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ORIGINAL ARTICLE

Plasma pTau181 is associated with subjective cognitive concerns but not objective cognitive decline or structural brain integrity measures in midlife

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Abstract Although plasma pTau181 has been shown to accurately discriminate patients with Alzheimer's disease from healthy older adults, there are few studies of plasma biomarkers among middle-aged populations. Given the potential utility of plasma AD biomarkers such as pTau181 in screening for disease risk, examining pTau181 in a middle-aged cohort without AD is important for future implementation. The objectives of this study were to characterise plasma pTau181 in a middle-aged birth cohort aged 45 years and to investigate associations with early indicators of dementia risk. Participants were members of the Dunedin Multidisciplinary Health and Development Study, a longitudinal study of 1037 people born in New Zealand in 1972–1973. Plasma pTau181, self-reported cognitive concerns, MRI-based brain structure, and DunedinPACE (an epigenetic biomarker of biological ageing) were measured at age 45; cognition was measured in childhood and age 45. Plasma pTau181 concentrations at age 45 ($n = 854$, 49% female) were associated with self-reported cognitive concerns ($\beta = 0.09$, $p = .008$); however, no significant associations were observed with objective cognitive decline, worse structural

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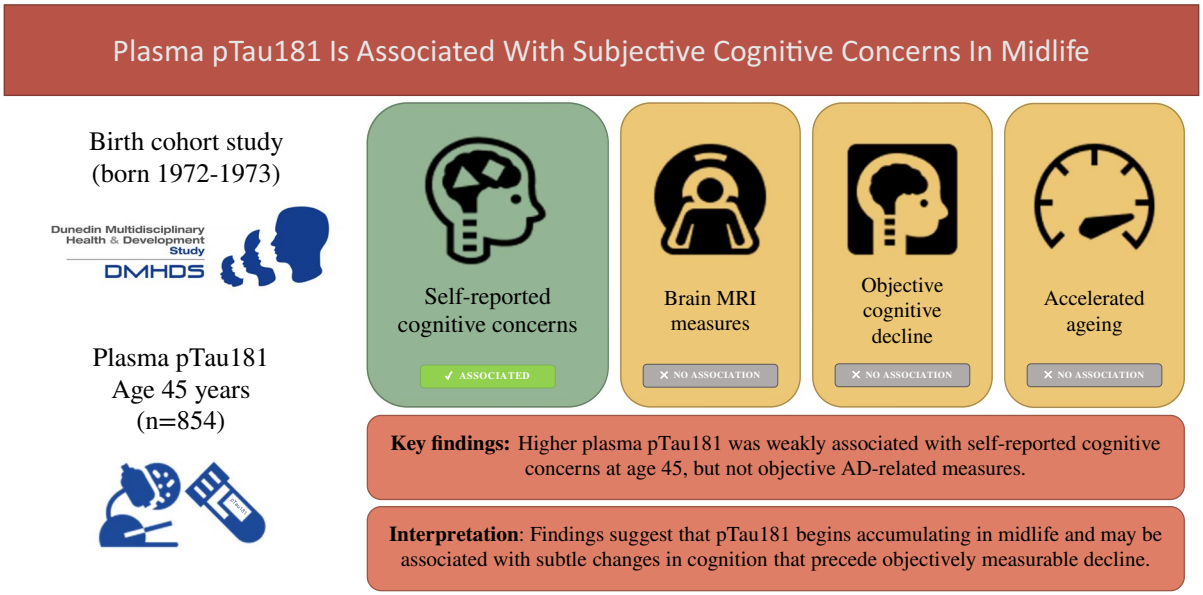
brain integrity, or biological ageing. Higher plasma pTau181 was associated with self-reported cognitive concerns at age 45, but not objective AD-related measures. The association of plasma pTau181 and self-reported cognitive concerns in this cohort suggests that AD pathology may begin to accumulate by age 45 and may be associated with subtle changes in cognition that are not at objectively measurable levels.

Graphical Abstract



Keywords Alzheimer disease · Dementia · Biomarkers · Blood biomarkers · Diagnosis · Phosphorylated tau · p-tau181 · Preclinical Alzheimer's disease

Abbreviations

Aβ	Amyloid beta
AD	Alzheimer's disease
*APOE*ε4	Apolipoprotein E isoform ε4
BMI	Body mass index
brainAGE	Brain age gap estimate
CKD	Chronic kidney disease
CV	Coefficient of variation
DunedinPACE	Dunedin Pace of Ageing Calculated from the Epigenome
EDTA	Ethylenediaminetetraacetic acid
FSIQ	Full scale IQ
GMV	Grey matter volumes
MRI	Magnetic resonance imaging
NFT	Neurofibrillary tangles
pTau181	Phosphorylated tau at threonine 181
SCD	Subjective cognitive decline
SRCC	Self-reported cognitive concerns
WMH	White matter hyperintensities

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Background

Blood-based biomarkers of Alzheimer's disease (AD) are increasingly appealing as a low-cost, minimally invasive part of the AD diagnostic pathway. However, these biomarkers are under-characterised in the general population, particularly in middle-aged individuals without dementia [1]. AD has a long preclinical phase, with pathology accumulating over 10–30 years prior to diagnosis [2]. Increasingly, the focus of AD treatments is on disrupting AD pathology progression in the preclinical stage, as pharmaceutical treatments have limited efficacy in preserving or restoring cognitive function in more advanced stages of AD [3]. Lifestyle interventions are also likely to be more effective at mitigating or delaying AD when implemented earlier in the lifecourse, taking a more preventive approach [4]. Thus, biomarkers that can reliably detect the earliest indications of AD pathology are critically important to the future implementation of AD treatments.

Blood-based AD biomarkers reflect the pathological hallmarks of AD and can correlate with amyloid-β (Aβ) pathology and hyperphosphorylated tau, which forms neurofibrillary tangles in the brain [5]. Elevated plasma concentrations of tau phosphorylated at threonine-181 (pTau181) are thought to be specific to AD [6–9] and plasma pTau181 has recently been approved in the USA as a blood biomarker to rule out the presence of amyloid pathology in primary care patients [10]. pTau181 concentrations increase with worsening AD symptoms, indicating that changes in pTau181 concentrations may be useful for monitoring disease progression [11, 12]. Higher plasma pTau181 concentrations may predict progression to AD in cognitively unimpaired individuals [13] and may be increased in Aβ-positive compared to Aβ-negative young adults [14], suggesting it may be a potential biomarker for the earliest stages of AD. However, while pTau181 is highly correlated with Aβ burden, the presence or extent of Aβ is not necessarily deterministic for AD [15].

