifically target its neurocognitive effects\textsuperscript{1}. 
Figures

Figure 1: Cognitive deficits are apparent with respect to both age and T2DM diagnosis. A: Using the UK Biobank dataset, we performed a quantitative analysis of the effects related to age on cognitive performance across five cognitive domains. Age was associated with significant deficits in all five domains, with the strongest effects observed in executive function and processing speed. B: Using the same dataset, we also analyzed cognitive performance in T2DM, with negative values on the y-axis representing performance below that of age, sex, and education-matched HC. As per age effects, executive function and processing speed showed the highest magnitude changes. C: Cognitive deficits identified in UK Biobank data were confirmed by our meta-analysis, which included 11 domains from 34 studies. Average effect sizes (Cohen’s d) corresponding to T2DM are shown on the y axis. Values below the cut-off line (y=0) indicate cases in which subjects with T2DM performed less well than age, sex, and education-matched HC. Numbers next to labels identify domains common across panels. Marker sizes represent sample sizes scaled as indicated in the bottom left corner of each panel. On panel C, sample size indicates the number of individual studies. Error bars are 95% CI. *P ≤ 0.05; **P ≤ 0.01; ***P ≤ 0.001, Bonferroni corrected.
Figure 2: Widespread gray matter atrophy can be observed with respect to both age and T2DM diagnosis status. Using the UK Biobank dataset, we measured gray matter atrophy across 45 anatomical regions. A: We observed significantly decreased gray matter volume in both cortical and subcortical brain regions with respect to age in HC. Age was associated with an average of ~0.5% brain-wide decrease in gray matter volume per year, most prominently for the ventral striatum and Heschl’s gyrus. B: Gray matter atrophy was also seen in patients diagnosed with T2DM compared to age matched HC, most prominently for the ventral striatum, cerebellum, and putamen. The distribution of T2DM-related effects overlapped with those associated with age, with degeneration of the ventral striatum and preservation of the thalamus and caudate. Error bars are 95% CI. *P ≤ 0.05; **P ≤ 0.01; ***P ≤ 0.001, Bonferroni corrected.
Figure 3: Overlap between age and T2DM with respect to reorganization of brain activity. A: For functional MRI data obtained from the UK Biobank dataset, we used the amplitude of low-frequency fluctuation (ALFF) to quantify brain activity. Effects linked to age are shown in the form of an unthresholded z-map represented by the pink-green color gradient, with pink indicating increased activation and green showing decreased. T2DM related effects were thresholded (minimum cluster size ~100mm$^3$, FDR $p<0.05$) to result in significant clusters. The outlines of these significant clusters are overlaid on the age-related z-map to demonstrate overlapping effects. The largest significant clusters with respect to T2DM were in the subgenual area (increase), the caudate (decreased), and frontal eye fields (decreased). All highlighted regions were similarly impacted across age, indicating substantial overlap between the two contrasts. B: Using multimodal neuroimaging data, we performed a meta-analysis for the same contrast using NeuroQuery. We extracted contrast maps for age and T2DM with NeuroQuery and overlaid the outlines of thresholded (minimum cluster size ~100mm$^3$, FDR $p<0.05$) z-maps from T2DM on unthresholded z-maps belonging to age. The overlapping effects were evident in several regions, most importantly in the cingulate gyrus, thalamus and premotor cortex. These results support the hypothesis that neurodegeneration in both T2DM and aging may be associated with common mechanistic pathways.
Figure 4: Progression of T2DM disease is significantly associated with gray matter atrophy, accelerating neurodegenerative effects seen in brain aging. For a quantitative evaluation of the impact of T2DM progression on gray matter volume, we considered time since T2DM diagnosis as the main factor of interest from the UK Biobank dataset. The T2DM+ cohort was divided into two groups based on disease duration (separated at 10 years) with a HC cohort also included for visualization purposes. We matched age, sex, education across these three groups and performed linear regression within T2DM+ subjects focusing on disease duration. Evaluation of our sample suggested that time since diagnosis was a significant factor, with each year after diagnosis of T2DM associated with an additional ~0.24 years of brain aging beyond that of age-matched T2DM−.

