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Midlife insulin resistance and brain beta-amyloid accumulation as predictors of change in late-life cognitive function – A 20-year follow-up study

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ABSTRACT

The number of people with dementia will increase as populations age. Insulin resistance (IR) is associated with cognitive decline and dementia. We studied in this longitudinal, population-based cohort study, if change in late-life cognitive function during 5-year follow-up would be predicted by midlife IR (measured 15 years before the first late-life visit) or by late-life brain beta-amyloid (Aβ) accumulation or longitudinal change in late-life Aβ accumulation. Participants (n = 43) were recruited from the population-based Finnish Health 2000 study according to their homeostatic model assessment of insulin resistance (HOMA-IR) values measured in midlife (mean age at midlife 55.1 years), and their *APOE* ε4 genotype. [^{11}C]PIB-PET imaging (n = 42) and neurocognitive testing (n = 43) were conducted at late-life baseline in 2014 −2016 and after 5-year follow-up in 2019 −2021 (mean age at follow-up 74.8 years). During 5-year follow-up, the decline in late-life (from 2014 −2016 to 2019 −2021) episodic memory was greater in midlife insulin resistance (IR+) group than in the group with normal midlife insulin sensitivity (IR−): IR+ group −0.92 (0.22) vs. IR− group −0.43 (0.26), $p = 0.03$, (adjusted mean change in episodic memory z-score (standard error)). Late-life brain Aβ burden predicted a greater decline in episodic memory ($p = 0.02$). The association between midlife IR and episodic memory decline was mediated through late-life Aβ burden. Change in Aβ accumulation during the follow-up was not associated with change in cognition at late-life. In conclusion, midlife IR and late-life brain Aβ burden increased the risk of episodic memory decline in late-life. Our results suggest a link between IR and Alzheimer's disease.

1. Introduction

Midlife diabetes has been associated with cognitive decline (Rawlings et al., 2014; Tuligenga et al., 2014) and dementia (Cheng et al., 2012; Gottesman et al., 2017; Xu et al., 2009) in late-life. Insulin resistance (IR) is defined as failure of target tissues to establish a normal response to insulin. In IR the pancreas secretes excess amounts of insulin into the blood flow in an attempt to overcome tissue insulin resistance and to maintain euglycemia (normal blood glucose levels), resulting in hyperinsulinemia. IR can precede the onset of type 2 diabetes for even a decade, as type 2 diabetes can only be diagnosed when blood glucose levels are elevated. (Zhao and Townsend, 2009). IR has been proposed to be a key factor linking diabetes with the pathogenesis of dementia, and particularly its most common cause, i.e. Alzheimer's disease (AD). Brain insulin resistance may stimulate the development of AD by several mechanisms. Insulin plays an important role in the central nervous system and it can directly influence the pathological process of AD, as brain insulin is linked to the clearance of amyloid-β (Aβ), the

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pathological hallmark of AD. Insulin and Aβ share a common degrading enzyme (insulin-degrading enzyme, IDE) in the brain. (Kellar and Craft, 2020). In IR conditions, where insulin levels are high, the IDE is targeted to insulin degradation and therefore degradation of Aβ is reduced which leads to the accumulation of Aβ in the brain. (Neth and Craft, 2017). Insulin also seems to play a role in inhibiting the phosphorylation of tau and a lack of insulin in the brain might lead to increased hyperphosphorylation of tau, thereby increasing the other pathological hallmark of AD, neurofibrillary tangles (Kellar and Craft, 2020). Moreover, brain insulin has been associated with cognitive functions via several neurobiological mechanisms as it is responsible for glucose uptake in the hippocampus and is known to modulate neurotransmitter systems, oxidative stress, neuroinflammation (Fanelli et al., 2022) and cerebrovascular function (Kellar and Craft, 2020).

There are only few prospective longitudinal studies examining the association of midlife IR and late-life cognitive performance (Ekblad et al., 2017; Lutski et al., 2017; Toppala et al., 2019; Tortelli et al., 2017). We have previously found that midlife IR, measured with Homoeostatic Model Assessment for Insulin Resistance (HOMA-IR), was associated with greater decline in executive functions and processing speed 15 years later (Toppala et al., 2019). Also findings from a population-based study utilizing the Health 2000 Survey cohort indicated that high HOMA-IR would predict poorer verbal fluency 11 years later (Ekblad et al., 2017). Furthermore, IR has been found to be associated with greater decline in overall cognition, memory and executive functions in longitudinal studies (Lutski et al., 2017; Tortelli et al., 2017).

Amyloid PET imaging is a highly accurate method to examine the presence of Aβ in the brain which is thought to define the initial stage of AD (Jack et al., 2024). In previous [^{11}C]PIB-PET imaging studies we

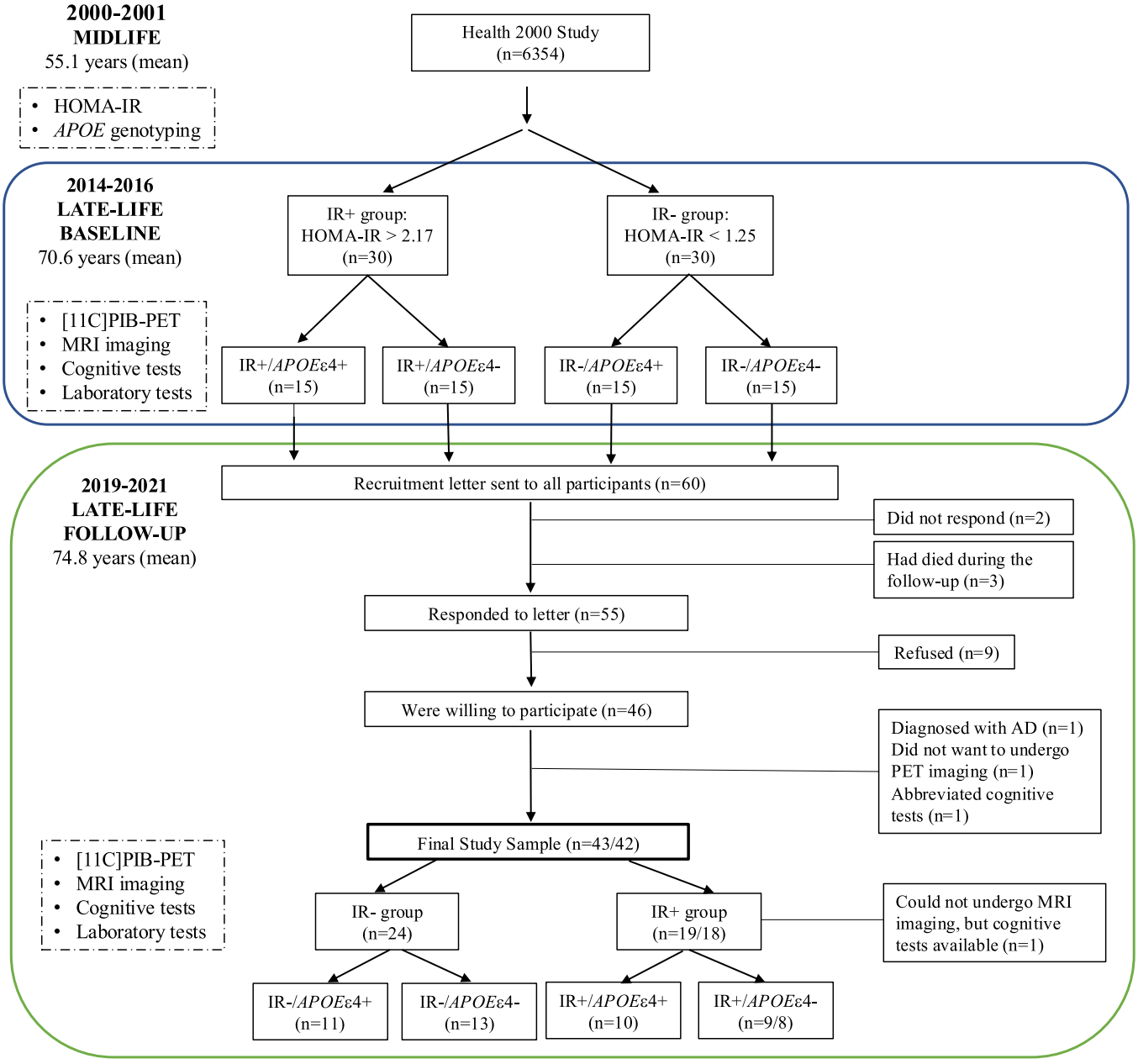


Fig. 1. Flow chart of the study population. The participants were recruited from the Health 2000 Study population according to their midlife Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) values and *APOE* genotype. The late-life studies were conducted at 15 and 20 years after the midlife measurements. Mean age at each time point is shown for the final study population included in the present study ($n = 43$ in cognitive function study and $n = 42$ in neuroimaging study).