It is not currently known how long before clinical presentation of AD differences in pTau181 concentrations can be observed [16]. Most studies of plasma AD biomarkers have been conducted in older-aged samples; few have characterised the range of plasma pTau181 in middle-aged population cohorts. In the Atherosclerosis Risk in Communities (ARIC) study, plasma pTau181 in midlife (mean age 58 years) was associated with incident all-cause dementia later in life (mean follow-up 7.4 years), as were increases in plasma pTau181 from midlife to later life [17]. Previous findings indicate that pTau181 may begin increasing later in life, although one study found that pTau181 concentrations began increasing before age 60 [18]. In combination with other AD risk indicators, pTau181 was an important predictor for AD in older individuals but less so for younger (< 65 years) individuals [19].

Assessing population-representative samples of middle-aged individuals free from dementia is critical to understanding the temporal nature of changes in plasma pTau181. The prognostic value of pTau181, like most putative AD-risk biomarkers, in real-world populations rather than highly selective research samples is an important step towards the translation of biomarkers to clinical care [20]. In the Dunedin Study, we have previously shown that MRI-based measures of worse brain structural integrity, accelerated biological ageing, and greater cognitive decline are interrelated by age 45 and predictive of risk for AD and related dementias [21]. These measures have also been shown to predict dementia in older cohorts [22]. Should pTau181 be associated with other indicators of AD risk, it would suggest that plasma pTau181 may reflect similar pathological processes to those associated with risk as measured by MRI, accelerated biological ageing, or sensitive cognitive tests, and consequently could be a useful biomarker for preclinical AD. Conversely, if pTau181 shows no association with such measures, it would suggest that pTau181 could independently shape AD risk in midlife.

The objectives of this study were to first quantify plasma pTau181 in a middle-aged, population-based cohort without dementia. Secondly, we aimed to examine whether plasma pTau181 was associated with AD-risk features of cognition, structural brain integrity, and biological ageing. We hypothesised that higher pTau181 at age 45 would be associated with greater cognitive impairment and decline, worse structural brain integrity, and accelerated biological ageing [22].

Method

Participants

Participants are members of the Dunedin Multidisciplinary Health and Development Study ("Dunedin Study"), a longitudinal investigation of health and

behaviour in a population-representative birth cohort of 1,037 individuals (91% of eligible births; 52% male) born between 1 April 1972 and 31 March 1973 in Dunedin, New Zealand. The longitudinal study was established at age 3 years based on residence in the province [23, 24]. Assessments were conducted at birth and at ages 3, 5, 7, 9, 11, 13, 15, 18, 21, 26, 32, 38, and most recently at age 45, when 94% of the 997 participants still alive took part. Each study member was brought to the research unit for a day of interviews and examinations. MRI scans were completed for 93% of eligible age-45 participants. The cohort represents the full range of socioeconomic status on NZ's South Island, and as adults matches the NZ National Health and Nutrition Survey on adult health indicators (e.g. body mass index (BMI), smoking, physical activity, general practitioner visits) [25] and matches the NZ Census on educational attainment [26]. As this is a population-based cohort, comorbidities may be present; of note, some participants in the sample had chronic kidney disease ($n=2$) or a history of moderate to severe brain injury ($n=15$). None of the analytic sample reported having been diagnosed with AD, dementia, or Down Syndrome. Study participants are primarily of New Zealand European ethnicity; 8.6% reported Māori ethnicity at age 45. Written informed consent was obtained from participants, and the study was approved by the New Zealand Health and Disability Ethics Committee (NZ-HDEC).

Plasma pTau181

Phlebotomy at age 45 was performed by Southern Community Laboratories in the late afternoon for all participants. Participants did not fast. Whole blood was collected in 10 mL K_2EDTA vacutainer tubes, centrifuged within 2 h of collection (1300×g for 10 min at room temperature), and plasma was aliquoted into polypropylene screw-top cryotubes that were immediately moved to ultra-low temperature (−80 °C) freezers at the University of Otago. Plasma was collected in 2017–2019 and stored frozen until January 2023, when samples underwent single thawing for 2 min in a 37 °C water bath and were pipetted up and down 3 times per sample, aliquoted, and immediately frozen prior to being shipped on dry ice to the University of Auckland for analysis. Anonymised aliquots of EDTA plasma were measured in duplicate using a Simoa SR-X platform at the University of Auckland. The immunoassaying kits used were pTau-181 Advantage V2.1 kits (QTX-104111; Quanterix), all from the same lot (503680). Lipemic samples were noted. Quality control (QC) materials supplied with the kits were analysed in duplicate at the start and end of each plate to assess precision. The mean concentration, repeatability, and intermediate precision for the low and high QC were 37.8 pg/mL, 8.4%, 14.2% and 568.5 pg/mL, 8.8%, 8.8%, respectively. Samples were diluted 1:4 per manufacturer's recommendations. If a sample did not return a value in either duplicate, the assay was repeated. All samples that returned a value were retained; data from all repeated samples were averaged. Samples below the lower limit of detection were imputed at 0 (LLOD = 3.3 pg/mL). The functional lower limit of quantification (LLOQ) was calculated as 12.44 pg/mL; samples below the LLOQ were retained. $N=867$ Study members had samples available for assaying; of these, $n=11$ did not return any data from assaying (too much debris/unable to locate all plexes in the assay/average enzymes per bead below range). Study members who had chronic kidney disease (CKD; $n=2$) were included in the distributional analysis (Fig. 1) but omitted from all other analyses. $N=854$ Study members were included in the final analytic dataset.

Self-reported cognitive concerns (SRCC)

Self-reported cognitive concerns were assessed at ages 38 and 45. Participants were asked to rate the frequency of cognitive difficulties (0 = no, 1 = sometimes, 2 = often) across 17 items based on the criteria for neurocognitive disorders from the DSM-5 [27] and the Cognitive Failures Questionnaire [28].