*P ≤ 0.05, **P ≤ 0.01, ***P ≤ 0.001, Bonferroni corrected.
Supplementary Figures

Cognitive and Structural Changes Associated with Age and T2DM: UK Biobank Dataset

A
Cognitive Performance across Age and T2DM Status

N_{T2DM+} = 568, N_{HC} = 568

T2DM+ vs HC: T = -3.8, p < 0.001***

B
Gray Matter Volume Across Age and T2DM Status

N_{T2DM+} = 982, N_{HC} = 982

T2DM+ vs HC: T = -5.0, p < 0.001***

Supplementary Figure 1: Aggregated whole brain measures represent the extent of accelerated brain aging with T2DM diagnosis. We used the UK Biobank dataset to address the extent by which aging is accelerated in individuals with T2DM. Subjects with T2DM were age, sex, and education matched with HC. A: We quantified a gross cognitive metric from the combination of multiple z-scored performance scores from five cognitive domains. This metric yielded an effective representation of the general decline across age, the gap between HC versus subjects diagnosed T2DM, and the relative extent of these two phenomena. We observed significantly decreased cognitive performance in subjects with T2DM: an increase of 3.8-years in age-related cognitive decline. B: An equivalent analysis was performed using whole brain gray matter volume. This metric yielded even stronger results compared to cognition. T2DM diagnosis was associated with significant atrophy: an increase of ~4.2-years in age-related neurodegeneration. Error bars are standard error of the mean. *P ≤ 0.05; **P ≤ 0.01; ***P ≤ 0.001, Bonferroni corrected.
Supplementary Figure 2: Effects of age and T2DM exhibited strong correlations within datasets and modalities, with no significant correlations observed across modalities. We considered six cases: 1. Age contrast, gray matter volume in UK Biobank; 2. T2DM contrast, gray matter volume in UK Biobank; 3. Age contrast, brain activation in UK Biobank; 4. T2DM contrast, brain activation in UK Biobank; 5. Age contrast, brain activation (aggregate) from NeuroQuery; 6. T2DM contrast, brain activation (aggregate) from NeuroQuery. Corresponding effects from region/domain specific analyses were taken as inputs and correlations were derived from all combinations of these six sets of effects. Age and T2DM were significantly correlated (Pearson’s r) within the same modality/dataset. No other significant correlations were observed across datasets or modalities. *P ≤ 0.05; **P ≤ 0.01; ***P ≤ 0.001, Bonferroni corrected.
Supplementary Figure 3: Treatment of T2DM patients with metformin had no impact on cognitive deficits or gray matter atrophy. We evaluated the UK Biobank dataset to determine whether treatment with metformin would prevent gray matter atrophy or the development of cognitive deficits associated with T2DM. Among T2DM diagnosed subjects only, we compared those subjects who reported using metformin but no other medications to those who reported not taking any medications to treat T2DM. We matched subjects for age, sex, education and T2DM disease duration, and controlled for BMI. The direction of theoretical improvement by metformin is indicated on both panels by an arrow. A: No statistically significant (α=0.05) differences in cognitive performance were detected when comparing subjects on metformin to unmedicated subjects. B: Neither our analysis of gray matter atrophy detected any significant (α=0.05) improvements associated with metformin treatment. Error bars are 95% CI.
## Supplementary Tables

**Supplementary Table 1. Summary of All Relevant UK Biobank data-fields.**

| Variable                        | Designation | Instance Number |
|---------------------------------|-------------|-----------------|
| Diagnosis (T2DM)                | 2443        | 0, 2            |
| Age                             | 21003       | 0, 2            |
| Sex                             | 31          | 2               |
| Education                       | 6138        | 2               |
| Age-of-onset (T2DM)             | 2976        | 0-2             |
| Body Mass Index (BMI)           | 21001       | 2               |
| Medication Status (Metformin)   | 20003       | 2               |
| Gray-Matter Volume              | 25005-25006, 25782-25920 | 2 |
| Resting-State MRI Images        | 20227       | 2               |
| Matrix-Pattern Completion       | 20016       | 2               |
| Alphanumeric Trail-Making Test  | 6350        | 2               |
| Symbol-Digit Substitution       | 23324       | 2               |
| Snap Game                       | 20023       | 0, 2            |
| Numeric Memory Test             | 4282        | 2               |
### Supplementary Table 2. Summary of Cognitive Functions Assessed, with Corresponding Instruments.

