Brain, Behavior, & Immunity - Health 41 (2024) 100862

Contents lists available at ScienceDirect

Brain, Behavior, & Immunity - Health

journal homepage: www.editorialmanager.com/bbih/default.aspx

Circulating Interleukin-17A is associated with executive function in middle aged adults with and without type 2 diabetes

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ARTICLE INFO

Keywords:
IL-17A
Executive function
Cognition
Type 2 diabetes
Midlife

ABSTRACT

Midlife cardiovascular risk factors such as Type 2 Diabetes (T2DM) and obesity are associated with the later development of cognitive impairment and dementia. Systemic inflammation is postulated as a crucial mechanism, yet there are few studies examining this at the earliest stages prior to overt cognitive impairment. To assess this, we recruited a cohort of middle-aged cognitively-unimpaired individuals with and without uncomplicated T2DM. Comprehensive neuropsychological assessment was performed at baseline and at 4-year follow-up. Ten serum chemokines and cytokines (Eotaxin, MCP-1, MIP-1β, CXCL10, IL-6, IL-10, IL12p70, IL-17A, IFN-γ and TNF-α) were measured at both baseline and follow-up using high-sensitivity assays. Overall, 136 participants were recruited including 90 with uncomplicated midlife T2DM (age 52.6 ± 8.3; 47% female) and 46 without (age 52.9 ± 8.03; 61% female). Cognitive trajectories were stable over time and did not differ with T2DM. Yet on cross-sectional analyses at both baseline and follow-up, greater circulating IL-17A was consistently associated with poorer performance on tests of executive function/attention (β: 0.21; −0.40, −0.02, p = 0.03 at baseline; β: 0.26; −0.46, −0.05, p = 0.02 at follow-up). Associations persisted on covariate adjustment and did not differ by T2DM status. In summary, we provide evidence that greater circulating IL-17A levels were associated with poorer executive function in midlife, independent of T2DM. Long-term follow-up of this and other cohorts will further elucidate the earliest stages in the relationship between systemic inflammation and cognitive decline to provide further mechanistic insights and potentially identify those at greatest risk for later cognitive decline.

1. Introduction

There is consistent evidence that chronic, low-grade sterile inflammation (or "inflammaging"), is associated with the development of cognitive impairment and dementia in later life (Kipinoinen et al., 2022). Systemic inflammation, often detected in serum as elevated levels of circulating Interuekin-6 (IL-6) and Tumor Necrosis Factor alpha (TNF-α), has been consistently linked to cognitive decline in longitudinal population based studies (Dyer et al., 2024; Walker et al., 2019). Importantly, midlife risk factors such as Type 2 Diabetes (T2DM) and obesity which are associated with an increased risk of cognitive impairment and dementia are also associated with elevated levels of circulating pro-inflammatory cytokines - supporting the central role of peripheral inflammation as a mechanistic link between midlife risk factors and later cognitive decline (Donath, 2014; Duncan et al., 2003; Gonzalez et al., 2018).

The exact pathways by which low-grade systemic inflammation may lead to cognitive dysfunction in currently unclear, although there is now substantial evidence that circulating immunologically-relevant molecules such as circulating cytokines and chemokines can have a direct impact on brain function (Walker et al., 2019, 2023). Systemic inflammation may result in reactive microglial responses in the Central

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https://doi.org/10.1016/j.bbih.2024.100862
Received 25 June 2024; Received in revised form 19 August 2024; Accepted 14 September 2024
Available online 16 September 2024

Nervous System and impair hippocampal neurogenesis (Yousef et al., 2019). Systemic inflammation may also directly contribute to blood-brain barrier breakdown and accelerate neurodegenerative pathology (Cunningham, 2011; Liu et al., 2020; Lopez-Rodriguez et al., 2021). Understanding the earliest possible stages linking systemic inflammation and later cognitive dysfunction may help in selecting-out individuals at greatest risk of later cognitive decline for potential preventative interventions.

Despite the significant body of literature supporting the relationships between midlife risk factors, systemic inflammation and later cognitive decline, few studies have examined the earliest possible signs of this link. In the landmark Edinburgh T2DM study, circulating IL-6 and TNF-α were associated with both cross-sectional and longitudinal cognitive performance in older adults with established T2DM including individuals with micro- and microvascular complications (Marioni et al., 2010; Sluiman et al., 2022). The relationship between early systemic inflammation and cognitive decrements in middle-aged adults with risk factors such as T2DM has been less frequently evaluated – at the precise age when these factors are exerting their risk. Further, studies have varied by cytokines and inflammatory markers studied (typically IL-6 and TNF-α due to assay performance and availability), and cognitive tests performed (typically brief tests of global cognitive function).

In aiming to address this gap, we recruited a longitudinal cohort of middle-aged individuals free from overt cognitive impairment with and without T2DM, one of the strongest midlife risk factors for later cognitive decline. We utilised a panel of high-sensitivity immunoassays enabling quantification of low abundant proteins at femtomolar concentrations and a comprehensive neuropsychological assessment battery including those domains of cognitive function affected earliest in T2DM-related cognitive dysfunction. We hypothesised that a greater level of systemic inflammation would be associated with poorer cognitive function in middle-aged adults, which may differ by T2DM status.