Cognitive testing

Cognitive function was assessed in childhood at ages 7, 9, and 11, and in adulthood at age 45. All tests were administered by trained professionals according to standard protocols. IQ scores were from the Wechsler Intelligence Scale for Children-Revised (WISC-R) [29] and the Wechsler Adult Intelligence Scale (WAIS-IV) [30], standardised to M = 100 and SD = 15. Childhood IQ scores were averaged across the three time points due to the labile nature of IQ measurements in childhood [31]. Full-scale IQ (FSIQ) is a measurement of global cognition derived from all

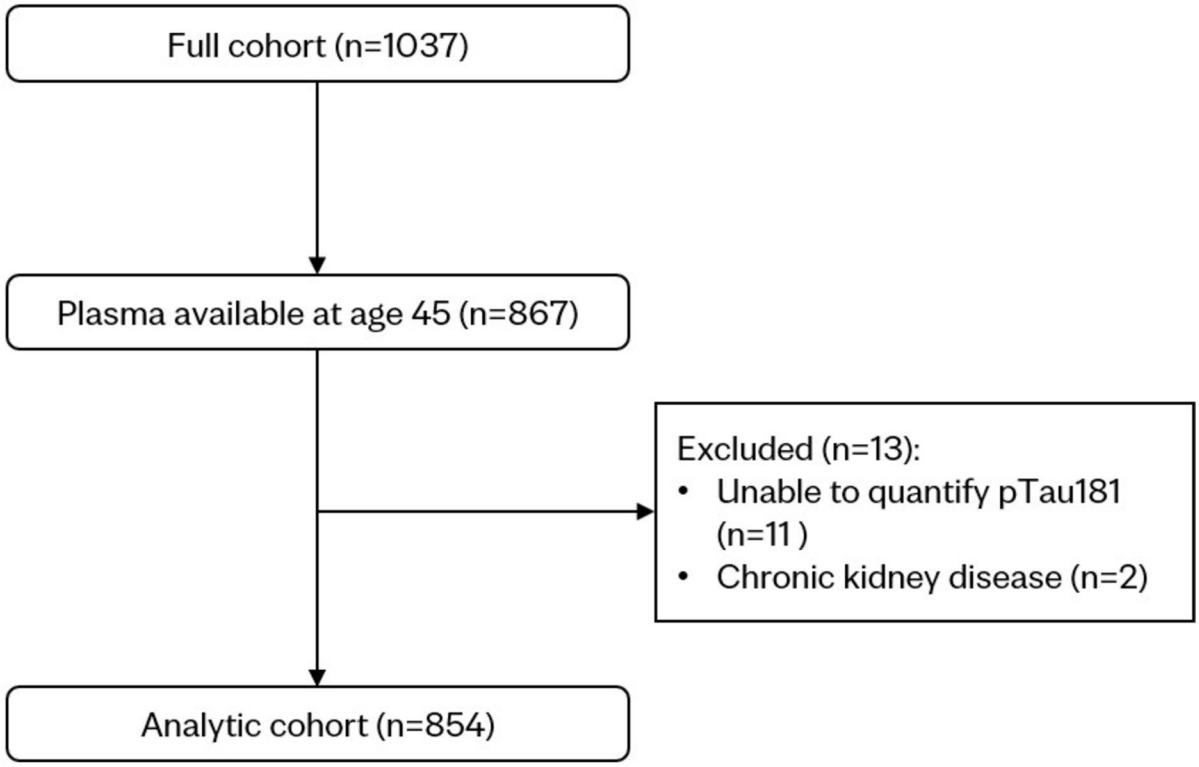

Fig. 1 Participant flow chart

subtests of the WISC-R or WAIS-IV. Composite indices (processing speed, working memory, perceptual reasoning, and verbal comprehension) were calculated at age 45 according to the test manual.

Cognitive decline from childhood (mean values from ages 7, 9, and 11) to adulthood (age 45 years) was calculated using a statistical adjustment approach, where a residualised change score was calculated by measuring the deviation in a participant's actual adult FSIQ from the adult score that was predicted based on their childhood FSIQ, as previously reported [32]. Negative scores indicated a decrease in cognitive performance.

Magnetic resonance imaging (MRI)

Briefly, study members were scanned using a MAGNETOM Skyra 3 T scanner (Siemens Healthcare, Erlangen, Germany) equipped with a 64-channel head-and-neck coil between August 2016 and April 2019. Measurements derived from structural MRI were brain age gap estimate (brainAGE; a score that represents the difference between a person's estimated age based on multiple features of brain structure and their chronological age) [33]; volume of white-matter hyperintensities (WMH); grey-matter volumes (GMV) of 10 subcortical structures; fractional anisotropy from 27 white-matter regions; and cortical surface areas and thicknesses for 360 cortical areas (see Supplementary Materials for full details).

Biological ageing (DunedinPACE)

The pace of whole-body biological ageing was measured using a third-generation epigenetic clock called the Dunedin Pace of Ageing Calculated from the Epigenome (DunedinPACE). Briefly, DunedinPACE was derived from DNA methylation measured from whole blood using Illumina Infinium MethylationEPIC BeadChip Arrays and run at the Molecular Genomics Shared Resource at the Duke Molecular Physiology Institute. Further details on DunedinPACE methods have been reported previously [34, 35].

APOEε4 status

Apolipoprotein E (*APOE*) protein isoform ε4 conveys increased risk of AD [36]. *APOE*ε4 was derived from phased haplotypes of SNPs rs7412 and rs429358 assayed on a genome-wide array, Infinium Omni-Express-12 v1.1 BeadChip array (Illumina Inc., San Diego, California; $n = 848$ with present data before imputation; *APOE* data available for 94% of the analytic sample). The number of *APOE*ε4 alleles was used in the analysis (i.e. 0, 1, or 2).

Education

Education was categorised as the highest education level achieved: no high school qualification; school certificate (equivalent to UK GCSE); high school graduate; or bachelor's degree or higher.

Data analysis

Analyses were conducted in R and Stata between November 2023–September 2025. Descriptive statistics for the unadjusted pTau181 concentrations are presented. Non-parametric tests were used to compare groups (Wilcoxon rank sum test for biological sex and Kruskal–Wallis for number of *APOE*ε4 alleles and education level). For regression analyses, pTau181 concentration was log transformed to meet assumptions of normality; to facilitate comparison of effect sizes, continuous variables were standardised for regression analysis. For each analysis, pTau181 was used to predict the variable of interest in a sex-adjusted model, followed by a model adjusted for sex and BMI, then a sex- and *APOE*ε4-adjusted model, and finally a sex- and education-adjusted model. First, pTau181 concentration was used to predict global cognitive decline on a continuous scale. For post hoc analyses, we categorised participants according to cognitive decline since childhood; first, those with greater than 1 standard deviation (> 15 IQ points) decline; and then those with greater than 2 standard deviations (> 30 IQ points) decline. Logistic regression models were constructed to predict whether pTau181 concentration, adjusted for sex, predicted each category of cognitive decline. We then tested whether pTau181 predicted SRCC cross-sectionally using linear regression models; to examine change in SRCC over time, we used models that included SRCC at age 38, allowing the coefficient to be interpreted as the association between pTau181 at age 45 and change in SRCC over the preceding 7 years.