| Domains              | Common Tests                                                                 | Description                                                                 |
|----------------------|------------------------------------------------------------------------------|------------------------------------------------------------------------------|
| Verbal Memory        | Rey & California Auditory Verbal Learning Tests, Hopkins Verbal Learning Test, Delayed Word Recall, Weschler Text Recall Sub, Word List Recall, Weschler Story Recall | Short and long-term recall of verbal information. Includes both auditory and visual encoding. |
| Executive Function   | Trail Making (B), Stroop (III), Brixton Spatial Anticipation, Wisconsin Card Sort, Color Trails (2), Weschler Letter Number Sequencing | Top-down coordination of other cognitive domains (e.g., memory, motor function) to solve problems and manage cognitive resources. Often exhibited in tasks that require a degree of planning. |
| Verbal Fluency       | Word & Semantic Fluency Tests, Controlled Oral word Association Test, Letter & Category Fluency Tests, Boston Naming Test | Language skills. Commonly measured by enumeration (e.g., name as many words as you can that begin with the letter “B”). |
| Information Processing Speed | Trail Making (A), Digit Symbol Substitution, Stroop (I-II), Choice Reaction Time, Color Trails (1) | Speedy encoding and use of information. Often measured by time-to-completion in tasks that require the manipulation of presented information. |
| Working Memory       | (Backwards) Digit Span, Corsi Block Tapping, N-back                          | Holding information for a short time for use on a current task. Characterized by both maintaining and manipulating stored information. Commonly measured by having subjects re-order learned information. |
| Visuospatial Reasoning | Rey-Osterreith Figure Copy, Taylor Complex Figure, Weschler Object Assembly | Manipulation or reconstruction of spatial information. |
| Abstract Reasoning   | Raven’s Progressive Matrices, Matrix Pattern Completion, Weschler Similarities, Standard Progressive Matrices | Manipulation of presented information to solve a problem without prior knowledge. Interrelated with fluid intelligence. Often presented as shape or logic puzzles. |
| Visual Memory        | Location Learning, Weschler Visual Memory Subtest, Rey-Osterreith Delayed Recall, Face Recognition Test | Short and long-term recall of visually encoded information. |

Harvey, (2019). Domains of Cognition and their Assessment. Dialogues of Clinical Neuroscience, 21(3), 227-237. doi:10.31887/DCNS.2019.21.3
**Supplementary Table 3. Studies Identified as Most Relevant for Each Key Word by NeuroQuery Algorithm.**

| T2DM studies                      | Aging studies                      |
|-----------------------------------|------------------------------------|
| 1. Chun-Xia Wang et al. 2014      | György A Homola et al. 2012        |
| 2. Xiangzhe Qiu et al. 2016       | Peiying Liu et al. 2013            |
| 3. Natalia García-Casares et al. 2016 | G Juckel et al. 2012               |
| 4. Z-L Wang et al. 2017           | Natalia C Ebner et al. 2013        |
| 5. Thomas J Marder et al. 2014    | Michelle Hampson et al. 2012       |
| 6. Franco Cauda et al. 2009       | Sien Hu et al. 2012                |
| 7. Ying Cui et al. 2015           | Yu-Chien Wu et al. 2011            |
| 8. Dae-Jin Kim et al. 2016        | Rafat S Mohtasib et al. 2012       |
| 9. Jung-Lung Hsu et al. 2012      | Vonetta M Dotson et al. 2016       |
| 10. Zhiye Chen et al. 2012        | Estela Câmara et al. 2007          |
| 11. Christopher M Marano et al. 2014 | Harri Littow et al. 2010         |
| 12. Olivia M Farr et al. 2016     | Andrew P Merluzzi et al. 2016      |
| 13. Dan-Miao Sun et al. 2017      | Emily S Nichols et al. 2016        |
| 14. Dewang Mao et al. 2015        | Maria Morozova et al. 2016         |
| 15. Rongfeng Qi et al. 2012       | Kristen M Kennedy et al. 2009      |
| 16. Dewang Mao et al. 2015        | Chiara Chiapponi et al. 2013       |
| 17. Xin Huang et al. 2016         | Kathrin Cohen Kadosh et al. 2013   |
| 18. Wenqing Xia et al. 2013       | Quinton Deely et al. 2008          |
| 19. Po Lai Yau et al. 2009        | Kristen M Kennedy et al. 2015      |
| 20. Reza Tadayonnejad et al. 2019 | Tatia M C Lee et al. 2006          |
| 21. Chen Liu et al. 2014          | Joshua Carp et al. 2011            |
| 22. Yue Cheng et al. 2017         | Esther H H Keulers et al. 2010     |
| 23. Chuanming Li et al. 2014      | Kristin Nordin et al. 2017         |
| 24. Zhilian Zhao et al. 2014      | Joshua Carp et al. 2010            |
| 25. Xiaofen Ma et al. 2015        | Mark B Schapiro et al. 2004        |
| 26. Jessica A Turner et al. 2013  | Nick S Ward et al. 2008            |
| 27. Jiaxing Zhang et al. 2016     | Nancy E Adleman et al. 2016        |
| 28. Yingying Yue et al. 2015      | Kaitlin L Bergfield et al. 2010    |
| 29. Nicola Pannacciuilli et al. 2006 | Jenny R Rieck et al. 2017         |
| 30. Xin Di et al. 2013            | Marco Hirmstein et al. 2011        |
### Supplementary Table 4. Study Estimates of Cognitive Meta-Analysis