2. Methods

2.1. Study setting, participant recruitment and clinical assessment

ENBIND (Exploring Novel Biomarkers of Brain Health in Type 2 Diabetes Mellitus) is a longitudinal study based in Tallaght University Hospital (TUH), Dublin, Ireland (Dyer et al., 2021). This study aims to assess novel biomarkers of brain health and cognitive function in otherwise healthy individuals with midlife T2DM, free from diabetes-related micro or macro-vascular complications and age-matched healthy controls. Ethical approval was granted from the Tallaght-St James's Joint Research Committee (Ref: 2018/09/02/2018-10 List 34). Baseline assessment occurred in 2018–2019 with participants re-assessed in 2023–2024 – an interval of 4 years since initial assessment. The duration of 4 years was selected between follow-up waves considering both the unimpaired nature of the included cohort as well as the aim of the ENBIND study – namely to detect the earliest possible indicators and biomarkers of cognitive dysfunction in individuals with midlife risk factors for later cognitive decline.

Both male and female participants with midlife physician-diagnosed T2DM and were recruited from tertiary-referral clinics at TUH. For the current study, midlife was defined as age between 35 and 65 at time of recruitment. Participants were free from any microvascular (nephropathy, retinopathy or neuropathy) or macrovascular (stroke/transient ischaemic attack, myocardial infarction, peripheral vascular disease) complications of T2DM – considered "uncomplicated T2DM". Individuals with active depression, diagnosed psychiatric or neurological disorder or other significant medical comorbidity (any medical condition which limits an individual's daily activities or with a known impact on cognitive function) were excluded from participation. Healthy controls were recruited by local advertisement and screened for T2DM (including measurement of HbA1c).

Study visits at baseline and at follow-up were identical in nature and performed by trained study physicians. All individuals underwent assessment of medical history, medication use, demographics and family history of cognitive impairment/dementia. Individuals with T2DM were assessed for duration of diagnosis, medication use and underwent physical examination for neuropathy and other T2DM related complications. The Diabetic Neuropathy Symptom Score (DNSS) was used to further assess for the presence of neuropathy and if positive individuals excluded from further participation (Meijer et al., 2002).

2.2. Cognitive and neuropsychological assessment

The Montreal Cognitive Assessment (MoCA) was conducted in all participants as a general cognitive screener and those with a cut off <23 excluded from further participation as the current study aimed to assess earliest possible cognitive decrements in middle-aged individuals without cognitive impairment. A one-point age-adjustment in MoCA score was applied where appropriate. In those scoring 23 or above, participants underwent comprehensive neuropsychological assessment using a custom Cambridge Neuropsychological Test Automated Battery (CANTAB). The battery was administered in an identical fashion at both baseline and follow-up visits and was designed to specifically probe memory, executive function and attention as these domains are some of those first affected by T2DM-related cognitive dysfunction.

The neuropsychological tests employed at both time points consisted of.

i. **Memory Assessments**:
   a. **Paired Associates Learning (PAL)**: a task where individuals have to memorize the locations of geometric patterns appearing on the screen
   b. **Spatial Working Memory (SWM):** individuals have to remember the locations on screen of certain "hidden tokens" and must remember the locations where they have previously found
   c. **Pattern Recognition Memory (PRM):** memorizing patterns with recall tested using a binary forced-choice paradigm after a delay of 20 min

ii. **Executive Function/Attention Assessments:**
   a. **Reaction Time Task (RTT):** pressing one of five circles with performance reported in milliseconds
   b. **Rapid Visual Processing (RVP):** detecting number sequences within a rapidly changing sequence of numbers
   c. **One Touch Stockings of Cambridge (OTS):** coloured balls are visualised inside stockings and the participant must move them one at a time to match a given pattern in the least number of moves possible.

2.3. Serum sampling and measurement of serum chemokines/cytokines

Prior to cognitive assessment at both baseline and follow-up, individuals had a peripheral blood sample taken for analysis of inflammatory chemokines/cytokines. Blood was collected in 6 mL serum clot activator tubes and processed as soon as possible after venepuncture. Samples were centrifuged at 1800×*g* with serum aliquoted in cryovials until further analysis. For the current study, an aliquot of serum from baseline and follow-up was used to assess for levels of circulating chemokines and cytokines. Chemokines and Cytokines were assessed using the MesoScaleDiscovery (MSD) Electrochemiluminesence (ECLIA) platform. A panel of 10 markers was chosen a priori based on associations with cognitive function/cognitive impairment through a thorough literature review and based on assay availability/configuration (Bettcher et al., 2016; Kim et al., 2018; Morgan et al., 2019; Shen et al., 2019a; Thomas et al., 2020).This panel included chemokines Eotaxin, Monocyte Chemoattractant Protein 1 (MCP-1), Macrophage Inflammatory Protein 1β (MIP-1B) and C-X-C Motif Chemokine Ligand (CXCL10) and cytokines Interleukin-6 (IL-6), Interleukin-10 (IL-10), Interleukin

Table 1

Baseline Characteristics, Serum Chemokine/Cytokine Concentration and Neuropsychological Performance in Middle-Aged Adults with and without Type 2 Diabetes Mellitus. Baseline characteristics are provided for both individuals with and without midlife type-2 diabetes. Data are provided as means with standard deviations, medians with interquartile ranges or total numbers with percentages as appropriate. Statistical tests consist of t-tests, wilcoxon rank-sum or Chi-square tests as appropriate with corresponding test statistic and p-value reported. SD: Standard Deviation; IQR: Inter-Quartile Range; BMI: Body Mass Index; HbA1c: Glycated Haemoglobin; T2DM: Type 2 Diabetes Mellitus