To test for associations between pTau181 and brain structural integrity, linear regression models were constructed where pTau181 was entered as a predictor of (1) brainAGE; (2) WMH volume (log transformed as the data were non-normal); (3) mean cortical thickness and total surface area; (4) mean fractional anisotropy; and (5) subcortical grey matter volumes. Finally, to explore the distribution patterns of associations, parcel-wise analyses of cortical thickness and surface area were conducted. In these post hoc analyses, we ran linear regressions using pTau181 to predict the surface area and thickness of 360 cortical parcels [37]. For further post hoc analysis, we categorised participants with the top 5% of brainAGE scores (indicating the most aged brains), and used logistic regression, adjusted for sex, to determine whether pTau181 predicted having the top 5% brainAGE score. Finally, we tested for an association between pTau181 concentration and DunedinPACE using linear regression.

We corrected for multiple comparisons across the subcortical and cortical parcel-wise analyses using a false discovery rate procedure [38]; for analyses of all other variables we used an alpha level of 0.05. All tests were two-sided. Analyses with subcortical grey matter volumes were repeated controlling for total brain volume, which tests relative size of a region rather than absolute size [39]. The premise and analysis plan for this study was preregistered (https://dunedinstudy.otago.ac.nz/files/1771390544_Barrett-Young_pTau181inDunedinStudy_CP_amended.pdf). Analyses were checked for reproducibility by a statistician (JK), who used the manuscript to verify the statistical code and applied it to a fresh copy of the dataset.

Results

Collection of plasma samples occurred at the Age-45 assessment ($M = 45.3$ years, SD = 0.55 years), between April 2017 and April 2019. The analytic dataset included Study members with plasma pTau181 data available ($N = 856$; female 49.3%, male 50.7%; Fig. 1). Participants with chronic kidney disease (CKD) had exceptionally high concentrations of

pTau181 (> 100 pg/mL); these Study members ($n = 2$) are included in the distribution of pTau181 (Fig. 2) but were removed from all other analyses, leaving $n = 854$.

A wide distribution of pTau181 concentrations was observed across the full sample ($M = 13.6$ pg/mL, SD = 9.1), with $n = 2$ under the lower limit of detection (functional LLOD = 3.3 pg/mL; Fig. 2). Once participants with CKD were removed, the maximum value was 90.6 pg/mL ($M = 13.4$ pg/mL, SD = 7.2). Males had higher pTau181 concentrations than females on average ($M(SD)_{male} = 14.7(8.5)$; $M(SD)_{female} = 12.0(5.4)$, $p < 0.001$; Table 1, Fig. 3). A post hoc two-way ANOVA was conducted to determine whether the sex difference was explained by a difference in BMI between the sexes; neither the main effect of BMI ($F(1, 848) = 0.0$, $p = 0.98$) nor the interaction of sex and BMI ($F(1, 848) = 0.33$, $p = 0.57$) was significant. Thus, the sex difference observed was independent of BMI.

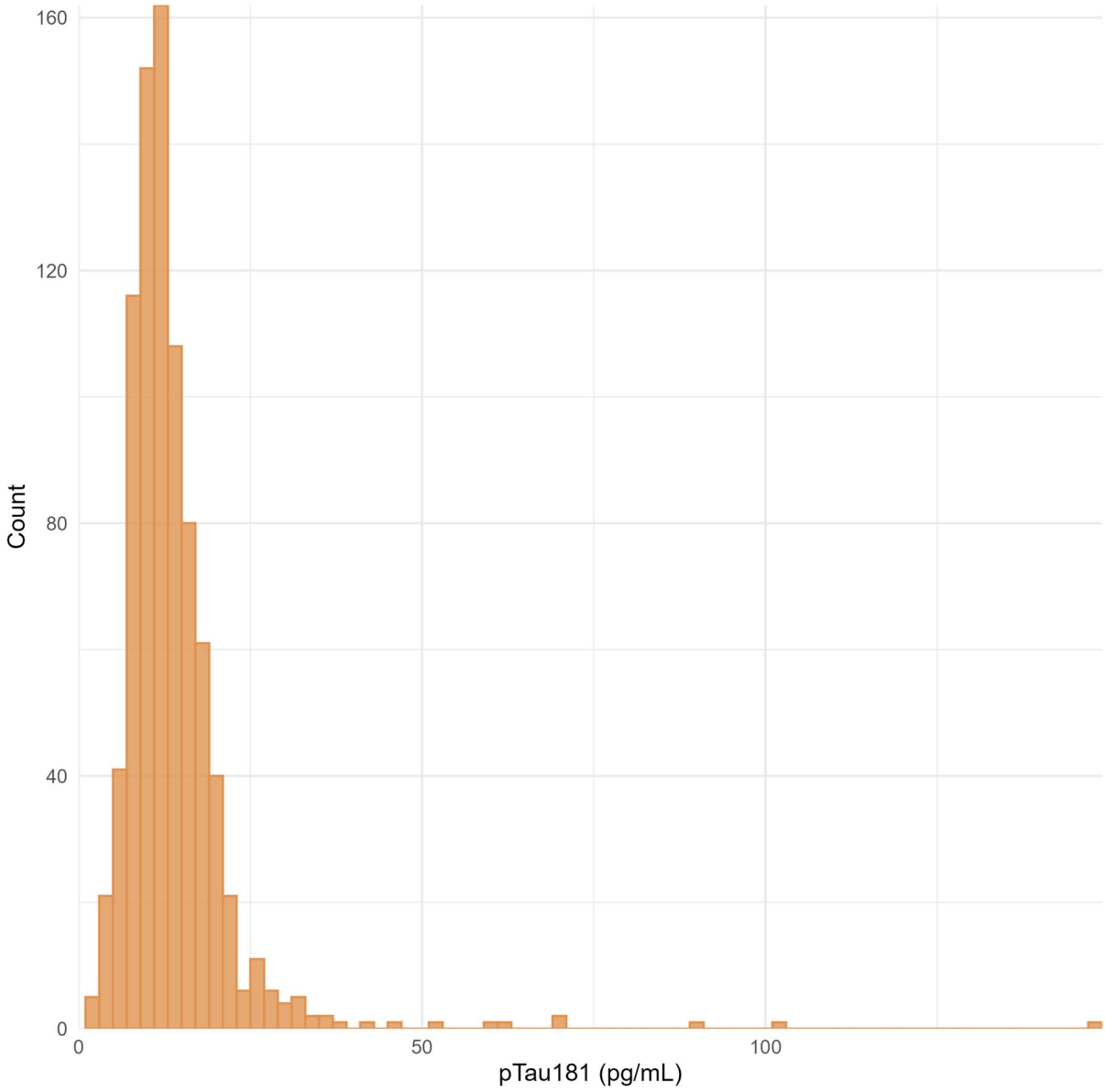

Fig. 2 Distribution of plasma pTau181 concentrations among a birth cohort of 45-year-olds