| Studies                          | Effect size (d) | Confidence Interval (95%) |
|----------------------------------|-----------------|---------------------------|
| **Executive Function**           |                 |                           |
| Bangen et al., 2015              | -0.21           | -0.33, -0.09              |
| Biessels at al., 2001            | -0.66           | -1.41, 0.09               |
| Brands et al., 2007              | -0.54           | -0.86, -0.21              |
| Cui et al., 2014                 | -0.54           | -1.07, -0.01              |
| Garcia-Casares et al., 2014      | -0.87           | -1.45, -0.29              |
| Kanaya et al., 2004              | 1.03            | 0.83, 1.24                |
| Lindeman et al., 2001            | -0.09           | -0.26, 0.08               |
| Liu et al., 2018                 | -0.54           | -1.04, -0.04              |
| Mehrebian et al., 2012           | -1.35           | -1.93, -0.76              |
| Mogi et al., 2004                | -0.36           | -0.81, 0.08               |
| Reijmer et al., 2016             | -0.33           | -0.80, 0.15               |
| Ryan & Geckle. 2008              | -0.31           | -0.71, 0.08               |
| Takeuchi et al., 2012            | -0.62           | -1.09, -0.15              |
| Van den Berg et al., 2010        | -0.65           | -1.05, -0.24              |
| Xia et al., 2010                 | -0.61           | -1.07, -0.16              |
| Yau et al., 2010                 | -0.14           | -0.80, 0.51               |
| Yeung et al., 2009               | -0.50           | -0.83, -0.18              |
| Zhou et al., 2010                | -0.48           | -1.10, 0.15               |

**Short-Term Verbal Memory**

| Studies                          | Effect size (d) | Confidence Interval (95%) |
|----------------------------------|-----------------|---------------------------|
| Aberle et al., 2008              | 0.02            | -0.31, 0.36               |
| Arvanitakis et al., 2006         | -0.05           | -0.25, 0.14               |
| Bangen et al., 2015              | -0.13           | -0.25, -0.02              |
| Brands et al., 2007              | -0.32           | -0.64, 0.00               |
| Cholerton et al., 2019           | 0.06            | -0.13, 0.25               |
| Cosway et al., 2001              | -0.32           | -0.81, 0.17               |
| Cui et al., 2014                 | -0.07           | -0.59, 0.46               |
| Dai et al., 2017                 | -1.7            | -2.24, -1.16              |
| Garcia-Casares et al., 2014      | -1.62           | -2.26, -0.98              |
| Liu et al., 2018                 | -0.49           | -0.99, 0.01               |
| Lowe et al., 1994                | -0.06           | -0.36, 0.25               |
| Mattei et al., 2019              | -0.3            | -0.42, -0.19              |
| Mehrebian et al., 2012           | -1.71           | -2.33, -1.10              |
| Mogi et al., 2004                | -0.29           | -0.74, 0.16               |
| Moran et al., 2013               | 0.31            | 0.16, 0.46                |
| Reijmer et al., 2016             | -0.23           | -0.70, 0.24               |
| Ryan & Geckle, 2008              | -0.41           | -0.81, -0.01              |
| Takeuchi et al., 2012            | -0.56           | -1.03, -0.09              |
| van den Berg et al., 2010        | -0.39           | -0.79, 0.01               |
| van Harten et al., 2007          | -0.35           | -0.71, 0.01               |
| Xia et al., 2015                 | -0.32           | -0.77, 0.13               |
| Yau et al., 2010                 | -0.70           | -1.37, -0.03              |
| Yeung et al., 2009               | -0.37           | -0.69, -0.04              |