have found midlife IR to be associated with brain Aβ accumulation (Ekblad et al., 2018). We have also previously reported an association between Aβ accumulation and a decline in processing speed (Toppala et al., 2019). Importantly, we have demonstrated that cognitively unimpaired individuals with both *APOE* ε4 genotype and midlife IR have a greater risk for increased late-life Aβ accumulation during 5 years when compared to those who had normal midlife insulin sensitivity and were *APOE* ε4 non-carriers (Pietilä et al., 2024), suggesting an interaction of these two risk factors. However, as pointed out in a recent systematic review, it remains uncertain whether the longitudinal change in Aβ accumulation is associated with cognitive decline (Parent et al., 2023).

The aim of this study is to evaluate if the change in late-life cognitive function during a 5-year follow-up would be predicted by midlife IR or late-life Aβ burden or change in late-life Aβ accumulation among cognitively healthy older adults to deepen our previous work examining the link between IR, Aβ accumulation and cognitive decline. We hypothesized that midlife IR would be associated with a greater decline in cognitive performance. In addition, we expected that a higher late-life brain Aβ burden and a greater increase in Aβ accumulation would predict poorer cognitive performance. Considering our previous work, we hypothesized that the association between midlife IR and cognition might be mediated by Aβ accumulation.

2. Methods

2.1. Participants

We examined a sample of 43 older adult participants who had taken part in the Finnish population-based Health 2000 study in midlife (Heistaro, 2008). The participants were selected for recruitment according to their midlife IR, measured by Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) values, and *APOE* ε4 genotype (Figure 1).

In the Health 2000 survey 8028 individuals aged 30 years or over were selected randomly from the Finnish population register. 6354 of them (79% participation rate, mean age 55.4 years) participated in the health examination proper (Heistaro, 2008). *APOE* genotype was defined with the MassARRAY System (Sequenom, San Diego, CA, USA) with a modified protocol (Jänis et al., 2004).

In the late-life baseline, in 2014, 60 community-dwelling participants without a minor or major cognitive disorder were recruited from those who had attended the population-based Health 2000 survey in the year 2000. The recruitment process has been presented in detail previously (Ekblad et al., 2018). The study population represented the Health 2000 Study population fairly well, but, due to the study design, the percentage of *APOE ε4* carriers was higher (Ekblad, 2017). The Health 2000 substudy cohort was designed to form the insulin resistance group (IR+ group, HOMA-IR $>$ 2.17, highest tertile of the Health 2000 study population) and the control group (IR− group, HOMA-IR $<$ 1.25, lowest tertile of the Health 2000 study population). Both groups were enriched for *APOE* ε4 carriers so that both groups included 30 participants and 50% (n = 15) of them were *APOE* ε4 carriers. The study volunteers took part in a multimodal neuroimaging study that was conducted at Turku PET Center, Turku University hospital and University of Turku, Turku, Finland in 2014–2016 (Ekblad et al., 2018). Exclusion criteria for the late-life baseline study were type 2 diabetes in midlife, history of major stroke, any major neurological disease, diagnosis of dementia, and a contraindication for PET or MRI scan and, for the IR− group, diagnosis of type 2 diabetes after the year 2000. Those with both a risk allele and a protective allele for AD (ε4/ε2) were excluded as well. The results of the late-life baseline [^{11}C]PIB-PET study have been published previously (Ekblad et al., 2018; Toppala et al., 2019, 2021).

All the 60 participants who had taken part in our multimodal imaging study in late-life baseline were invited to participate in re-examinations after 5 years in a late-life follow-up study in the years 2019–2021. Of them 55 individuals responded to the invitation letter; 46 individuals were willing to participate; nine people refused; two people did not respond; and three people had died during the follow-up. Three people were further excluded from the present study due to i) diagnosis AD; ii) other neurological disease; iii) having performed only abbreviated cognitive tests. Altogether, 43 older adults took part in the 5-year late-life follow-up and were included in the analyses of the present study. One of them could not undergo MRI imaging and was excluded from [^{11}C]PIB-PET study analyses, therefore there were altogether 42 participants in the [^{11}C]PIB-PET study. (Figure 1.)

The sample size was based on power calculations of test–retest analyses of [^{11}C]PIB-PET scans, which showed that for a 90% power to obtain a statistically significant difference between groups, 5 persons per group would be needed to detect a 15% difference in Aβ accumulation in the frontal cortex (Aalto et al., 2009).

The [^{11}C]PIB-PET imaging studies at late-life baseline and follow-up were approved by the Ethics Committee of the Hospital District of Southwest Finland. All participants gave written informed consent before attending the studies. All study procedures were conducted according to Good Clinical Practice guidelines and the Declaration of Helsinki.

2.2. Laboratory assessments

The laboratory examinations in the Health 2000 study (Toppala et al., 2019), late-life baseline study in 2014–2016 (Ekblad et al., 2018; Toppala et al., 2019) and the late-life follow-up study in 2019–2021 (Pietilä et al., 2024) have been previously described. IR measured by HOMA-IR was calculated by equation: fasting insulin (μU/mL) × fasting glucose (mmol/L)/22.5 to assess peripheral insulin resistance (Matthews et al., 1985).

2.3. Cognitive tests

Comprehensive neurocognitive tests were performed by trained psychology students both at late-life baseline (Toppala et al., 2019) and 5 years later at late-life follow-up to obtain domain-specific z-scores for executive functions, processing speed, episodic memory and language. The test battery included parts from the Finnish version of the Wechsler Memory Scale (WMS-R) and the Wechsler Adult Intelligence Scale (WAIS-R), Boston Naming Test (BNT), Trail Making Tests A and B (TMT-A and TMT-B), S-fluency, categorical fluency and Stroop (Army Individual Test Battery, 1944; Kaplan et al., 1983; Stroop, 1935; Wechsler, 1981, 1987), and also the Finnish version of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) test (Morris et al., 1989). CERAD total score was calculated as previously reported (Chandler et al., 2005).

Consistently with our previous study (Toppala et al., 2019) the executive function domain included TMT-B (time to completion) minus TMT-A (time to completion), Stroop (time to complete the inhibition part minus time to complete the colour naming part), digit span backwards and letter-fluency (S). The processing speed domain included TMT-A (time to completion) and digit symbol test. The episodic memory domain consisted of WMS-R logical memory (delayed recall) and verbal learning (delayed recall). The language domain included category fluency (animals), Boston naming test and WAIS-R similarities. Z-scores for the neurocognitive tests were formed by standardizing the raw test scores of each individual to the late-life baseline population's mean and standard deviation of each test. The domain-specific test scores were formed by calculating the mean of the z-scores of all tests included in each domain, separately at the two measurement time points (late-life baseline in 2014–2016 and late-life follow-up in 2019–2021). The scores of Stroop and TMT-A and TMT-B were reversed before the analyses, so that a lower test score indicated poorer performance on each test. In other tests a higher score indicated better performance.

The change in cognitive performances were obtained by subtracting the mean z-transformed performance in each cognitive domain at

follow-up (2019–2021) from the performance at baseline (2014–2016).

2.4. Brain imaging

MRI imaging was performed with a 3-T MRI scanner (Philips Ingenuity TF PET-MR device, Philips Healthcare, Amsterdam, the Netherlands). The same scanner and the same scanning protocol was used at the late-life baseline and the follow-up.