Table 1 Descriptive statistics for plasma pTau181 concentrations (pg/mL) across groups

	n (%)	*M* (pg/mL)	SD (pg/mL)	*p*
Sex				
Female	422 (49.4%)	12.0	5.37	<.001
Male	432 (50.6%)	14.7	8.49	
***APOE*ε4 allele**				
None	556 (69.3%)	13.2	6.34	0.40
One	220 (27.4%)	13.0	7.12	
Two	26 (3.2%)	13.5	6.05	
Education				
No high school qualification	120 (14.1%)	13.5	8.76	0.95
School certificate	118 (13.8%)	13.2	7.59	
High school graduate	342 (40.1%)	13.2	6.72	
Bachelors' degree or higher	273 (32.0%)	13.5	7.03	

There were no statistically significant differences in pTau181 concentrations between participants with one or two copies of the APOEε4 allele and those with none ($H(2) = 1.8$, $p = 0.4$; Table 1,Fig. 4). Likewise, differences in pTau181 concentrations between education levels were not statistically significant ($H(3) = 0.3$, $p = 0.95$; Table 1).

Higher concentrations of pTau181 were associated with higher self-reported cognitive complaints measured cross-sectionally at age 45 ($\beta = 0.09$, $p = 0.008$, Tables 2 and 3). This association remained significant after controlling for sex, BMI, APOEε4, and education level. The effect of pTau181 on SRCC at age 45 remained significant after accounting for SRCC at age 38 (in a model that adjusted for sex), indicating that higher levels of pTau181 were associated with an increase in SRCC between ages 38 and 45 ($\beta = 0.05$, $p = 0.04$; Table 2). We did not observe any associations between pTau181 and objective measures of cognitive decline; structural brain integrity including brainAGE, WMH volume, mean cortical thickness, total cortical surface area, mean fractional anisotropy, and subcortical grey matter volumes; or accelerated biological ageing (Table 2). No significant associations were observed with objective domain-specific cognitive measures at age 45 (Supplementary Table 1). Exploratory analyses with parcel-wise cortical thickness and surface area as well as tract-wise fractional anisotropy revealed no statistically significant associations after correction for multiple comparisons (Supplementary Tables 2–4). In post hoc analyses, we categorised participants according to cognitive decline (greater than 1 standard deviation decline in cognition since childhood ($n = 137$; 16% of the analytic sample); greater than 2 SD decline in cognition since childhood ($n = 15$, 1.8% of the analytic sample)). Logistic regression revealed that pTau181 did not predict having more than 1 SD decline in cognition ($\chi^2(2) = 3.6$, $p = 0.16$; OR = 0.77 (95% CI: 0.51, 1.15), $p = 0.21$), nor did it predict greater than 2 SD decline in cognition ($\chi^2(2) = 2.5$, $p = 0.29$; OR = 0.46 (95% CI: 0.16, 1.31), $p = 0.15$), adjusted for sex. In addition, we categorised participants with the oldest 5% of brainAGE scores; logistic regression adjusted for sex showed that pTau181 did not predict being in the top 5% of oldest brainAGE scores ($\chi^2(2) = 3.3$, $p = 0.19$; OR = 0.82 (95% CI: 0.41, 1.63), $p = 0.57$).

Discussion

Higher plasma pTau181 concentrations were associated with higher self-reported cognitive concerns (SRCC) at age 45, as well as with worsening SRCC over the preceding 7 years. However, pTau181 was not associated with objective measures of cognitive decline, nor with MRI-based structural brain integrity or biological ageing. Despite the relatively young age of our sample, we found a wide range of pTau181 concentrations among our population-representative sample of 45-year-olds. Males had, on average, slightly higher pTau181 concentrations than females. Taken together, these findings suggest that plasma pTau181 may be an early biomarker for subjective cognitive concerns in midlife, though not yet associated with objective measures of cognitive decline, structural brain integrity, or biological ageing.