**Verbal Fluency**

| Studies                          | Effect Size (d) | Confidence Interval (95%) |
|----------------------------------|-----------------|---------------------------|
| Aberle et al., 2008              | 0.06            | -0.27, 0.39               |
| Arvanitakis et al., 2006         | -0.12           | -0.31, 0.08               |
| Atiea et al., 1995               | -0.32           | -0.86, 0.22               |
| Studies                          | Effect Size (d) | Confidence Interval (95%) |
|---------------------------------|-----------------|---------------------------|
| Arvanitakis et al., 2006        | -0.04           | -0.24, 0.15               |
| Atiea et al., 1995              | -0.48           | -1.02, 0.07               |
| Biessels et al., 2001           | -0.63           | -1.38, 0.12               |
| Brands et al., 2007             | -0.36           | -0.69, -0.04              |
| Lowe et al., 1994               | -0.04           | -0.35, 0.26               |
| Mankovsky et al., 2018          | -0.07           | -0.57, 0.44               |
| Mattei et al., 2019             | -0.27           | -0.38, -0.15              |
| Ryan & Geckle, 2008             | -0.34           | -0.73, 0.06               |
| Solanki et al., 2009            | -1.33           | -1.83, -0.84              |
| Takeuchi et al., 2012           | -0.56           | -1.03, -0.10              |
| van den Berg et al., 2010       | -0.50           | -0.90, -0.10              |
| Zihl et al., 2010               | -0.17           | -0.82, 0.49               |

Abstract Reasoning

| Studies                          | Effect Size (d) | Confidence Interval (95%) |
|---------------------------------|-----------------|---------------------------|
| Arvanitakis et al., 2006        | -0.24           | -0.43, -0.04              |
| Bangen et al., 2015             | -0.48           | -0.59, -0.36              |
| Brands et al., 2007             | -0.19           | -0.51, 0.13               |
| Cosway et al., 2001             | -0.10           | -0.59, 0.38               |
| Lowe et al., 1994               | -0.41           | -0.73, -0.10              |
| Ryan & Geckle, 2008             | -0.27           | -0.67, 0.12               |
| van den Berg et al., 2010       | -0.38           | -0.78, 0.02               |
| Zihl et al., 2010               | -1.06           | -1.82, -0.29              |
## Processing Speed

\[ d = -0.34, K = 31, p < 0.001, Q = 227.3, I^2 = 82.3\% \]

| Studies                  | Effect Size (d) | Confidence Interval (95%) |
|--------------------------|----------------|---------------------------|
| Aberle et al., 2008      | 0.00           | -0.33, 0.33               |
| Arvanitakis et al., 2006 | -0.14          | -0.34, 0.05               |
| Atiea et al., 1995       | 0.05           | -0.49, 0.59               |
| Bangen et al., 2015      | -0.22          | -0.34, -0.11              |
| Biessels et al., 2001    | 0.19           | -0.54, 0.92               |
| Brands et al., 2007      | -0.26          | -0.58, 0.06               |
| Cholerton et al., 2019   | -0.43          | -0.62, -0.24              |
| Cosway et al., 2001      | -0.30          | -0.79, 0.19               |
| Cui et al., 2014         | -0.68          | -1.22, -0.14              |
| Dai et al., 2017         | 0.25           | -0.21, 0.72               |
| Garcia-Casares et al., 2014 | -0.66        | -1.23, -0.09              |
| Lindeman et al., 2001    | -0.02          | -0.19, 0.15               |
| Liu et al., 2018         | -0.36          | -0.86, 0.13               |
| Mattei et al., 2019      | -0.37          | -0.49, -0.25              |
| Mehrebian et al., 2012   | -1.23          | -1.8, -0.65               |
| Mogi et al., 2004        | -0.59          | -1.04, -0.14              |
| Moran et al., 2013       | 0.16           | 0.02, 0.31                |
| Naseer et al., 2014      | -0.61          | -1.25, 0.02               |
| Rawlings et al., 2015    | -0.65          | -0.70, -0.60              |
| Redondo et al., 2016     | -0.54          | -1.15, 0.07               |
| Reijmer et al., 2016     | -0.06          | -0.53, 0.41               |
| Ryan & Geckle, 2008      | -0.43          | -0.83, -0.03              |
| Solanki et al., 2009     | -0.93          | -1.41, -0.46              |
| Takeuchi et al., 2012    | -0.61          | -1.08, -0.14              |
| van den Berg et al., 2010| -0.11          | -0.51, 0.29               |
| van Harten et al., 2007  | -0.48          | -0.84, -0.11              |
| Xia et al., 2015         | -0.27          | -0.71, 0.18               |
| Yau et al., 2010         | -0.69          | -1.37, -0.02              |
| Yeung et al., 2009       | -0.38          | -0.70, -0.06              |
| Zhou et al., 2010        | -0.27          | -0.89, 0.35               |
| Zihl et al., 2010        | -1.28          | -2.07, -0.49              |