[^{11}C]PIB-PET images (n = 42) were acquired using a brain-dedicated high-resolution PET scanner, the ECAT HRRT (Siemens Medical Solutions, Knoxville, TN). The same scanner was used at both time points. The protocol of the PET-scanning at late-life baseline in 2014–2016 has been previously described (Ekblad et al., 2018). The dynamic duration of the [^{11}C]PIB-PET scan was 90-min. In 2019–2021 a shorter study protocol was used for better compliance, and it has been described in our previous article (Pietilä et al., 2024). The PET scan was started at 40 min from injection and the scan time was 50 min (40–90 min). To minimize head movement, an individually shaped thermoplastic mask was used and to monitor possible movements of the head an external position detector (Polaris Vicra; Northern Digital, Waterloo, Canada) was utilized.

[^{11}C]PIB was manufactured as previously reported (Snellman et al., 2017). At late-life baseline in 2014–2016 the mean molar activity at the time of injection was 670 ± 260 MBq/nmol and the median injected mass of PIB was 0.19 μg with an interquartile range of 0.14 −0.26 μg in the whole sample. At late-life follow-up in 2019–2021 the mean molar activity at the time of injection was 320 ± 210 MBq/nmol and the median injected mass of PIB was 0.48 μg with an interquartile range of 0.31−0.74 μg in the whole sample. There were no differences between the IR-groups in the molar activity at the time of injection or the injected masses at either of the late-life time points ($p > 0.05$).

2.5. Brain PET data analysis

The PET data was processed and kinetically modelled using a standardized and fully automated in-house toolbox pipeline (Karjalainen et al., 2020). The pipeline is running on MATLAB (The MathWorks, Inc., Natick, MA, USA), and includes brain image preprocessing methods from SPM12-toolbox (Statistical Parametric Mapping; Wellcome Trust Centre for Neuroimaging, London, UK) and FreeSurfer (version 6.3, http://freesurfer.net/). The PET data from the both time points were processed similarly and using Magia, PET images were co-registrated with the T1 MRI. Then the pipeline produced voxel-by-voxel [^{11}C]PIB standardized uptake value ratio (SUVr) images. We utilized a composite cortical [^{11}C]PIB (PIB composite) score which was calculated as a volume-weighted average of regions of interest (ROI) by using FreeSurfer anatomical parcellations. ROIs were: parietal cortex, prefrontal cortex, anterior cingulum, posterior cingulum, precuneus, lateral temporal cortex. These ROIs are based on regions where Aβ accumulation typically appears first in AD (Grothe et al., 2017). Cerebellar cortex was used as a reference region (Lopresti et al., 2005). Additionally, the [^{11}C]PIB SUVr images were spatially normalized and smoothed with 3D Gaussian 8 mm FWHM (Full Width at Half Maximum) filter, in order to carry out voxel level analyses.

The change in [^{11}C]PIB composite score from late-life baseline to follow-up was calculated as [^{11}C]PIB composite score at late-life follow-up (years 2019–2021) subtracted by [^{11}C]PIB composite score at late-life baseline (years 2014–2016).

2.6. Statistical analysis

Study characteristics of the differences between IR− and IR+ groups were analyzed with Student's two-sample *t*-test for variables if normally distributed, the Wilcoxon rank sum test for variables with a skewed distribution, and Pearson's ChiSquare test for categorical variables. Differences between the 17 individuals who did not attend the follow-up analyses and those who attended were compared with Wilcoxon test or Pearson's ChiSquare test.

Group comparisons (IR−/IR+) of the domain-specific cognitive z-scores at the late-life follow-up and the change in cognitive test scores from late-life baseline to follow-up were conducted with Student's two-sample *t*-test. Adjusted analyses were performed using multivariate linear models. The linearity assumption was inspected from the residuals of the models. The cognitive z-scores at late-life follow-up were adjusted for age, sex, and level of education and *APOE* ε4 genotype and further adjusted with late-life baseline body mass index (BMI), LDL and hypertension medication. The change in cognitive domains during the 5-year follow-up were adjusted for age, sex, and level of education, *APOE* ε4 genotype and domain-specific cognitive z-scores at late-life baseline, and further adjusted with late-life baseline BMI, LDL and hypertension medication. Associations between the domain-specific cognitive z-scores at late-life follow-up and the change in domain-specific cognition, and [^{11}C]PIB composite standardized uptake value ratio (SUVr) at late-life baseline and the change in [^{11}C]PIB composite SUVr were evaluated by multivariable linear regression analysis. Analyses were adjusted for age, sex, level of education and domain-specific cognition at late-life baseline, and further adjusted for *APOE* ε4 genotype.

Since previous studies have suggested an interaction for IR and *APOE* genotype on late-life Aβ accumulation, the interaction of 'IR group × *APOE* ε4 genotype' on both the association with each late-life cognitive domain and the change in each cognitive domain during the 5-year follow-up was evaluated with linear models where IR group, *APOE* ε4 genotype and the interaction term were entered as predictors, together with age, sex and education. To evaluate if the association between IR and cognitive performance and decline in cognition were mediated through brain Aβ burden, we explored the association among IR, [^{11}C]PIB composite SUVr at the late-life baseline and the cognitive tests with mediation analyses. The mediation analyses were performed in R (version 4.6.0) with the package "mediation" (Tingley et al., 2014) bootstrapping with 500 replications and 95% (CI) was performed to estimate the variability of direct, indirect, and total effects. Statistical significance was set at $p < 0.05$ (two-sided) for all analyses. All other analyses were performed with SAS JMP Pro 16.1 (SAS Institute, Cary, NC).

3. Results

3.1. Demographics

The study characteristics at each assessment time point and for each IR status are shown in Table 1. Our study included 43 participants: the IR− group (n = 24) and the IR+ group (n = 19). At late-life follow-up the mean age was 74.8 years (SD 3.5 years). The status of IR was determined when the participants were middle-aged (mean 55.1, SD 3.4).

There were no differences between IR− and IR+ regarding mean age, sex ($p = 0.47$), *APOE* ε4 carriership status ($p = 0.43$), mean time from midlife to [^{11}C]PIB-PET scans or mean time between [^{11}C]PIB-PET scans. There was no difference in either mean years of education ($p = 0.055$) or level of education ($p = 0.17$) between IR+ and IR− groups. At late-life follow-up, the IR+ group had a higher HOMA-IR ($p < 0.0001$), BMI ($p = 0.0004$), HbA1c ($p = 0.008$) and more often medication for type 2 diabetes ($n = 5$ vs $n = 0$, $p = 0.012$). All five participants with type 2 diabetes in the IR+ group were receiving metformin and one of these participants was also taking liraglutide. There were significant differences in CERAD total score and [^{11}C]PIB SUVrs between the IR+ and IR− groups. The IR+ group had lower CERAD total scores ($p = 0.0002$) and higher Aβ accumulation ($p = 0.045$) than the IR− group.

Those participants ($n = 17$) who were examined in the late-life baseline in 2014–2016 but did not participate in the late-life follow-up study in 2019–2021 did not differ from those who participated in both

Table 1
Characteristics of the study population according to insulin resistance groups at different time points.