	Healthy Controls (N = 46)	Midlife T2DM (N = 90)	Statistic
Baseline Characteristics			
Age, years (mean, SD)	52.6 (8.3)	52.9 (8.0)	$t = -0.18$, $p = 0.57$
Sex, female (n, %)	28 (61%)	42 (47%)	$\chi^2 = 2.5$, $p = 0.12$
BMI, kg/m^2 (mean, SD)	26.9 (3.0)	32.1 (7.3)	$t = -4.6$, $p < 0.001$
Educational Attainment	3 (6.5%)	12 (13.3%)	$\chi^2 = 1.7$, $p = 0.42$
Primary (n; %)	33 (71.7%)	63 (70%)	
Secondary (n; %)	10 (21.7%)	15 (16.7%)	
Tertiary (n; %)			
Family History of Dementia (n; %)	12 (26.1%)	21 (23.3%)	$\chi^2 = 0.1$, $p = 0.72$
Hypertension (n, %)	6 (13.0%)	48 (53.3%)	$\chi^2 = 20.1$, $p < 0.001$
Hyperlipidaemia (n, %)	5 (10.9%)	54 (60.0%)	$\chi^2 = 29.9$, $p < 0.001$
HbA1c, mmol/mol (mean, SD)	36.7 (3.0)	60.5 (19.7)	$t = -7.5$, $p < 0.001$
T2DM Duration, years (median, IQR)		5 (2–10)	
Assessment Details			
Full Blood Samples/Cognitive Data Available	45 (97.8%)	78 (86.7%)	$\chi^2 = 4.4$, $p = 0.04$
Baseline (n; %)	36 (78.3%)	65 (72.2%)	$\chi^2 = 0.6$, $p = 0.45$
Follow-Up (n; %)	35 (76.1%)	53 (58.9%)	$\chi^2 = 3.9$, $p = 0.05$
Both Timepoints (n; %)			
Follow-Up Duration, years (mean, SD)	4.4 (0.27)	4.4 (0.28)	$t = -0.33$, $p = 0.63$
Cognitive Assessment	29 (28–30)	27 (28–30)	$z = 2.41$, $p = 0.01$
Baseline Montreal Cognitive Assessment (median, IQR)	28 (27–29)	27 (25–28)	$z = 2.15$, $p = 0.03$
Follow-Up Montreal Cognitive Assessment (median, IQR)	1 (0–2)	1 (0–2)	$z = 0.08$, $p = 0.98$
Change in Montreal Cognitive Assessment, incident errors (median, IQR)			
Baseline Neuropsychological Assessment	403 (386–424)	418 (391–452)	$z = -1.88$, $p = 0.06$
Reaction Time Task, ms (median; IQR)	13 (9–15)	11 (7–14)	$z = 1.61$, $p = 0.10$
Paired Associates Learning, First Attempt Memory Score (median; IQR)	9 (7–11)	9 (7–10)	$z = 0.88$, $p = 0.38$
Spatial Working Memory Score (median; IQR)	83.3 (72.2–94.4)	77.8 (72.2–88.9)	$z = 1.26$, $p = 0.21$
Delayed Pattern Recognition, Percentage Correct (median, IQR)	9 (7–12)	10 (7–11)	$z = 0.24$, $p = 0.81$
One Touch Stockings of Cambridge, Problems Solved on First Choice (median; IQR)	0.90 (0.85–0.93)	0.89 (0.86–0.93)	$z = 0.08$, $p = 0.94$
Rapid Visual Processing Prime Score (median; IQR)			
Follow-Up Neuropsychological Assessment	390 (356–409)	407 (381–457)	$z = -2.5$, $p = 0.01$
Reaction Time Task, ms (median; IQR)	10.5 (8.5–14)	11 (7–14)	$z = 0.76$, $p = 0.45$
Paired Associates Learning, First Attempt Memory Score (median; IQR)	9 (7–11)	9 (7–11)	$z = 0.97$, $p = 0.33$
Spatial Working Memory Score (median; IQR)	88.9 (72.2–94.4)	77.8 (72.2–88.9)	$z = 1.77$, $p = 0.08$
Delayed Pattern Recognition, Percentage Correct (median, IQR)	10 (8–12)	10 (8–11)	$z = 0.25$, $p = 0.81$
One Touch Stockings of Cambridge, Problems Solved on First Choice (median; IQR)	0.90 (0.85–0.93)	0.89 (0.86–0.93)	$z = 1.41$, $p = 0.16$
Rapid Visual Processing Prime Score (median; IQR)			
Difference in Neuropsychological Assessment (Z-Scores)	−0.26 (−0.64-0.33)	−0.24 (−0.58-0.31)	$z = -0.61$, $p = 0.54$
Reaction Time Task Z-Score (median; IQR)	0.11 (−0.67-0.67)	0 (−0.45-0.45)	$z = 0.12$, $p = 0.90$
Paired Associates Learning Z-Score (median; IQR)	0 (−0.57-0.75)	0 (−0.57-0.38)	$z = 0.11$, $p = 0.92$
Spatial Working Memory Z-Score (median; IQR)	0 (−0.74-1.11)	0 (−0.74-0.37)	$z = 0.91$, $p = 0.36$
Delayed Pattern Recognition Z-Score (median, IQR)	0 (−0.62-0.62)	0 (−0.31-0.62)	$z = 0.57$, $p = 0.57$
One Touch Stockings of Cambridge Z-Score (median; IQR)	0.18 (−0.25-0.63)	0.02 (−0.39-0.35)	$z = 1.25$, $p = 0.21$
Rapid Visual Processing Prime Z-Score (median; IQR)			
Baseline Cytokines/Chemokine Concentration	371 (235–491)	351 (251–480)	$z = 0.18$, $p = 0.86$
Eotaxin, pg/mL (median, IQR)	0.64 (0.46–0.89)	0.58 (0.36–0.87)	$z = 1.23$, $p = 0.22$
Interferon-γ, pg/mL (median, IQR)	0.69 (0.52–0.22)	0.74 (0.38–1.22)	$z = -0.19$, $p = 0.85$
IL-10, pg/mL (median, IQR)	0.57 (0.39–0.96)	0.44 (0.32–0.72)	$z = 1.89$, $p = 0.06$
IL-12p70, pg/mL (median, IQR)	0.72 (0.44–0.96)	0.66 (0.42–0.99)	$z = 0.27$, $p = 0.78$
IL-17A, pg/mL (median, IQR)	2.70 (1.93–6.40)	3.13 (1.91–4.77)	$z = 0.09$, $p = 0.93$
IL-6, pg/mL (median, IQR)	210 (156–307)	180 (133–239)	$z = 1.64$, $p = 0.10$
CXCL10, pg/mL (median, IQR)	242 (188–325)	260 (204–360)	$z = -0.83$, $p = 0.41$
MCP-1, pg/mL (median, IQR)	151 (89–181)	117 (86–176)	$z = 0.85$, $p = 0.40$
MIP-1β, pg/mL (median, IQR)	1.55 (1.20–2.97)	1.57 (1.21–2.55)	$z = 0.52$, $p = 0.60$
TNF-α, pg/mL (median, IQR)			
Follow-Up Cytokines/Chemokine Concentration	298 (235–379)	340 (230–441)	$z = -0.93$, $p = 0.35$
Eotaxin, pg/mL (median, IQR)	0.58 (0.46–0.97)	0.61 (0.47–0.97)	$z = 0.19$, $p = 0.85$
Interferon-γ, pg/mL (median, IQR)	0.85 (0.64–1.27)	0.87 (0.63–1.20)	$z = 0.06$, $p = 0.95$
IL-10, pg/mL (median, IQR)	0.70 (0.49–0.88)	0.55 (0.44–0.72)	$z = 1.89$, $p = 0.06$
IL-12p70, pg/mL (median, IQR)	0.66 (0.47–1.07)	0.80 (0.57–1.20)	$z = -1.28$, $p = 0.20$
IL-17A, pg/mL (median, IQR)	2.59 (1.69–3.32)	3.04 (1.95–4.82)	$z = -1.75$, $p = 0.08$
IL-6, pg/mL (median, IQR)	179 (145–257)	165 (140–236)	$z = 0.88$, $p = 0.38$
CXCL10, pg/mL (median, IQR)	260 (216–316)	258 (206–332)	$z = 0.26$, $p = 0.79$
MCP-1, pg/mL (median, IQR)	94 (77–137)	100 (78–120)	$z = 0.34$, $p = 0.73$
MIP-1β, pg/mL (median, IQR)	1.28 (1.08–1.56)	1.47 (1.22–1.86)	$z = -2.62$, $p = 0.02$
TNF-α, pg/mL (median, IQR)			