## Visuospatial Reasoning

\[ d = -0.32, K = 13, p < 0.001, Q = 27.3, I^2 = 56.6\% \]

| Studies                  | Effect Size (d) | Confidence Interval (95%) |
|--------------------------|----------------|---------------------------|
| Arvanitakis et al., 2006 | -0.11          | -0.31, 0.09               |
| Bangen et al., 2015      | -0.18          | -0.30, -0.07              |
| Biessels et al., 2001    | -0.25          | -0.98, 0.49               |
| Brands et al., 2007      | -0.21          | -0.53, 0.11               |
| Garcia-Casares et al., 2014 | -0.79        | -1.36, -0.21              |
| Lowe et al., 1994        | -0.16          | -0.47, 0.15               |
| Mattei et al., 2019      | -0.33          | -0.45, -0.21              |
| Moran et al., 2013       | -0.56          | -0.71, -0.41              |
| Ryan & Geckle, 2008      | -0.38          | -0.78, 0.01               |
| Takeuchi et al., 2012    | -0.41          | -0.87, 0.06               |
| van den Berg et al., 2010| -0.16          | -0.56, 0.24               |
### Delayed Verbal Memory

| Studies                        | Effect Size (d) | Confidence Interval (95%) |
|-------------------------------|-----------------|---------------------------|
| Arvanitakis et al., 2006      | -0.01           | -0.21, 0.18               |
| Bangen et al., 2015           | -0.07           | -0.19, 0.05               |
| Brands et al., 2007           | -0.28           | -0.60, 0.04               |
| Cholerton et al., 2019        | 0.04            | -0.15, 0.23               |
| Cosway et al., 2001           | -0.24           | -0.73, 0.24               |
| Cui et al., 2014              | -0.08           | -0.60, 0.45               |
| Dai et al., 2017              | -0.75           | -1.22, -0.27              |
| Liu et al., 2018              | -0.62           | -1.13, -0.12              |
| Lowe et al., 1994             | -0.10           | -0.41, 0.21               |
| Mehrebian et al., 2012        | -0.76           | -1.31, -0.22              |
| Mogi et al., 2004             | 0.18            | -0.26, 0.63               |
| Moran et al., 2013            | 0.20            | 0.05, 0.35                |
| Rawlings et al., 2015         | -0.40           | -0.45, -0.35              |
| Reijmer et al., 2016          | -0.13           | -0.60, 0.34               |
| Ryan & Geckle, 2008           | -0.22           | -0.61, 0.17               |
| Takeuchi et al., 2012         | -0.36           | -0.82, 0.10               |
| van den Berg et al., 2010     | -0.40           | -0.80, 0.00               |
| van Harten et al., 2007       | -0.42           | -0.78, -0.05              |
| Xia et al., 2015              | -0.15           | -0.59, 0.30               |
| Yeung et al., 2009            | -0.07           | -0.39, 0.25               |
| Zhou et al., 2010             | -0.96           | -1.62, -0.31              |