	IR-	IR+	p value
Midlife Health 2000 Study in 2000			
N (n/%)	24 (56 %)	19 (44 %)	
Women (n/%)	14 (58 %)	9 (47 %)	0.47
Age (years)	55.0 (3.7)	55.3 (3.2)	0.84
HOMA-IR	0.9 (0.2)	3.3 (0.9)	< 0.0001
APOE ε4 genotype (n/%)	11 (46%)	11 (58%)	0.43
Education (years)	13.5 (3.8)	11.4 (4.2)	0.055
Late-life baseline in 2014 −2016			
Age at cognitive test (years)	70.5 (3.7)	70.8 (3.1)	0.75
Time from Health 2000 (years)	15.4 (0.7)	15.6 (0.6)	0.50
HOMA-IR	1.8 (1.0)	5.5 (4.4)	< 0.0001
BMI (kg/m^2)	24.4 (2.6)	30.1 (4.4)	< 0.0001
HbA1c (mmol/mol)	34.4 (3.6)	37.7 (6.7)	0.045
Serum total cholesterol (mmol/l)	5.3 (1.1)	5.0 (0.8)	0.35
Medication for dyslipidemia(n (%))	5 (21%)	5 (26%)	0.67
Medication for T2DM (n(%))	0 (0%)	4 (21%)	0.031
Antihypertensive medication (n (%))	14 (58%)	6 (32%)	0.08
CERAD total score	92 (88–95)	86 (78–91)	0.016
[^{11}C]PIB (SUVr)	1.4 (1.3–1.6)	1.7 (1.4–1.9)	0.038
[^{11}C]PIB dose (MBq)	497 (490–508)	496 (482–507)	0.37
Late-life follow-up in 2019 −2021			
Age at cognitive test (years)	74.7 (3.9)	75.0 (3.0)	0.81
Time [^{11}C]PIB-PET scans (years)	4.8 (0.6)	4.6 (0.6)	0.22
Time between cognitive tests (years)	4.3 (0.6)	4.2 (0.8)	0.69
Time from Health 2000 (years)	19.7 (0.6)	19.7 (0.6)	0.86
HOMA-IR	1.9 (1.1)	4.8 (2.7)	< 0.0001
BMI (kg/m^2)	25.5 (4.0)	31.1 (5.8)	0.0004
HbA1c (mmol/mol)	37.5 (3.4)	41.3 (5.5)	0.008
Serum total cholesterol (mmol/l)	5.1 (1.0)	4.3 (0.9)	0.012
Medication for dyslipidemia (n (%))	6 (25%)	9 (47%)	0.13
Medication for T2DM (n(%))	0 (0%)	5 (26%)	0.012
Antihypertensive medication (n (%))	14 (58%)	11 (58%)	0.66
CERAD total score	90 (82–93)	78 (72–82)	0.0002
[^{11}C]PIB (SUVr)	1.7 (1.5–2.4)	2.2 (1.7–2.8)	0.045
[^{11}C]PIB dose (MBq)	490 (476–503)	501 (488–506)	0.14

Study population characteristics according to participants' midlife insulin resistance (IR). IR was defined by Homeostatic Model Assessment for Insulin Resistance (HOMA-IR). Differences between the IR groups were assessed with Two Sample *t*-test for normally distributed variables; with the Wilcoxon Rank sum test for variables with a skewed distribution (CERAD total scores, [^{11}C] PIBcomposite and [^{11}C]PIB dose); and with Pearson's Chi-Square test for categorical variables. A logarithmic transformation was used for education, HOMA-IR at all time points, and HbA1c (hemoglobin A1c) at baseline and BMI (body mass index) at follow-up to achieve normal distribution. In the IR- group, one of the participants was using metoprolol as a preventive medication for migraine. The results are shown as mean (SD) or median (interquartile range) unless stated otherwise. *p*-value indicates differences between groups. SUVr = standardized uptake value ratio.

neuroimaging studies ($n = 43$) in terms of age at baseline neuroimaging study ($p = 0.20$), CERAD total score ($p = 0.24$), or [^{11}C]PIB composite score at late-life baseline ($p = 0.54$). In addition, the participants who did not participate in the follow-up did not differ from those who did in medication for type 2 diabetes ($p = 0.67$) or antihypertensive medication ($p = 0.97$) or other cardiovascular disease than hypertension ($p = 0.72$) at late-life baseline.

3.2. Midlife IR predicts poorer cognitive performance 20 years later

The unadjusted estimate (β) with 95% confidence intervals for IR group predicting each cognitive domain in each model are presented in Table 2 and the adjusted means for each domain by IR group are presented in Figure 2A. The IR+ study population had poorer cognitive performance at the late-life follow-up in 2019 −2021 than the IR- group in all of the investigated cognitive domains; executive functions ($p = 0.0014$), processing speed ($p = 0.016$), episodic memory ($p = 0.0072$) and language ($p = 0.0066$). The group differences remained significant in executive functions ($p = 0.007$), episodic memory ($p = 0.022$) and language ($p = 0.034$) even after adjusting for age, sex, and level of education and *APOE* ε4 carriership. Processing speed was not significantly lower ($p = 0.15$) in the IR+ group after adjustments. (Table 2, Figure 2A.) The association between midlife IR and worse late-life cognitive performance at follow-up remained significant even after adding adjustments for age, sex, level of education and *APOE* ε4 carriership with further adjustments for late-life baseline BMI, LDL and hypertension medication in episodic memory ($p = 0.008$) and executive functions ($p = 0.02$), in addition processing speed ($p = 0.03$) became significant. However, the association between IR and late-life follow-up language ($p = 0.10$) attenuated to nonsignificant in similar fully adjusted multivariable models.

There was no interaction for 'IR group × *APOE* ε4 genotype' on the association with any of the late-life follow-up cognitive domains (all *p*-values > 0.15). Thus, analyses stratified for *APOE* genotype were not performed.

3.3. Late-life decline in cognition as a function of midlife IR-status

The late-life 5-year change in cognition is presented in Figure 2B. In the unadjusted models, there were no significant differences in any cognitive domains between the midlife IR+ and IR– group (all $p > 0.17$). However, after adjustments for age, sex, level of education, *APOE* ε4 carriership and cognition at late-life baseline there was a steeper decline in late-life episodic memory in the IR+ group than in the IR– group ($p = 0.027$). (Table 2) The association between IR and late-life episodic memory remained significant after adjusting for late-life baseline BMI, LDL and hypertension medication ($p = 0.005$). No significant differences in other neurocognitive domains were found. The changes in cognitive domains are presented in Figure 2B. As presented in supplement Table A.1, the association between IR and change in late-life episodic memory attenuated to nonsignificant after adjusting for age, sex, level of education, *APOE* ε4 carriership but without adjusting for cognition at late-life baseline ($p = 0.10$).

The interaction analyses for 'IR group × *APOE* ε4 genotype' on the association with change in any of the cognitive domains during the 5-year follow-up were not significant (all p-values > 0.13).

3.4. Late-life baseline PIB-PET predicts poorer performance in processing speed and episodic memory

Higher [^{11}C]PIB SUVr at late-life baseline in 2014–2016 predicted poorer performance in tests of processing speed (β −0.83, 95% Cl −1.37 to −0.30, $p = 0.003$) and episodic memory (β −0.69, 95% Cl −1.31 to −0.06, $p = 0.032$) at follow-up 5 years later in 2019–2021 after adjusting for age, sex, level of education and *APOE* ε4 genotype (Model 2) (Table 3). The association between PIB composite score at late-life baseline and change in late-life episodic memory was statistically significant after adjusting for age, sex, level of education but without adjusting cognition at late-life baseline or *APOE* ε4 carriership ($p = 0.02$). (Supplement Table A.1). However, further adjusting for *APOE* ε4 carriership attenuated this association to nonsignificant ($p = 0.051$).

3.5. Late-life baseline PIB-PET predicts cognitive decline in episodic memory during the 5-year follow-up

Higher [^{11}C]PIB SUVr at late-life baseline in 2014–2016 predicted a greater decline in episodic memory (β −0.67, 95% CI −1.25 to −0.10,

Table 2
Results for the association between IR group and A) cognitive z-scores at late-life follow-up and B) 5-year change in cognition.

A. Cognition at late-life follow-up in the years 2019 −2021	**Executive functions**	**Processing speed**	**Episodic memory**	**Language**
Model 1. Unadjusted				
IR group, β	0.40**	0.27*	0.34**	0.36**
(95% CI)	(0.16–0.63)	(0.05–0.49)	(0.10–0.59)	(0.11–0.62)
Model 2. Adjusted: age, sex, and level of education and *APOE* ε4				
IR group, β	0.33**	0.16	0.27*	0.29*
(95% CI)	(0.10–0.57)	(−0.06–0.38)	(0.04–0.51)	(0.02–0.56)
B. The change in cognition at late-life during 5 years	**Executive functions**	**Processing speed**	**Episodic memory**	**Language**
Model 1. Unadjusted				
IR group, β	0.10	−0.10	0.13	0.09
(95% CI)	(−0.07–0.27)	(−0.23–0.04)	(−0.10–0.37)	(−0.06–0.25)
Model 2. Adjusted: age, sex, and level of education, *APOE* ε4, and cognition at late-life baseline.				
IR group, β	0.17	−0.05	0.25*	0.10
(95% CI)	(−0.04–0.38)	(−0.19–0.10)	(0.03–0.46)	(−0.09–0.29)

The results are derived from linear models and shown as estimate (β) with 95% confidence intervals for each variable in each model. A negative β indicates an inverse association, i.e., that a model associates with a lower cognitive test score. A) Cognition at late-life follow-up and B) the 5-year change in cognition at late-life by midlife insulin resistance (IR). Model 1: unadjusted. Model 2: adjusted for age, sex, level of education and *APOE* ε4 at late-life follow-up. Additionally for the 5-year change in cognition outcome Model 2: further adjusted for cognition at late-life baseline. Midlife IR– (n = 24), Midlife IR+ (n = 19). * $p < 0.05$, ** $p < 0.01$.