12p70 (IL-12p70), Interleukin 17A (IL-17A), Interferon gamma (IFN-γ) and Tumor Necrosis Factor alpha (TNF-α). Chemokines were measured in serum from both timepoints using a custom V-PLEX panel and cytokines using an ultra-sensitive S-PLEX panel which enables quantification of low-abundance proteins in the fg/mL range (Hawerkamp et al., 2023). Assays were performed as per manufacturer's instructions and read using an MSD QuickPlex SQ 120 mm analyser with data processed using MSD Discovery Workbench Software.

2.4. Statistical analysis

Descriptive results are presented as means with standard, medians with Interquartile Range (IQR) or proportions as appropriate. To assess for differences between two groups, t-tests, wilcoxon sign-rank tests and chi square tests were used. For neuropsychological test performance, z-scores were computed at baseline across the entire cohort for each test. The same mean and SD were used to compute z-scores at the follow-up timepoint to assess change over time. The data for chemokines/cytokines exhibited strong positive skew and so were natural log (ln) transformed. Log-transformed cytokines were then z-scored in a similar fashion to the neuropsychological test scores. To assess the relationships between cytokine/chemokine concentration and neuropsychological function, linear regression was used. In the first instance, cross-sectional analyses assessed the association between log transformed, z-scored cytokine concentration as the independent variable and neuropsychological test performance (z-score) as the dependent variable. Models were then adjusted for age, sex, BMI and education. As neuropsychological performance and analyte concentration did not consistently differ by T2DM status, associations were assessed in the entire cohort in the first instance, with any significant associations undergoing further analysis by T2DM status. This involved including a *concentration*T2DM* interaction term in the models to examine if associations significantly differed by T2DM status.