### Short-Term Memory

| Studies                        | Effect Size (d) | Confidence Interval (95%) |
|-------------------------------|-----------------|---------------------------|
| Arvanitakis et al., 2006      | -0.13           | -0.33, 0.06               |
| Atiea et al., 1995            | -0.47           | -1.01, 0.08               |
| Biessels et al., 2001         | -1.05           | -1.83, -0.27              |
| Brands et al., 2007           | -0.08           | -0.40, 0.24               |
| Dai et al., 2017              | -0.66           | -1.14, -0.19              |
| Lindeman et al., 2001         | -0.17           | -0.33, 0.00               |
| Liu et al., 2018              | -0.53           | -1.03, -0.03              |
| Lowe et al., 1994             | 0.14            | -0.17, 0.45               |
| Mankovsky et al., 2018        | 0.17            | -0.34, 0.67               |
| Mattei et al., 2019           | -0.11           | -0.22, 0.01               |
| Moran et al., 2013            | 0.08            | -0.07, 0.22               |
| Naseer et al., 2014           | 0.04            | -0.57, 0.66               |
| Solanki et al., 2009          | -0.92           | -1.39, -0.44              |
| Takeuchi et al., 2012         | -0.33           | -0.80, 0.13               |
| van den Berg et al., 2010     | -0.12           | -0.52, 0.27               |
| Yau et al., 2010              | -0.30           | -0.96, 0.36               |

### Recognition Verbal Memory

| Studies                        | Effect Size (d) | Confidence Interval (95%) |
|-------------------------------|-----------------|---------------------------|
| Arvanitakis et al., 2006      | 0.00            | -0.20, 0.20               |
| Studies                        | Effect Size (d) | Confidence Interval (95%) |
|-------------------------------|-----------------|---------------------------|
| Bangen et al., 2015           | -0.06           | -0.17, 0.06               |
| Brands et al., 2007           | -0.38           | -0.70, -0.06              |
| Dai et al., 2017              | -0.61           | -1.08, -0.14              |
| Liu et al., 2018              | -0.53           | -1.02, -0.03              |
| Lowe et al., 1994             | -0.07           | -0.38, 0.24               |
| Mattei et al., 2019           | -0.17           | -0.28, -0.05              |
| Mehrebian et al., 2012        | -0.46           | -1.00, 0.07               |
| Moran et al., 2013            | 0.16            | 0.01, 0.31                |
| Takeuchi et al., 2012         | 0.12            | -0.34, 0.58               |
| van den Berg et al., 2010     | -0.51           | -0.92, -0.11              |
| Zhou et al., 2010             | -0.89           | -1.55, -0.24              |

Visual Memory: $d = -0.13$, $p = 0.32$, $K = 8$, $Q = 19.9$, $I^2 = 66.6\%$
## Supplementary Table 5. Characteristics of patients who underwent cognitive testing in studies included in our meta-analysis.

| Author            | Year | N  | Age (Mean) | Education (Years) | Female (%) |
|-------------------|------|----|------------|-------------------|------------|
| Aberle et al.     | 2008 | 38 | 62.9       | 9.94              | 48.5       |
| Arvanitakis et al.| 2006 | 116| 78         | 13.7              | 78         |
| Atiea et al.      | 1995 | 40 | 69.05      | 68.1              | 31         |
| Bangen et al.     | 2015 | 378| 75.4       | 9.9               | 67         |
| Biessels et al.   | 2001 | 13 | 57.7       | 11.2              | 41.3       |
| Brands et al.     | 2007 | 119| 65.9       | 14.5              | 49.4       |
| Cholerton et al.  | 2019 | 185| 53         | 12                | 70.4       |
| Cosway et al.     | 2001 | 33 | 57.7       | 11.2              | 59.2       |
| Cui et al.        | 2014 | 29 | 58.3       | 10.4              | 55.4       |
| Dai et al.        | 2017 | 41 | 65.51      | 16.35             | 52         |
| Garcia-Casares et al. | 2014 | 25 | 60         | 18.3              | 38         |
| Kanaya et al.     | 2004 | 118| 73.55      | 14.7              | 57.2       |
| Lindeman et al.   | 2001 | 188| 73.4       | 10.9              | -          |
| Liu et al.        | 2018 | 32 | 58.09      | 9                 | 12.3       |
| Lowe et al.       | 1994 | 80 | 59.3       | 11.3              | 63.9       |
| Mankovsky et al.  | 2018 | 93 | 62.3       | 14.7              | 70.2       |
| Mattei et al.     | 2019 | 465| 58.9       | 14.7              | 73.1       |
| Mehrbain et al.   | 2012 | 37 | 56         | 14                | 56.5       |
| Mogi et al.       | 2004 | 69 | 71.6       | 10.4              | 64.5       |
| Moran et al.      | 2013 | 350| 67.8       | 11.3              | 43.2       |
| Naseer et al.     | 2014 | 20 | 53.3       | -                 | -          |
| Rawlings et al.   | 2015 | 1779| 58.2       | 56.8              | -          |
| Redondo et al.    | 2016 | 20 | 70.82      | 6.79              | 46         |
| Reijmer et al.    | 2016 | 35 | 71.1       | 4*                | 41.4       |
| Ryan & Geckle     | 2008 | 50 | 50.8       | 14.4              | 73         |
| Solanki et al.    | 2009 | 50 | 50         | -                 | -          |
| Takeuchi et al.   | 2012 | 42 | 62.4       | 13.7              | 40         |
| van den Berg et al.| 2010 | 68 | 65.6       | 4*                | 48.1       |
| van Harten et al. | 2007 | 92 | 73.2       | 4*                | 55.8       |
| Xia et al.        | 2015 | 38 | 56         | 9.6               | 51.3       |
| Yau et al.        | 2010 | 18 | 16.46      | 10.75             | -          |
| Yeung et al.      | 2009 | 41 | 68.59      | 15.12             | 68         |
| Zhou et al.       | 2010 | 21 | 68         | 12.48             | 50         |
| Zihl et al        | 2010 | 12 | 42.45      | 10.5              | -          |