$p = 0.022$) during the 5-year follow up, after adjusting for age, sex, level of education, *APOE* ε4 genotype and cognition at late-life baseline (Model 2). No associations were found between the [^{11}C]PIB SUVr and the other neurocognitive domains (executive functions $p = 0.78$; processing speed $p = 0.29$; language $p = 0.40$). (Table 3). The association between PIB composite score at late-life baseline and change in late-life episodic memory was statistically significant after adjusting for age, sex, level of education but without adjusting cognition at late-life baseline or *APOE* ε4 carriership (p = 0.02). (Supplement Table A.1). However, further adjusting for *APOE* ε4 carriership attenuated this association to nonsignificant (p = 0.051).

3.6. The change in PIB-PET SUVr was not associated with the change in cognition at late-life

There were no significant associations between the change in cognitive domains and in the change in [^{11}C]PIB SUVr during the 5-year follow up. The change in [^{11}C]PIB SUVr and the change language domain remained non-significant in Model 2 ($p = 0.07$) (Table 3).

3.7. Late-life baseline PIB-PET partially mediated the association between IR and episodic memory

Mediation analyses were conducted to test whether late-life [^{11}C]PIB-PET SUVr mediates the relationship between IR group and episodic memory at late-life follow-up or the change in late-life episodic memory. Bootstrap analysis with 500 samples showed that the Average Causal Mediation Effects of the mediation analysis were significant and that the effect of IR on episodic memory was partially mediated through [^{11}C]PIB-PET SUVr (Figure 3A). Similar analyses for the change in episodic memory decline (Figure 3B) indicated that the effect of IR on the change in episodic memory was fully mediated through late-life [^{11}C]PIB-PET SUVr.

3.8. Additional stratified analysis

None of the participants had diabetes in midlife. However, during 20 years follow-up 4 participants (21% of IR+ group) at late-life baseline and 5 participants (26% of IR+ group) at late-life follow-up had medication for type 2 diabetes. None of the participants in the IR− group developed T2DM by late-life follow-up. We redid an additional stratified analysis by excluding the 5 participants who developed diabetes within 20 years (n = 38). Nevertheless, the main results of our manuscript, firstly that midlife insulin resistance was associated with increased risk of episodic memory decline in late-life and secondly that late-life brain Aβ burden increased the risk of episodic memory decline in late-life, remained unchanged in spite of excluding from analyses the five participants who developed T2DM during the follow-up. (Supplement Table A.2 and A.3)

4. Discussion

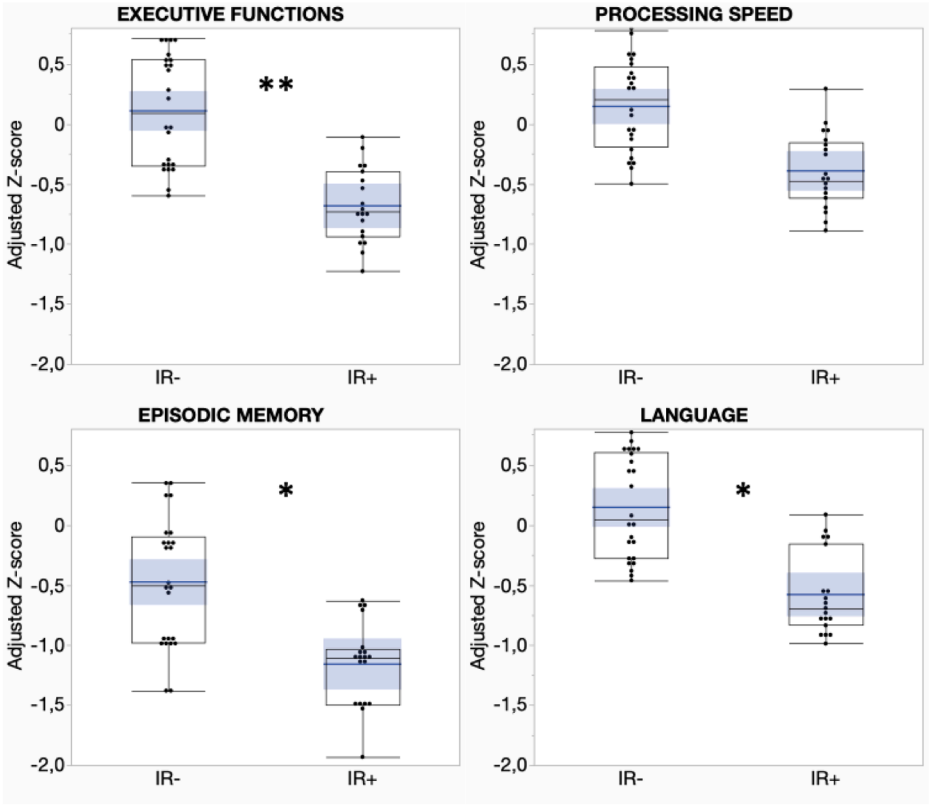
4.1. Summary of findings

In this longitudinal cohort study, we found greater decline in episodic memory during the late-life 5-year follow-up in the midlife IR+ group than in the group with normal midlife insulin sensitivity. IR in midlife also predicted poorer cognitive performance in executive function, episodic memory and language cognitive domains 20 years later. To our knowledge, this is the first study that investigated midlife IR and late-life cognition with a follow-up of 20 years. Late-life brain Aβ burden predicted a greater decline in episodic memory during the 5-year follow-up in accordance with earlier results (Ellis et al., 2013; Farrell et al., 2017; Lim et al., 2014). In line with previous research (Parent et al., 2023) longitudinal change in [^{11}C]PIB-PET SUVr was not associated with the change in cognition at late-life in any cognitive domain.

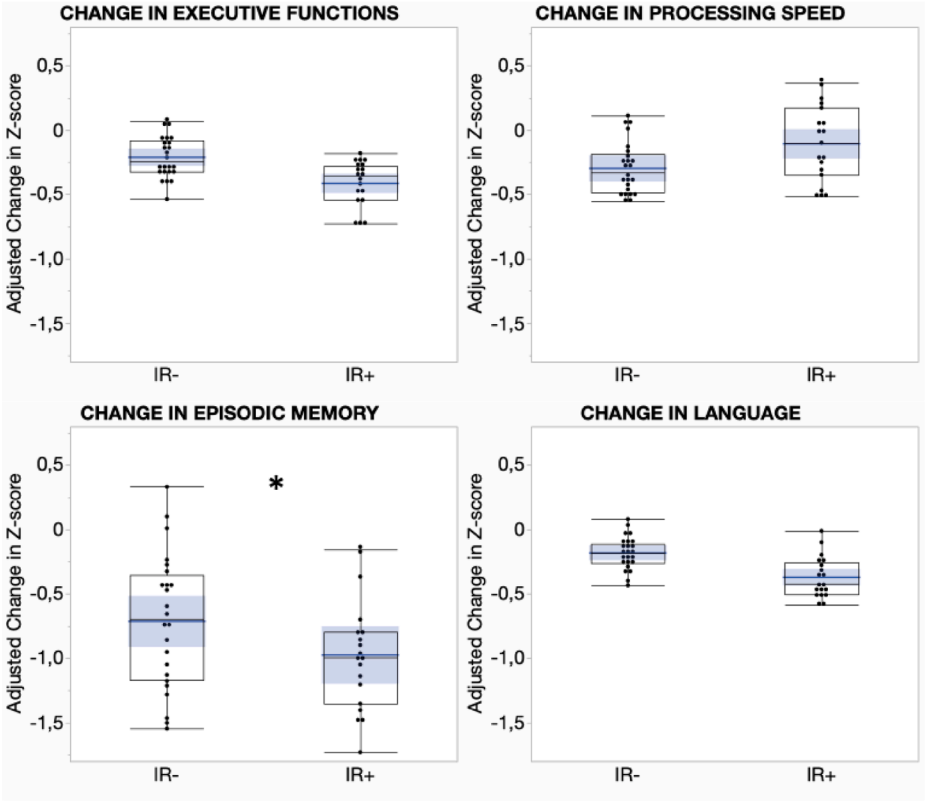
4.2. Midlife IR, cognitive performance and change in late-life cognition