For longitudinal analysis, change in neuropsychological test z-score was considered as the dependent variable with a *cytokine*time* (in years) interaction term as the predictor variable of interest in order to assess the relationship between marker concentration and change in cognitive function over time. Again, unadjusted models were performed in the first instance, with adjustment then performed for age, sex, BMI and education. As T2DM status did not significantly influence cognitive trajectories, associations were conducted in the entire cohort overall, followed by T2DM-specific analysis as above. Results of models are reported as Beta Coefficients (β) with corresponding 95% Confidence Intervals (95% CI). Individuals with missing data at either timepoint were excluded from cross-sectional analysis without imputation. For longitudinal analysis, only individuals with complete data at both timepoints were included. An alpha level of $p < 0.05$ was considered statistically significant. As the current analyses were considered exploratory, formal correction for multiple testing was not applied.

3. Results

One-hundred and thirty-six participants were recruited, including 90 with uncomplicated midlife T2DM (age 52.6 ± 8.3; 47% female) and 46 healthy controls (age 5 2.9 ± 8.03, 61% female). At baseline, 123 individuals had both blood samples and complete cognitive assessment available. At a median follow-up time of just-over 4 years (4.4 ± 0.3 years), 101 attended for repeat blood samples and cognitive assessment performed (65 individuals with T2DM and 36 healthy controls). Baseline characteristics are detailed in Table 1. On detailed neuropsychological assessment, there was a trend for poorer performance on the Paired Associates Learning Task at baseline, but not at follow-up, in individuals with T2DM (Table 1) with no other differences in baseline cognitive performance observed.

On examining longitudinal neuropsychological performance, individuals with T2DM exhibited slower reaction times at follow-up ($z = -2.5$, $p = 0.01$, Supplementary Fig. 1). Otherwise, cognitive trajectories remained stable over time. T2DM was not associated with a greater longitudinal change in cognitive performance (Supplementary Fig. 1). Given the lack of effect of T2DM on longitudinal cognitive performance, we assessed cross-sectional and longitudinal relationships between cytokine/chemokine concentrations and neuropsychological performance in the entire cohort first (combining healthy controls and those with T2DM), followed by T2DM-specific analysis as described above - to examine the interaction between T2DM and any significant relationships identified linking inflammatory cytokines/chemokines and cognition in the overall cohort.

At baseline, there were no significant differences in serum chemokine or cytokine concentrations by T2DM status. At follow-up, TNF-α levels were higher in those with T2DM ($z = -2.52$, $p = 0.02$, Table 1). Chemokine/cytokine concentrations are provided in Table 1 and Fig. 1. Significant correlations were seen for several pairs of analytes, namely between chemokines MCP-1 and Eotaxin, between CXCL10 and IFN-γ, IL-10 and IL-12p70 and IL-6, TNF-α and MIP-1β at baseline and at follow-up between IFN-γ and IL-12p70, IL-10 and TNF-α, IL-17A and IL-12p70 and between IL-6 and TNF-α (Fig. 1B–Supplemental Table 1).

We assessed cross-sectional relationships between log-scored z-transformed cytokine concentration and cognitive performance across each of the 6 neuropsychological tasks at both time-points. At baseline, greater levels of Eotaxin were associated with poorer performance on both Paired Associates Learning (β: 0.19; −0.37, −0.00, $p = 0.04$) and on the One Touch Stockings of Cambridge (β: 0.27; −0.44, −0.08, $p = 0.004$) tasks, although these associations were attenuated on adjustment (Supplementary Table 2). At baseline, increasing levels of IL-17A were significantly associated with poorer performance on both the Rapid Visual Processing (β: 0.21; −0.39, −0.03, $p = 0.02$) and One Touch Stockings of Cambridge Tasks (β: 0.23; −0.41, −0.05, $p = 0.01$) – both tests probing executive function/attention. Associations persisted after adjustment for Rapid Visual Processing (β: 0.21; −0.40, −0.02, $p = 0.03$) but not for the One Touch Stockings of Cambridge. On further analysis, none of these associations differed by T2DM status.