T2DM, type-2 diabetes mellitus; HC, healthy control

*median education
**Supplementary Table 6.** List and justification for studies excluded from our cognitive meta-analysis.

| Studies                  | Justification for Exclusion                     |
|--------------------------|-------------------------------------------------|
| Asimakopoulou et al., 2002 | Did not match for education                     |
| Brands et al., 2007      | Identical sample of study already included       |
| Bruehl et al., 2009      | Authors did not provide requested data           |
| Callisaya et al., 2018   | Identical sample of study already included       |
| Chen et al., 2014        | Inadequate cognitive testing                     |
| Chen et al., 2017        | Inadequate cognitive testing                     |
| Christman et al., 2010   | Did not match for education                     |
| Cooray et al., 2011      | Authors did not provide requested data           |
| Cui et al., 2015         | Identical sample of study already included       |
| Cui et al., 2017         | Identical sample of study already included       |
| Cui et al., 2017         | Authors did not provide requested data           |
| Degen et al., 2016       | Inadequate cognitive testing                     |
| Dey et al., 1997         | Authors did not provide requested data           |
| Dore et al., 2009        | No baseline data in longitudinal design          |
| Elias et al., 1997       | Inadequate cognitive testing                     |
| Grodstein et al., 2001   | Unclear sizes of sample sub-groups               |
| Hassing et al., 2004     | Did not match for education                     |
| Helkala et al., 1995     | Authors unable to be reached                     |
| Kinga & Anett, 2016      | Did not match for education                     |
| Kumari et al., 2005      | Identical sample of study already included       |
| Liu et al., 2016         | Identical sample of study already included       |
| Liu et al., 2018         | Identical sample of study already included       |
| Liu et al., 2020         | Identical sample of study already included       |
| Manschot et al., 2006    | Inadequate cognitive testing                     |
| Mooradian et al., 1988   | Authors did not provide requested data           |
| Nazaribadie et al., 2013 | Did not match for education                     |
| Nealon et al., 2017      | Authors did not provide requested data           |
| Nooyens et al., 2010     | Inadequate cognitive testing                     |
| Perlmutter et al., 1984  | Authors did not provide requested data           |
| Ravona-Springer et al., 2018 | Authors did not provide requested data       |
| Reijmer et al., 2011     | Identical sample of study already included       |
| Robertson-Tchabo et al., 1986 | Inadequate cognitive testing                |
| Ruis et al., 2009        | Authors did not provide requested data           |
| Scott et al., 1998       | Identical sample of study already included       |
| Sinclair et al., 2000    | Inadequate cognitive testing                     |
| Smith et al., 2009       | Identical sample of study already included       |
| Spauwen et al., 2015     | Authors did not provide requested data           |
| van Gemert et al., 2018  | Authors did not provide requested data           |
| Watari et al., 2006      | Authors did not provide requested data           |
| Xia et al., 2013         | Identical sample of study already included       |
| Xia et al., 2015         | Identical sample of study already included       |
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