Our results are in line with previous longitudinal studies (Ekblad et al., 2017; Livingston et al., 2024; Lutski et al., 2017; Toppala et al., 2019; Tortelli et al., 2017) examining the association of midlife IR and late-life cognitive performance, and our study extends the follow-up time of the previously published studies. We have previously demonstrated that midlife IR is associated with poorer executive function and processing speed, but not episodic memory, at the 15-year follow up (late-life baseline) of the present study (Toppala et al., 2019). Interestingly, at the 20-year follow-up (late-life follow-up) we found that midlife IR predicted poorer performance in the domains of executive function, language and episodic memory. In line with our results, three of five longitudinal studies examining the relationship of IR at late-life utilizing follow-up times ranging from 3 to 15 years reported that IR reduces cognitive performance globally and possibly in specific cognitive domains (Kim and Arvanitakis, 2023). These findings highlight the

A.



B.



(caption on next page)

Fig. 2. Adjusted results for cognitive z-scores and for 5-year change in cognition at late-life. A) Domain-specific cognitive test scores with adjusted means at late-life follow-up by midlife insulin resistance group. B) 5-year change in domain-specific cognitive test scores with adjusted means at late-life follow-up by midlife insulin resistance group. Blue lines represent adjusted means and blue boxes 95 % confidence intervals that are derived from linear models adjusted for age, sex, level of education and *APOE* ε4 carriership and at 5-year change in cognition further adjusted with cognition at late-life baseline. Midlife IR– (n = 24), Midlife IR+ (n = 19). * p < 0.05, ** p < 0.01.

Table 3
Adjusted results for the association between cognition and Aβ accumulation.

Cognition at late-life follow-up in the years 2019–2021	**Executive functions**	**Processing speed**	**Episodic memory**	**Language**
Model 1. Adjusted: age, sex and education				
PIB composite score at late-life baseline, β (95% CI)	−0.53 (−1.1–0.04)	−0.82 (−1.27 to −0.37)***	−0.79 (−1.32 to −0.27)**	−0.42 (−1.05–0.20)
Model 2. Adjusted: age, sex, education and *APOE* ε4				
PIB composite score at late-life baseline, β (95% CI)	−0.50 (−1.2–0.18)	−0.83 (−1.37 to −0.30)**	−0.69 (−1.31 to −0.06)*	−0.33 (−1.08–0.41)
The change in cognition at late-life during 5 years	**Executive functions**	**Processing speed**	**Episodic memory**	**Language**
Model 1. Adjusted: age, sex, education, cognition at late-life baseline				
PIB composite score at late-life baseline, β (95% CI)	−0.04 (−0.54–0.46)	−0.23 (−0.58–0.12)	−0.74 (−1.22 to −0.26)**	−0.13 (−0.54–0.28)
Model 2. Adjusted: age, sex, education, *APOE* ε4 and cognition at late-life baseline				
PIB composite score at late-life baseline, β (95% CI)	−0.08 (−0.65–0.50)	−0.22 (−0.62–0.19)	−0.67 (−1.25 to −0.10)*	−0.20 (−0.68–0.28)
The change in cognition at late-life during 5 years	**Executive functions**	**Processing speed**	**Episodic memory**	**Language**
Model 1. Adjusted: age, sex, education, cognition at late-life baseline				
The change in PIB composite score, β (95% CI)	−0.28 (−0.78–0.23)	0.08 (−0.28–0.43)	−0.16 (−0.77–0.46)	0.42 (−0.04–0.87)
Model 2. Adjusted: age, sex, education, *APOE* ε4, cognition at late-life baseline				
The change in PIB composite score, β (95% CI)	−0.42 (−1.0–0.19)	0.20 (−0.21–0.61)	0.16 (−0.55–0.87)	0.49 (−0.03–1.0)

The results are derived from linear models and shown as estimates (β) with 95% confidence intervals for each variable in each model. A negative β indicates an inverse association, i.e., that a model associates with a lower cognitive test score. Model 1: Analyses adjusted for age, sex, level of education. Model 2: further adjusted for *APOE* ε4. Midlife IR– (n = 24), Midlife IR+ (n = 18). * p < 0.05, ** p < 0.01, *** p < 0.001.

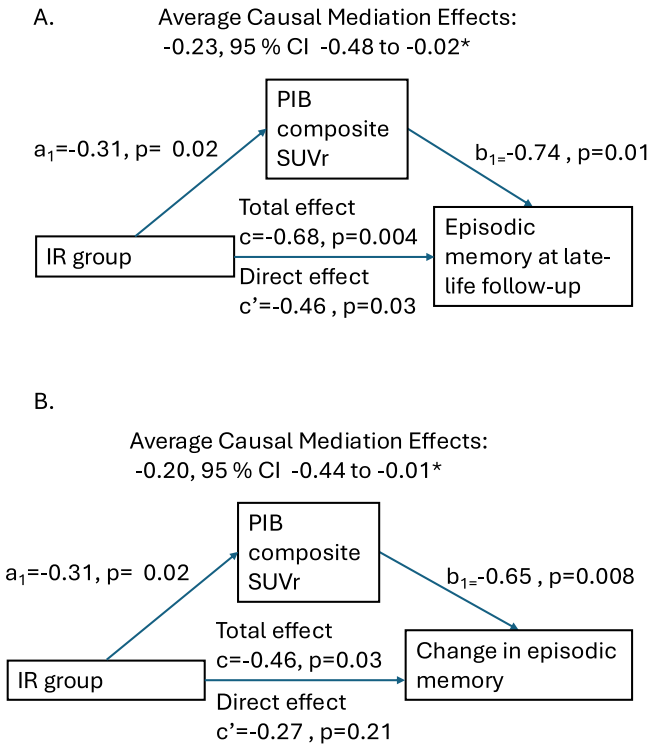


Fig. 3. Late-life baseline PIB-PET partially mediate the effect of midlife IR on late-life episodic memory. Mediation Models showing late-life baseline [^{11}C]PIB-PET is significantly mediating the association between midlife insulin resistance and A) late-life episodic memory at late-life follow-up or B) the change in late-life episodic memory. * p < 0.05.

importance of long-term exposure to insulin resistance on cognitive functions.

Moreover, we found midlife IR to be associated with greater decline in episodic memory during a late-life 5-year follow-up independently of *APOE ε4* genetic status or episodic memory at late-life baseline. In our previous research, we have shown that midlife IR independently predicts late-life amyloid accumulation after 15 years, which could precede episodic memory decline (Ekblad et al., 2018). Others have shown that midlife IR is associated with reduced gray matter volume four years later in regions affected by early AD, e.g. the medial temporal lobe including the hippocampus – an essential brain region for episodic memory (Willette et al., 2013). Furthermore, insulin receptors are present in high concentrations in the hippocampus, which suggests that insulin plays a key role in learning and memory (Neth and Craft, 2017). Also, large epidemiological studies have showed that impaired insulin secretion in midlife increases the risk of AD in late-life (Rönnemaa et al., 2008). Therefore, our results between midlife IR and episodic memory decline in late-life could be mediated though AD pathology.