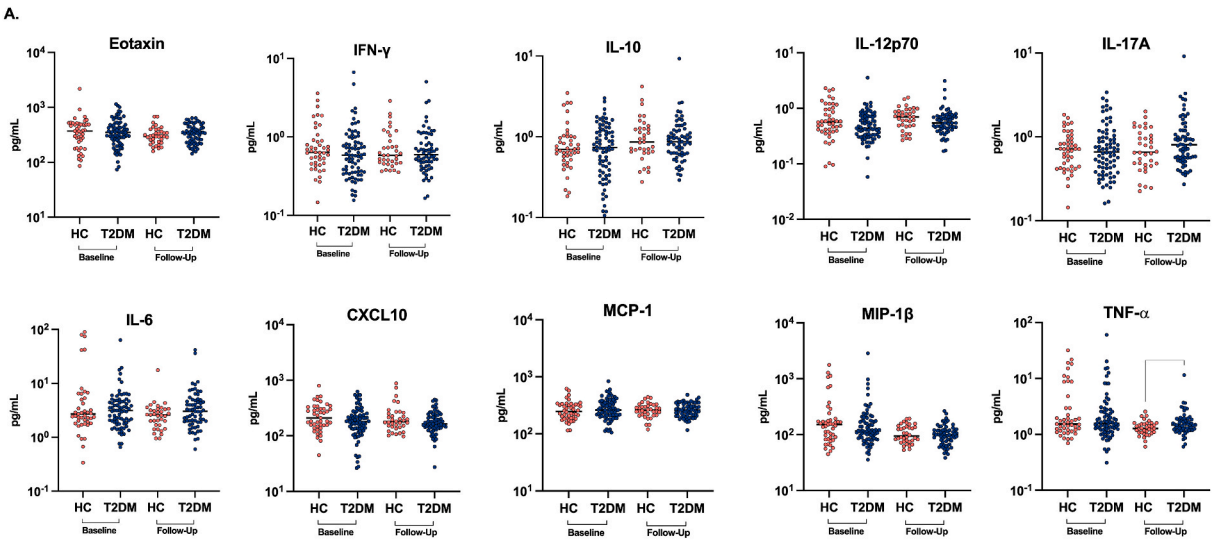
On cross-sectional analyses at follow-up visit, an association was observed between greater IL-10 levels and poorer performance on the reaction time task (β: 0.39; −0.06, −0.71, $p = 0.02$). Greater levels of both IL-6 and IL-17A were significantly associated with poorer performance on the reaction time task (β: 0.58; 0.22, 0.93, $p = 0.002$/β: 0.36; 0.13, 0.58, $p = 0.002$) which persisted on covariate adjustment (β: 0.47; 0.09, 0.85, $p = 0.02$/β: 0.34; 0.12, 0.56, $p = 0.003$ respectively, Fig. 1C). Again, greater IL-17A levels were associated with poorer performance on the Rapid Visual Processing Task at follow-up (β: 0.26; −0.46, −0.05, $p = 0.02$) which persisted on covariate adjustment (β: 0.22; −0.42,-0.01, $p = 0.04$, Fig. 1D).

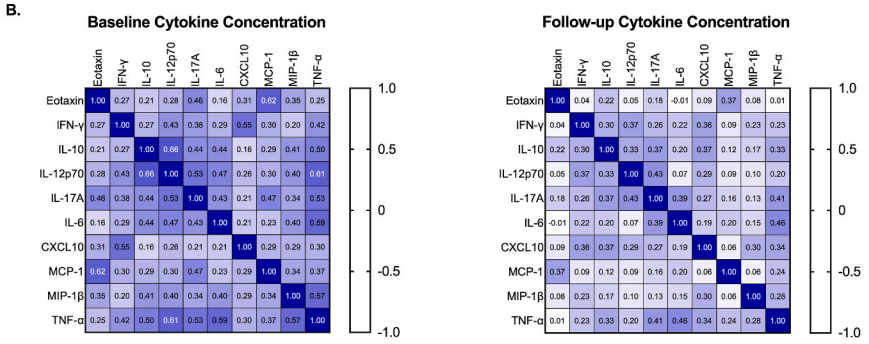
None of these associations differed by T2DM status – assessed by a *cytokine*T2DM* interaction. On longitudinal assessment of the relationship between baseline chemokine/cytokine level and change in cognitive function over time, no associations were observed either in individuals with midlife T2DM or healthy controls (See Supplementary Table 3).

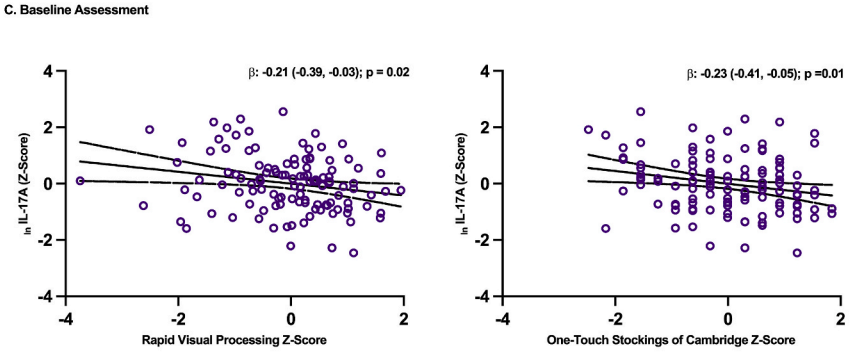
4. Discussion

In the current study of cognitively-unimpaired middle-aged individuals, we demonstrated consistent associations between increasing levels of IL-17A and poorer performance on neuropsychological tests of executive function, attention and processing speed – independent of T2DM status. These associations persisted after covariate adjustment for and were seen at both baseline and follow-up time points. Our findings are particularly novel given the otherwise healthy nature of the cohort under study (individuals with midlife uncomplicated T2DM and healthy controls) and the measurement of IL-17A using a high-sensitivity assay.