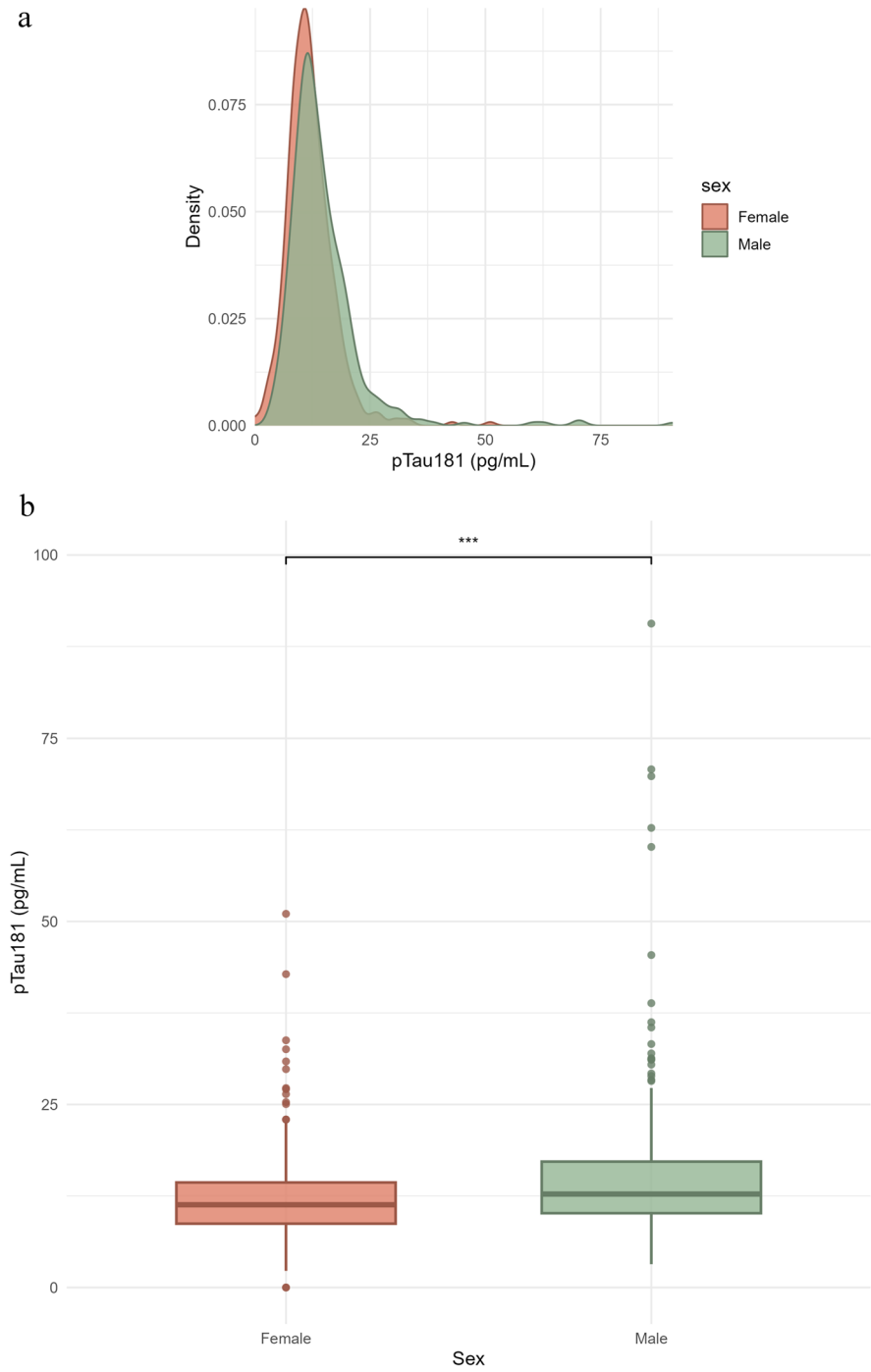

Fig. 3 Sex differences in plasma pTau181 concentrations. **A** Density plot of pTau181 concentration (pg/mL) for females (orange) and males (green). **B** Box plot showing mean, interquartile range, minimum and maximum concentrations of pTau181 by sex (females shown in orange, males in green). The asterisk "***" denotes that the difference between groups was statistically significant ($p < .001$)

Subjective cognitive decline (SCD) is the self-reported persistent decline in cognitive performance with normal performance on objective cognitive tests, in the absence of another explanation (such as an acute event or medical condition) [40]. NIA-AA recognises SCD as a distinct, transitional stage of AD, between the fully asymptomatic and mild cognitive impairment stages [41]. However, conversion rates from SCD to dementia are relatively low, suggesting that SCD may, in many cases, not be indicative of

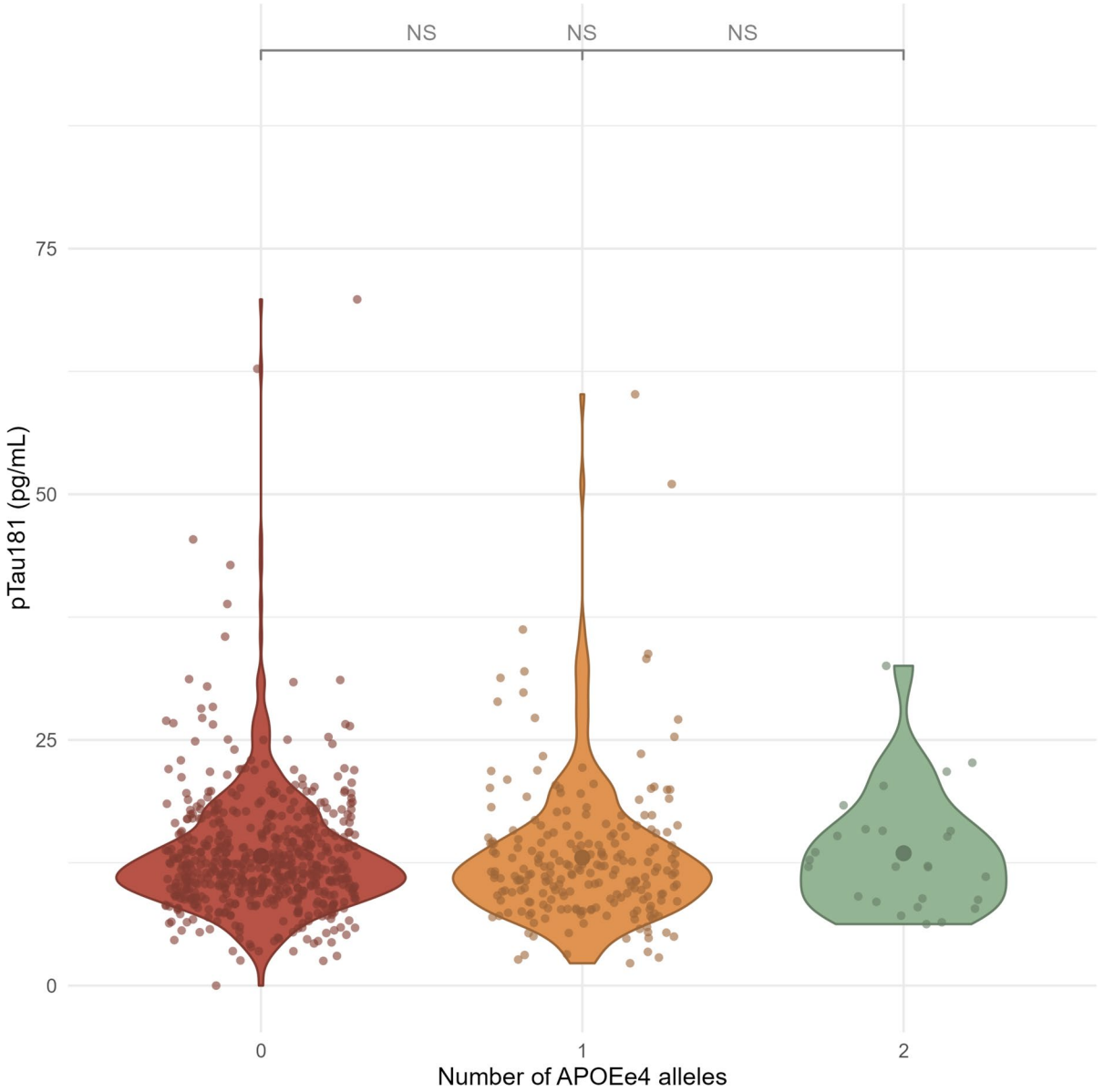

Fig. 4 Plasma pTau181 concentrations by number of *APOEε*4 alleles. Descriptive statistics for pTau181 levels according to APOEε4 groups can be found in Table 1. *NS* = differences between groups were not statistically significant

pathological processes but merely normative ageing [42]. The combination of AD biomarkers and SCD, however, may improve identification and risk stratification of individuals who are most at risk for conversion to AD [42, 43].