IR may contribute to the etiopathogenesis of AD through a variety of mechanisms, most importantly, by regulating the function of insulin degrading enzyme, IDE, that also degrades Aβ in the brain (Michailidis et al., 2022). IR-related diseases, such as type 2 diabetes, are associated with worse cognitive functioning (Fanelli et al., 2022) and an increased risk for dementia (Chatterjee and Mudher, 2018). However, type 2 diabetes does not seem to associate with greater levels of AD pathology in the brain (Chornenkyy et al., 2019). IR precedes the onset of type 2 diabetes typically for years or even decades as IR and hyperinsulinemia can occur at normal blood glucose levels. Thus, IR could influence brain Aβ accumulation already for a long time-period before an individual is diagnosed with type 2 diabetes. Therefore, it is plausible that the associations between IR and brain Aβ differ from the associations between type 2 diabetes and AD pathology.

Our finding that midlife IR increases the risk of episodic memory decline in late-life suggests a link between IR and AD. In addition, findings from existing research suggest that diabetes medications can delay cognitive impairment and dementia (Tian et al., 2023). There is an interesting trial to study metformin and its effects on IR and cognition on MET-FINGER trial (Barbera et al., 2024) to expand the FINGER multimodal lifestyle intervention trials (Baker et al., 2025; Ngandu et al., 2015) which have shown an improvement in executive functions.

4.3. The association between PIB-PET SUVr and the change in cognition at late-life

We found that late-life baseline in 2014–2016 [^{11}C]PIB-PET predicts a greater decline in episodic memory performance in older adults who were cognitively unimpaired at baseline. Similar findings have been reported in longitudinal studies in which increasing baseline Aβ-PET SUVr has been associated with increasing decline in episodic memory (Ellis et al., 2013; Farrell et al., 2017; Lim et al., 2014). It is well-established that the first symptom of AD is typically a decline in episodic memory, although, according to the new criteria for the diagnosis of AD, abnormalities of Aβ, detected either by Aβ-PET or from cerebrospinal fluid samples, are sufficient for the conclusion that the biological process of AD has begun despite the absence of cognitive symptoms (Jack et al., 2024). Nevertheless, our findings showing an association between higher late-life baseline [^{11}C]PIB-PET and a decline in episodic memory suggest that some of the participants included in our study most likely showed signs of very mild cognitive impairment due to underlying AD pathology at follow-up. It is worth noticing that the study was enriched for *APOE* ε4 carriers, who were thus at an increased risk to develop clinical AD at late-life (Fortea et al., 2024).

We did not find associations between a 5-year longitudinal change in amyloid accumulation and the change in late-life cognition. However, previous longitudinal studies have reported mixed findings (Parent et al., 2023). First of all, late-life PIB-PET amyloid imaging studies with a mean follow-up over 3 years for both cognition and for Aβ (Hanseeuw et al., 2019; Hatashita et al., 2019; Xiong et al., 2016) have not yielded a significant positive association between change in Aβ accumulation and cognitive decline in cognitively healthy adults. However, in late-life florbetapir-PET amyloid studies (Farrell et al., 2018; Jagust et al., 2021; Landau et al., 2018) with a mean follow-up of over 3 years, associations have been found between Aβ change and declining episodic memory. In accordance with our findings, in a study (Chen et al., 2024) with a longer mean follow-up 6 years, late-life baseline PIB-PET was sufficient to predict cognitive decline, whereas longitudinal measures of Aβ accumulation did not improve the accuracy of prediction of cognitive decline.

A possible explanation for these negative results of longitudinal change in Aβ and change in cognition might be that amyloid accumulation first increases and then reaches a plateau (Jack et al., 2013). Most probably, some of our participants who were already amyloid positive at baseline were close to reaching the plateau of Aβ accumulation at the late-life baseline. Thus, we speculate that for those participants who already had a high Aβ load at the late-life baseline the increase in [^{11}C]PIB SUVr was lower than for those who were only starting to accumulate Aβ in their brains. In turn, it is expected that those with high Aβ levels (and only a modest increase in Aβ during the follow-up) would have a largest decline in cognition during the follow-up. Another explanation is that the follow-up time for Aβ accumulation was too short to capture a meaningful change in Aβ levels. The average estimated time required to progress from a SUVr of 1.5 to a SUVr of 2.5 is supposed to be 15 years (Jack et al., 2013). This is in line with our study as during the 5-year late-life follow-up [^{11}C]PIB SUVr increased from median 1.4–1.7 in IR- group and from median 1.7–2.2 in IR+ group.

4.4. Aβ as a mediator between midlife insulin resistance and late-life cognition

Here, we have shown that midlife IR and late-life Aβ both associate with late-life episodic memory decline after a 20-year follow-up, and that the effect of IR on poorer episodic memory is partially mediated through Aβ, and that the decline in episodic memory is fully mediated through Aβ. In our previous work on the same study population, we have found that midlife IR is an independent predictor of late-life Aβ accumulation after a 15-year follow-up (Ekblad et al., 2018), but no association was found between midlife IR and episodic memory performance at the 15-year follow-up visit (Toppala et al., 2019). We have also previously demonstrated that individuals with midlife IR who are *APOE*ε 4 carriers are at increased risk for a greater increase in late-life Aβ accumulation during a 5-year interval (the change from the 15-year follow-up to the 20-year follow-up after measuring IR) (Pietilä et al., 2024). Since IR can directly influence Aβ accumulation through several different pathways (Fanelli et al., 2022; Kellar and Craft, 2020; Michailidis et al., 2022) and the accumulation of Aβ starts up to two decades before the earliest symptoms of AD, i.e. episodic memory decline, can be detected, it is reasonable to believe that amyloid accumulation lies on the pathogenetic pathway from midlife IR to cognitive decline in late-life. The results of our present study support this hypothesis.

4.5. Strengths and limitations

A major strength of our study is its longitudinal design with IR measurements in midlife, and amyloid PET imaging and repeated neurocognitive testing 15 and 20 years later in late-life. The sample was drawn from a large population-based cohort enhancing the generalizability of the results. Reporting *APOE* ε4 status is to be regarded as a strength as it is an established risk factor for dementia and thus a possible source of confounding bias. As cognitive decline and dementia exist on a continuum, a very long follow up spanning decades is needed to examine these associations with IR. The possibility to perform repeated [^{11}C]PIB-PET scans with a 5-year interval in older adults and to analyze the PET-images with an automated, in-house pipeline (Magia) to obtain quantitative results can also be considered as strengths. This study also has some limitations. Our study was relatively small and the possibility of selection bias cannot be entirely excluded, as factors such as cognitive impairment may have influenced retention in the study sample. However, there were only a few dropouts since the late-life baseline study and they were mostly from the IR+/ *APOE* ε4 − group. This is important, considering that the analyses were adjusted with *APOE* ε4 carriership. We found no significant differences between the dropouts and the follow-up study population among medication for type 2 diabetes, antihypertensive medication, or other cardiovascular diseases than antihypertensive treatment at the baseline. The Health 2000 study was a representative sample of the Finnish adult population. This neuroimaging substudy has been shown to represent the Health 2000 Study population fairly well. However, since participating to the neuroimaging substudy was voluntary, and there were pre-defined recruitment criteria, such as age, IR status and *APOE* genotype, this neuroimaging substudy cannot claim to represent the Finnish adult population. Moreover, the vast majority of the participants of the Health 2000 study were of Caucasian origin, and in our substudy all the participants were Caucasian, which is why the results might not be generalizable populations of different origins. In our study we did not measure tau, although it has been suggested that tau tangles correlate with cognition better than Aβ plaques (Tosun et al., 2017).

5. Conclusions

In conclusion, we found that midlife IR increases the risk of episodic memory decline in late-life, suggesting a link between IR and AD. Furthermore, late-life brain Aβ accumulation predicted a greater decline in episodic memory during the 5-year follow-up. However, late-life longitudinal change in brain Aβ accumulation was not associated with the change in late-life cognitive function. Longitudinal studies with data of midlife IR and even longer follow-up data would perhaps give further insights regarding the association of changes in late-life cognition and IR. Targeting life-style and pharmacological interventions to individuals with midlife IR could prove to be important in reducing the risk of cognitive decline.