The main results of the current study are surprising given the fact that many previous studies examining the links between systemic







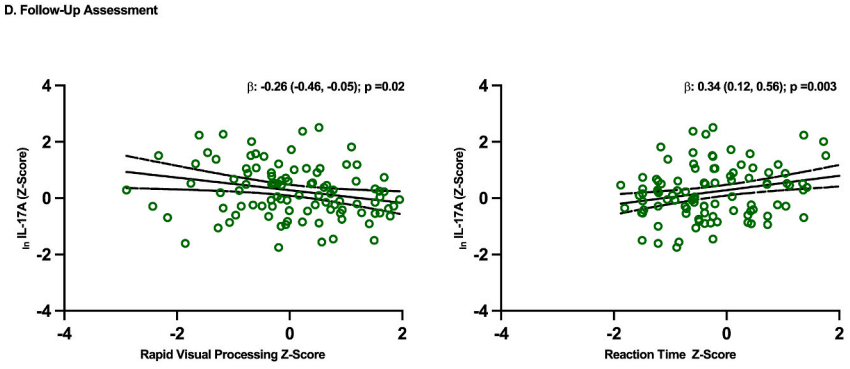


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Fig. 1. Serum Chemokine/Cytokine Concentrations and Cognitive Performance in Middle-Aged Adults With and Without Type 2 Diabetes Mellitus. A. Concentrations of 10 chemokines/cytokines were determined using high sensitivity immunoassays. Results in pg/mL are presented in log scale for each of the 10 selected chemokines/cytokines. At baseline, there were no significant differences between individuals with type 2 diabetes and healthy controls in the concentration of any of the analytes measured. At follow-up, only TNF- α significantly differed, being slightly higher in Type 2 Diabetes in comparison to healthy controls (Wilcoxon rank-sum, $z = -2.62$, $p = 0.02$). **B.** Correlation matrices are provided examining the correlations between each inflammatory marker (log-transformed and z-scored) both at baseline and follow-up timepoints individually. **C.** Greater IL-17A levels were associated with poorer performance on the Rapid Visual Processing Task as well as the One Touch Stockings of Cambridge Task. **D.** On cross-sectional analysis at the follow-up timepoint, greater levels of IL-17A were associated with poorer reaction times and again poorer performance on the Rapid Visual Processing Task. Results of unadjusted linear models are provided as β Coefficients with 95% Confidence Intervals and corresponding p-values.

inflammation and cognitive function have not assessed IL-17A. In a meta-analysis of 170 studies exploring inflammatory cytokine/chemokine concentration in older adults with cognitive impairment, only 3 studies examined IL-17A – with increased serum IL-17A seen in individuals with cognitive impairment (Chen et al., 2014; D'Anna et al., 2017; Leung et al., 2013; Shen et al., 2019b). One reason for this may be due to assay sensitivity and analyte availability. IL-17A is a particularly low abundant cytokine in serum and employing conventional assays may result in undetectable levels. Importantly, in the current study, we used ultra-sensitive ECLIA technology, with detectable results for IL-17A for all participants detected in the fg/mL range.

Perhaps surprisingly, levels of circulating cytokines and chemokines did not differ by T2DM status – apart from a small but statistically significant increase at the follow-up timepoint in TNF-α in individuals with T2DM not seen at baseline. However, this may reflect treatment in individuals with T2DM with previous studies demonstrating that treatment with metformin and other T2DM medication may reduce peripheral inflammatory markers and responses which may be elevated in untreated T2DM (Dyer et al., 2022; Hogan et al., 2014; Lee et al., 2013). Apart from IL-17A, we also observed associations between Eotaxin and memory/executive function at baseline as well as between IL-10 and Reaction Time at follow-up. These findings however were only observed at single time-points, not as robust to covariate adjustment and thus not as consistent as our findings linking IL-17A with neuropsychological performance on tests of attention and executive function.

In comparison to studies of other circulating inflammatory markers, there has been relatively few studies examining mechanistic links between IL-17A and cognitive dysfunction in humans. IL-17A is the principal cytokine released from Th17 cells and this axis has important roles in auto-inflammatory conditions such as psoriasis and multiple sclerosis. Increasing evidence points to important roles for IL-17A in neuroinflammation and neurodegeneration (Chen et al., 2020). Circulating IL-17A may promote glial cell activation and potentiate neuroinflammation (Chen et al., 2020) and has been recently shown to have a role in inducing microglia to produce greater levels of TNF-α in response to pathogenic amyloid plaque (Cao et al., 2023). IL-17A has also been implicated in promoting the infiltration of $CD8^+$ T Cells into the Alzheimer Disease mouse models – again exacerbating neuroinflammatory responses (Ye et al., 2023). A recent study has also demonstrated a sex and APOE-specific association between IL-17 gene module expression in neutrophils and cognitive decline in Alzheimer Disease brain, with increased influx of $IL\text{-}17^+$ neutrophils at the site of Alzheimer Disease pathology (Rosenzweig et al., 2024). Thus, IL-17 likely has multiple roles to play in the pathogenesis of cognitive impairment as well as potentially reflecting shared vascular and other risk factors.

An important question arising from the findings of the current study centres around the potential source of elevated serum IL-17A and whether it reflects early neuroinflammation given its association with cognitive function in our data or indeed peripheral inflammatory processes (e.g. cardiovascular disease burden)- which may also influence cognitive function. Interestingly, previous studies have demonstrated that IL-17 exerts a critical role in mediating cognitive dysfunction as a result of hypertension in mice models (Santisteban et al., 2024). In these studies, meningeal IL-17 produced by T cells in the dura mater was demonstrated to play a direct role in mediating neurovascular and cognitive disorders in hypertension. Whether the IL-17A association with executive dysfunction in the current study is directly associated with cognitive dysfunction or rather reflects midlife vascular risk factors is beyond the scope of the current study, but is an important area for future research.