Our finding that plasma pTau181 was associated with self-reported cognitive concerns is consistent with findings in SCD samples. In a sample of Hispanic/Latino adults in the USA, plasma pTau181 was associated with higher SCD scores, specifically memory concerns [44]. Plasma pTau181 was found to be elevated at baseline and to increase more rapidly in amyloid-positive individuals with SCD in a memory-clinic-based sample, supporting the assertion that the combination of SCD with AD biomarkers is a distinct stage in the AD progression pathway [43].

Table 2 Tests of associations between plasma pTau181 concentrations and measures of self-reported cognitive concerns, objective cognitive decline, structural brain integrity, and biological ageing

	Model 1				Model 2				Model 3				Model 4			
	n	*β*	95% CI	*p*	*n*	*β*	95% CI	*p*	*n*	*β*	95% CI	*p*	*n*	*β*	95% CI	*p*
SRCC age 45	849	0.09	0.02,0.16	.008**	848	0.09	0.02,0.15	.009**	798	0.10	0.03,0.17	.005**	848	0.10	0.03,0.16	.005**
SRCC age 45[a]	839	0.05	0.001,0.09	.044*	838	0.05	0.001,0.09	.045*	791	0.06	0.02,0.11	.010*	839	0.05	0.005,0.10	.032*
Cognitive decline	841	0.05	−0.02,0.12	.13	840	0.05	−0.02,0.12	.13	790	0.05	−0.02,0.12	.17	840	0.04	−0.03,0.11	.23
brainAGE	821	−0.03	−0.10,0.04	.41	820	−0.03	−0.10,0.04	.40	772	−0.05	−0.13,0.02	.14	820	−0.02	−0.09,0.05	.52
Total SA	816	0.00	−0.06,0.06	.97	815	0.00	−0.06,0.06	.97	767	0.02	−0.04,0.08	.48	815	−0.01	−0.07,0.04	.71
Mean CT	816	0.00	−0.07,0.07	.94	815	0.00	−0.07,0.07	.92	767	0.03	−0.05,0.10	.46	815	−0.01	−0.08,0.06	.85
Mean FA	811	0.00	−0.07,0.07	.93	810	0.00	−0.07,0.07	.92	762	0.04	−0.04,0.11	.32	810	−0.01	−0.08,0.06	.82
WMH volume	807	0.01	−0.06,0.08	.79	806	0.01	−0.06,0.08	.80	758	0.02	−0.06,0.09	.66	806	0.02	−0.05,0.09	.64
DunedinPACE	795	−0.04	−0.12,0.03	.23	793	−0.06	−0.12,0.01	.07	786	−0.05	−0.12,0.02	.19	794	−0.03	−0.09,0.04	.45

[a]Controlled for SRCC at age 38

Model 1 was adjusted for sex. Model 2 was adjusted for sex and BMI. Model 3 was adjusted for sex and APOEε4 count. Model 4 was adjusted for sex and highest education level. *β* standardised regression coefficient, *CI* 95% confidence interval, *SRCC* self-reported cognitive concerns, *SA* surface area, *CT* cortical thickness, *FA* fractional anisotropy, *WMH* white matter hyperintensities, *DunedinPACE* Dunedin Pace of Ageing Calculated in the Epigenome

*$p < .05$, **$p < .01$

Table 3 Mean and standard deviation of self-reported cognitive complaints by pTau181 quintiles

	SRCC age 45	
	M	**SD**
pTau181 quintiles		
Lowest	8.24	4.42
2	9.02	5.47
3	9.61	5.24
4	9.73	6.25
Highest	9.12	5.50

Although AD is more prevalent in older people [45] evidence suggests AD pathology begins to accumulate decades prior [46, 47]. Previous research in clinical populations has shown that plasma pTau181 is associated with Aβ burden, tauopathy consistent with AD, and cognitive impairment [9, 48, 49]. Plasma pTau181 predicted future AD diagnosis and greater hippocampal atrophy among the Alzheimer's Disease Neuroimaging Initiative cohort [50]. Therefore, a possible interpretation of our findings is that the association of pTau181 and self-reported cognitive concerns in this cohort suggests that AD pathology may begin before age 45 and is associated with subtle changes in cognition that are not at measurable levels. However, it is also possible that pTau181 is not associated with AD pathology at this age and that cognitive complaints may reflect other processes that are not specific to AD.

Plasma pTau181 may be particularly sensitive to intra/inter-assay differences and variation depending on pre-analytic and analytic methods. pTau181 has been found to be subject to cross-lot bias [18]; we minimised intra-assay differences using kits from the same lot, running all analyses on the same machine, and running samples in duplicate. Plasma pTau181 has been shown to be stable across up to three freeze-thaw cycles [51]. The majority of the samples in this study underwent two freeze-thaw cycles ($n=749$). A minority ($n=29$) were freeze-thawed 4–5 times; these samples may have returned inaccurate results due to unstable pTau181, although the CVs for these samples did not differ from the CVs of samples with fewer freeze-thaw cycles. Furthermore, there may be differences in the raw concentrations of plasma pTau181 reported by various studies due to methodological differences, including different assaying technologies used. A study using the same device (Simoa SR-X) and immunoassaying kits (Quanterix pTau181 Advantage V2.1) as the present study found plasma pTau181 concentrations among $n=20$ cognitively unimpaired individuals ranged from 5.33 to 78.2 pg/mL ($M=18.1$ pg/mL) [52], a similar range to that found in our study. In one study of $n=16$ cataract patients with normal cognition, plasma pTau181 range was 0.66–17.7 pg/mL ($M=3.2$ pg/mL) [53]; another study of $n=65$ cognitively normal older adults found a mean of 23.5 pg/mL (SD = 9.6 pg/mL), though no range was reported [54]. The wide ranges and variation in mean concentrations observed in these studies, in which the same equipment was used, could be due to low sample sizes that do not represent the full range of plasma pTau181 in the population. Thus, our study of $n=854$ individuals, none of whom have been diagnosed with AD, suggests the range of plasma pTau181 concentrations in the midlife population is wide.