CRediT authorship contribution statement

Pietilä Elina: Writing – review & editing, Writing – original draft, Visualization, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Karrasch Mira:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Jula Antti:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Rinne Juha:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Funding acquisition, Conceptualization. **Ekblad Laura:** Writing – review & editing, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Helin Semi:** Writing – review & editing, Supervision, Software, Resources, Project administration, Methodology, Investigation, Conceptualization. **Snellman Anniina:** Writing – review & editing, Conceptualization. **Viitanen Matti:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Conceptualization.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendices

Table A.1
Additional analysis on the association of IR, Aβ accumulation and change in cognition without adjusting for late-life baseline cognition

The change in cognition at late-life during 5 years	**Executive functions**	**Processing speed**	**Episodic memory**	**Language**
Model 2. Adjusted: age, sex, level of education and *APOE* ε4				
IR group, β (95% CI)	0.13 (−0.07–0.32)	−0.14 (−0.29–0.02)	0.21 (−0.04–0.46)	0.08 (−0.09–0.26)
The change in cognition at late-life during 5 years	**Executive functions**	**Processing speed**	**Episodic memory**	**Language**
Model 1. Adjusted: age, sex and education				
PIB composite score at late-life baseline, β (95% CI)	0.02 (−0.43–0.47)	0.12 (−0.24–0.48)	−0.68 (−1.23 to −0.13)*	−0.11 (−0.50–0.29)
Model 2. Adjusted: age, sex, education and *APOE* ε4				
PIB composite score at late-life baseline, β (95% CI)	−0.03 (−0.56–0.51)	0.15 (−0.28–0.58)	−0.66 (−1.32–0.002)	−0.19 (−0.67–0.28)
The change in cognition at late-life during 5 years	**Executive functions**	**Processing speed**	**Episodic memory**	**Language**
Model 1. Adjusted: age, sex and education				
The change in PIB composite score, β (95% CI)	−0.27 (−0.77–0.23)	0.13 (−0.28–0.53)	−0.26 (−0.93–0.41)	0.41 (−0.02–0.84)
Model 2. Adjusted: age, sex, education and *APOE* ε4				
The change in PIB composite score, β (95% CI)	−0.42 (−1.0–0.16)	0.16 (−0.33–0.64)	−0.05 (−0.84–0.74)	0.49 (−0.02–1.0)

The results are derived from linear models and shown as estimates (β) with 95% confidence intervals for each variable in each model. A negative β indicates an inverse association, i.e., that a model associates with a lower cognitive test score. Model 1: Analyses adjusted for age, sex, education. Model 2: further adjusted for *APOE* ε4. Any of models are not adjusted with baseline cognition. Midlife IR– (n = 24), Midlife IR+ (n = 19 and in PIB imaging analyses n = 18). * $p < 0.05$

Table A.2
Additional analyses by excluding 5 participants who developed diabetes after midlife, during 20 years follow-up. Results for the association between IR group and A) cognitive z-scores at late-life follow-up and B) 5-year change in cognition. N = 38

A. Cognition at late-life follow-up in the years 2019 −2021	**Executive functions**	**Processing speed**	**Episodic memory**	**Language**
Model 1. Unadjusted				
Without T2DM, IR group, β	0.35*	0.29*	0.40**	0.37*
(95% CI)	(0.09–0.62)	(0.04–0.54)	(0.13–0.67)	(0.08–0.67)
p value	0.011	0.02	0.005	0.013
Model 2. Adjusted: age, sex, level of education and *APOE* ε4				
Without T2DM, IR group, β	0.26	0.16	0.14*	0.32*
(95% CI)	(−0.02–0.54)	(−0.10–0.43)	(0.06–0.63)	(0.01–0.63)
p value	0.06	0.21	0.02	0.041
B. The change in cognition at late-life during 5 years	**Executive functions**	**Processing speed**	**Episodic memory**	**Language**
Model 1. Unadjusted				

(*continued on next page*)

Table A.2 (*continued*)

Without T2DM, IR group, β	0.07	−0.10	0.20	0.08
(95% CI)	(−0.12–0.26)	(−0.24–0.03)	(−0.06–0.46)	(−0.09–0.24)
p value	0.47	0.14	0.13	0.34
Model 2. Adjusted: age, sex, level of education, *APOE* ε4, and cognition at late-life baseline.				
Without T2DM, IR group, β	0.12	−0.04	0.31*	0.07
(95% CI)	(−0.13–0.38)	(−0.21–0.13)	(0.04–0.58)	(−0.14–0.28)
p value	0.33	0.62	0.026	0.51

The results are derived from linear models and shown as estimate (β) with 95% confidence intervals for each variable in each model. A negative β indicates an inverse association, i.e., that a model associates with a lower cognitive test score. A) Cognition at late-life follow-up and B) the 5-year change in cognition at late-life by midlife insulin resistance (IR). Model 1: unadjusted. Model 2: adjusted for age, sex, level of education and *APOE* ε4 at late-life follow-up. Additionally for the 5-year change in cognition outcome Model 2: further adjusted for cognition at late-life baseline. Midlife IR– (n = 24), Midlife IR+ (n = 14). * $p < 0.05$, ** $p < 0.01$.

Table A.3
Additional analyses by excluding 5 participants who developed diabetes after midlife, during 20 years follow-up. Adjusted results for the association between Aβ accumulation and cognition. N = 38.

Cognition at late-life follow-up in the years 2019–2021	**Executive functions**	**Processing speed**	**Episodic memory**	**Language**
Model 1. Adjusted: age, sex and education				
Without T2DM, PIB composite score at late-life baseline, β	−0.56	−0.78**	−0.78**	−0.35
(95% CI)	(−1.13 to 0.004)	(−1.24 to −0.32)	(−1.35 to −0.20)	(−1.0 to 0.29)
p value	0.051	0.002	0.0097	0.27
Model 2. Adjusted: age, sex, education and *APOE* ε4				
Without T2DM, PIB composite score at late-life baseline, β	−0.40	−0.80**	−0.66	−0.22
(95% CI)	(−1.06 to 0.25)	(−1.33 to −0.25)	(−1.33 to 0.01)	(−0.97 to 0.53)
p value	0.22	0.006	0.055	0.49
The change in cognition at late-life during 5 years	**Executive functions**	**Processing speed**	**Episodic memory**	**Language**
Model 1. Adjusted: age, sex, education, cognition at late-life baseline				
Without T2DM, PIB composite score at late-life baseline, β	−0.12	−0.15	−0.77**	−0.11
(95% CI)	(−0.65 to 0.41)	(−0.53 to 0.23)	(−1.29 to −0.24)	(−0.50 to 0.28)
p value	0.65	0.43	0.006	0.58
Model 2. Adjusted: age, sex, education, *APOE* ε4, cognition at late-life baseline				
Without T2DM, PIB composite score at late-life baseline, β	−0.08	−0.14	−0.67*	−0.17
(95% CI)	−0.67 to 0.50)	(−0.57 to 0.29)	(−1.28 to −0.06)	(−0.62 to 0.28)
p value	0.77	0.52	0.03	0.45
The change in cognition at late-life during 5 years	**Executive functions**	**Processing speed**	**Episodic memory**	**Language**
Model 1. Adjusted: age, sex, education,cognition at late-life baseline				
Without T2DM, the change in PIB composite score, β	−0.37	0.08	−0.21	0.45*
(95% CI)	(−0.91 to 0.17)	(−0.29 to 0.45)	(−0.91 to 0.49)	(0.004 to 0.89)
p value	0.18	0.66	0.54	0.048
Model 2. Adjusted: age, sex, education, *APOE* ε4, cognition at late-life baseline				
Without T2DM, the change in PIB composite score, β	−0.44	0.18	0.14	0.53*
(95% CI)	(−1.11 to 0.22)	(−0.27 to 0.62)	(−0.66 to 0.95)	(0.008 to 1.05)
p value	0.18	0.42	0.72	0.047

The results are derived from linear models and shown as estimates (β) with 95% confidence intervals for each variable in each model. A negative β indicates an inverse association, i.e., that a model associates with a lower cognitive test score. Model 1: Analyses adjusted for age, sex, education. Model 2: further adjusted for *APOE* ε4. Midlife IR– (n = 24), Midlife IR+ (n = 14). * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Data Availability

The data are available from the corresponding author on reasonable request.

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