It is surprising that the individuals in our study with T2DM did not demonstrate a significant change in cognitive function over time. One of the main reasons for this may be the follow-up period considered. Much of the epidemiological work on midlife T2DM and later risk of cognitive impairment and dementia has included follow-up time points of 2 or 3 decades (Gottesman et al., 2017). Nevertheless, our associations between IL-17A and executive function were observed at both time points, even though not associated with the overall rate of decline. As the current study was designed to detect the earliest possible signs of cognitive dysfunction in individuals with and without midlife vascular risk factors such as uncomplicated T2DM, our relatively short interval of 4 years may be too short to demonstrate significant cognitive dysfunction in the cohort under study. Future waves of the ENBIND study will enable us to tease-out this relationship over a longer time period.

There are two important novel aspects to our study. Firstly, we recruited a mid-life cohort of individuals free from objective cognitive impairment. In doing so, this allowed us to purposefully examine the earliest possible signs of the link between systemic inflammation and cognitive dysfunction mid-life T2DM. The cohort under study of individuals with T2DM were free from any established microvascular or macrovascular complications. This is in contrast to previous studies which have included older individuals with T2DM-related complications. Longitudinal analysis of this and other cohorts is crucial to examine whether the findings between IL-17A and executive function predict long-term changes in cognitive function and dementia risk in individuals with and without midlife risk factors such as T2DM. Secondly, we used high-sensitivity assays enabling us to examine cytokines, such as IL-17A that are typically not detectable using standard immunoassays. This meant that all individuals in the study had detectable levels of IL-17A allowing us to assess the link between circulating inflammatory markers and cognitive function in a way not permitted by traditional ELISA/immunoassay technology. In sum, by examining a largely healthy, cognitively unimpaired cohort and by using a high-sensitivity immunoassay, we were able to demonstrate a consistent relationship between IL-17A and executive function across two-separate time-points in a population free from objective cognitive impairment.

Our study has several important limitations. In the first instance, whilst our study is notable for its detailed neuropsychological assessment and broad panel of markers assessed, our sample size is relatively small. This limits the analysis that can be performed and the subsequent interpretation of findings. As our findings were exploratory, we did not perform formal correction for multiple testing as some of these methods may be particularly conservative and not allow exploratory assessment such as that performed in the current analysis (VanderWeele and Mathur, 2019). It is important to note that our findings for IL-17A and executive function/attention and processing speed were demonstrated on multiple tests across two different time points, which supports that these observed associations are less likely the result of type I error. Whilst our findings should be considered exploratory in nature and causality cannot be inferred from the nature of our data, they offer a novel insight into potential relationships between different inflammatory processes and early cognitive dysfunction in middle aged

individuals with and without uncomplicated T2DM. Similarly, due to the exploratory nature of our investigation, a formal sample size calculation was not possible, which may mean that potential associations were missed due to small sample size. Finally, our study only considered peripheral inflammatory markers in plasma and so does not directly reflect neuroinflammatory processes. Future studies examining central markers of inflammation (such as biomarkers from cerebrospinal fluid) and also studies examining plasma biomarkers such as Glial Fibrillary Acidic Protein (GFAP) more directly reflecting neuroinflammation may add further insight into the inflammation-cognition link in midlife T2DM (Cicognola et al., 2021; Pereira et al., 2021).

In conclusion, we observed significant relationships at both baseline and 4-year follow-up assessment between greater levels of circulating IL-17A in serum and poorer performance on neuropsychological tests of executive function, independent of T2DM status. Further studies examining the subtle relationships between peripheral inflammatory markers and cognition should include assessment of serum IL-17A using a suitably sensitive platform to further elucidate the potential role of IL-17A in early cognitive dysfunction in individuals with risk factors for later cognitive decline.

Funding

AHD has been awarded the Irish Clinical Academic Training (ICAT) Programme, supported by the Wellcome Trust and the Health Research Board (Grant Number, 203930/B/16/Z), the Health Service Executive, National Doctors Training and Planning and the Health and Social Care, Research and Development Division, Northern Ireland. AHD and SPK are additionally funded by the Meath Foundation, Tallaght University Hospital (MFRG 121/2021).

Data availaility

Due to risk of participant identification, data are not publicly available but can be obtained by communication with with the corresponding author (Laura.Morrison@tuh.ie)

CRediT authorship contribution statement

Laura Morrison: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Adam H. Dyer:** Writing – review & editing, Visualization, Methodology, Formal analysis, Data curation, Conceptualization. **Helena Dolphin:** Writing – review & editing, Investigation, Formal analysis. **Isabella Batten:** Writing – review & editing, Methodology. **Conor Reddy:** Methodology. **Matthew Widdowson:** Methodology. **Conor P. Woods:** Methodology. **James Gibney:** Methodology. **Nollaig M. Bourke:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Sean P. Kennelly:** Writing – review & editing, Visualization, Supervision, Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Sean P. Kennelly reports financial support was provided by Meath Foundation. Adam H. Dyer reports financial support was provided by Wellcome Trust. Adam H. Dyer reports financial support was provided by Health Research Board. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The data that has been used is confidential.

Acknowledgements

The authors wish to acknowledge all ENBIND participants for generously donating biological samples and allowing use of data for research purposes in addition to administrative staff at the Meath Foundation for administrative support.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbih.2024.100862.

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