Females are diagnosed with AD at a higher rate than males [55]; in our study, we found that males had greater pTau181 concentrations. Although studies on sex differences in pTau181 are mixed [6, 18, 56], one study found that even when females and males had similar levels of plasma pTau181, females tended to have worse phenotypic outcomes [57]. A recent meta-analysis of tau-PET studies found that females accumulated tau tangles faster than men, suggesting that, in those with high Aβ burden, tauopathy may be more aggressive and accumulate faster [58]. Furthermore, the decreasing oestradiol levels that occur during the menopausal period may reduce the neuroprotective effects of oestrogen, meaning that menopause could mark an inflection point after which neuropathology may begin to accumulate [59, 60]. Thus, while in our cohort males had higher pTau181 than females, the rate of pathogenic tau accumulation and resulting phenotypic alterations may differ between the sexes later in life but are not yet apparent in this midlife cohort. Interestingly, one of the few studies of plasma pTau181 in midlife also found that males had higher pTau181 concentrations than females, supporting the hypothesis that pTau181 may accumulate at different rates between the sexes [61].

A limitation of this study is that we were only able to measure one blood biomarker from the cohort at this age, so we were unable to compare performance of different biomarkers. Other variants of phosphorylated tau may be more suitable for AD screening in the general population; in particular, pTau217 has emerged as the best-performing biomarker for identifying AD pathology in the earliest stages [62]. Furthermore, it is likely

that blood biomarkers of AD provide the greatest predictive power when used in combination [1]; accordingly, we intend to increase the panel of biomarkers measured at the next assessment wave of the Dunedin Study, including measures of amyloid-β and neuroinflammation as well as phosphorylated tau. Future assessments of this cohort will allow us to examine the progression of plasma pTau181 concentrations across midlife and into later life, enabling us to examine if or when this biomarker begins to index preclinical AD.

Blood biomarkers are ideal for screening in primary care as they are minimally invasive and have the potential to be low cost and widely accessible [63]. Therefore, it is imperative that plasma pTau181 is studied in population-based, unselected cohorts in natural settings. This study was conducted in a birth cohort that is representative of the general population of Aotearoa New Zealand on socioeconomic status and physical health. It has achieved exceptionally high retention rates (>90% at every adult assessment), so it is less subject to attrition or selection biases than many other studies. However, this means that this sample is likely to include individuals who are experiencing cognitive decline due to other, non-AD-related reasons, including acquired brain injuries, pharmaceutical effects, substance and/or alcohol use, or other factors that may affect cognition. The cohort is also predominantly of European descent and is under-representative of Māori compared to New Zealand population statistics [64]. Thus, the findings presented here should be interpreted cautiously as they may not apply to other populations and ethnicities.

We were unable to account for every potential confounding factor in all analyses. Of potential comorbidities that may affect plasma pTau181, CKD has been clearly established as influencing pTau181 concentrations [65, 66, 67], although the direction of causality is not entirely clear [68]. Notably, participants with clinician-confirmed and biomarker-confirmed CKD diagnoses recorded the highest pTau181 concentrations in this sample (>100 pg/mL). BMI is negatively associated with pTau181 concentrations [69]; however, adding BMI to the analysis did not change our results. Importantly, more research in population-based cohorts is needed to understand which factors affect pTau181 and should therefore be considered when interpreting biomarker results.

According to the ATN model, biomarkers of Aβ, tauopathy, and neurodegeneration are used to classify AD stages [41, 70]. In the absence of Aβ or neurodegeneration markers, we are currently unable to distinguish individuals in the Dunedin Study cohort who are Aβ-positive from those who are Aβ-negative and are therefore unable to conclusively determine whether any of our participants have preclinical AD, or whether the variation in pTau181 levels observed in our cohort is non-specific for AD. Thus, any cognitive decline and neurostructural abnormalities among the sample cannot be singularly attributed to preclinical AD and may be due to other neurocognitive disorders, such as dementia with Lewy bodies or frontotemporal dementia, long-term lead exposure [71], or some mental health disorders [72].

The main limitation of this study is that our data are largely cross-sectional at age 45, so we currently lack data at older ages that would allow us to test if plasma pTau181 at age 45 is an independent predictor of dementia at later ages. At this stage, it is unclear if the pTau181 levels observed in midlife are true prognostic indicators of AD, or whether they reflect normal variation in the population. One potential implication of our findings is that plasma pTau181 should not be used for early detection of dementia in young-middle-aged people; another implication is that, because pTau181 is associated with SRCC but not with other risk factors, it may be an independent predictor of dementia that could improve early identification at the very early stage of the pre-dementia/AD continuum. Without long-term follow-up into old age, we are currently unable to adjudicate between these two implications, but future assessment phases of this cohort will provide further insights.

There is potential clinical utility of blood biomarkers of AD in the early part of the AD diagnostic pathway, and plasma pTau181 is a promising biomarker of AD pathology. In this middle-aged birth cohort without AD, we found that pTau181 concentration was associated with self-reported cognitive concerns; however, pTau181 concentrations were not associated with cognitive decline (measured from childhood to age 45), worse structural brain integrity, or biological ageing. Thus, midlife plasma pTau181 concentrations may reflect AD-related processes not yet detectable by objective risk measures, but already perceptible through subjective cognitive concerns.

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Data availability Proposed data-analysis projects from qualified scientists must have a concept paper describing the purpose of data access, IRB approval at the applicants' university, and provision for secure data access. We offer secure access on the Otago campus. These access requirements parallel those used by dbGap and the Health and Retirement Study.

Declarations

Competing interests Drs. Terrie Moffitt, Avshalom Caspi, Karen Sugden, and Richie Poulton are inventors on a license issued by Duke University for DunedinPACE. The algorithm to calculate DunedinPACE is publicly available on Github, https://github.com/danbelsky/DunedinPACE. No other authors have conflicts of interest to report.

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