

RESEARCH ARTICLE

Association between serum urate and CSF markers of Alzheimer's disease pathology in a population-based sample of 70-year-olds

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Abstract

Introduction: The relationship between urate and biomarkers for Alzheimer's disease (AD) pathophysiology has not been investigated.

Methods: We examined whether serum concentration of urate was associated with cerebrospinal fluid biomarkers, amyloid beta ($A\beta$)₄₂, $A\beta$ ₄₀, phosphorylated tau (p-tau), total tau (t-tau), neurofilament light (NfL), and $A\beta$ ₄₂/ $A\beta$ ₄₀ ratio, in cognitively unimpaired 70-year-old individuals from Gothenburg, Sweden. We also evaluated whether possible associations were modulated by the apolipoprotein E (APOE) ϵ 4 allele.

Results: Serum urate was positively associated with $A\beta$ ₄₂ in males ($\beta = 0.55$ pg/mL, $P = .04$). There was a positive urate–APOE ϵ 4 interaction (1.24 pg/mL, $P_{\text{interaction}} = .02$) in relation to $A\beta$ ₄₂ association. The positive urate and $A\beta$ ₄₂ association strengthened in male APOE ϵ 4 carriers ($\beta = 1.28$ pg/mL, $P = .01$).

Discussion: The positive association between urate and $A\beta$ ₄₂ in cognitively healthy men may suggest a protective effect of urate against deposition of amyloid protein in the brain parenchyma, and in the longer term, maybe against AD dementia.

KEYWORDS

Alzheimer's disease, apolipoprotein E ϵ 4, cerebrospinal fluid biomarkers, dementia, urate

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1 | BACKGROUND

Dementia is the most common neurodegenerative disorder, with Alzheimer's disease (AD) constituting \approx 60% to 70% of the cases.¹ The global prevalence of dementia in individuals aged \geq 60 years ranges between 5% and 7%.² Dementia due to AD is preceded by years of progressive cognitive impairment.³ AD neuropathology is characterized by formation of amyloid plaques and aggregation of hyperphosphorylated tau (p-tau) into paired helical filaments forming dystrophic neurites surrounding the plaques and intraneuronal neurofibrillary tangles, leading to synaptic and neuronal degeneration and loss, finally resulting in overt brain atrophy. The main component of amyloid plaques is the amyloid beta ($A\beta$) peptide, which is composed of a family of peptides produced by proteolytic cleavage of the type I transmembrane spanning glycoprotein, the amyloid precursor protein (APP).⁴ $A\beta_{40}$ and $A\beta_{42}$ are two major isoforms of $A\beta$; however, amyloid plaques in AD brains mostly, or sometimes only, consist of $A\beta_{42}$.⁵ $A\beta_{40}$, on the other hand, can reliably be used as a surrogate marker for increased amyloidogenic APP processing in AD.⁶ Some studies have also reported that the ratio of $A\beta_{42}/A\beta_{40}$ may be more important to the neurobiology in sporadic AD than the absolute levels of $A\beta_{42}$.^{7,8} Cerebrospinal fluid (CSF) neurofilament light (NfL) is another marker that is used to indi-

cate unspecific axonal damage in AD that is suggested to progress with age independent of $A\beta$ pathology.⁹

The main pathological changes in AD can be monitored by three CSF biomarkers, that is, a decrease in CSF $A\beta_{42}$ (or the CSF $A\beta_{42}/A\beta_{40}$ ratio)¹⁰ and increase in CSF levels of p-tau and total tau (t-tau). Such changes in CSF biomarkers are detectable in cognitively unimpaired elderly as the earliest signatures of AD.^{11,12} Evidence from biomarker and brain autopsy studies has shown that $A\beta$ pathology and increased tau phosphorylation and secretion start as early as 20 years before clinical symptoms,¹³ which is reflected by the CSF biomarkers.¹⁴ Considering that the pathological process of AD is slow and gradual, it is important to find risk and protective factors early in the disease course.

Urate is a naturally occurring antioxidant that accounts for about 60% of the free-radical scavenging capacity in humans.¹⁵ There is evidence that the development of AD is accompanied by exposure of brain tissue to oxidative stress.¹⁶ Because urate is an antioxidant, it has been suggested to exert neuroprotective effects and may thus alter the risk of AD via its antioxidant ability.¹⁷ Lower urate concentrations have also been associated with faster disease progression and an increased risk of neurodegenerative disorders including Parkinson's and AD dementia.^{18,19} A meta-analysis of data across 21 case-control studies indicated that in patients with AD, serum urate concentrations

were significantly lower than in healthy controls.²⁰ Two longitudinal studies have previously investigated the relationship between serum urate and long-term risk of dementia in European populations, with contradictory results.^{21,22} We recently reported a protective role of higher midlife serum urate levels for the development of dementia, irrespective of dementia subtypes, in a longitudinal study of Swedish women followed over 44 years.²³ To date, only one study has investigated the association between serum urate and cerebral A β deposition in non-demented Korean individuals (age range = 55 to 90 years), indicating no association.²⁴ However, the relationship between serum urate concentration and CSF markers of preclinical AD in healthy older people has not been examined.

Genetic studies have identified polymorphisms in apolipoprotein E (APOE) as the main genetic determinant of late-onset sporadic AD.²⁵ The *apoE* protein is mainly involved in cholesterol metabolism in humans. Having at least one copy of the APOE ϵ 4 allele increases the risk 3-fold for developing AD at an early age in almost all ethnic groups.^{26,27} The APOE ϵ 4 allele has also been reported to be associated with a slightly higher risk of primary hyperuricemia in Chinese men (mean age = 47.2).²⁸ Yet, there are no reports on the relationship between APOE ϵ 4 and serum urate concentrations in older individuals with a higher likelihood of preclinical AD. Because serum urate, AD biomarkers, and AD incidence rise at a higher age in women compared to men and because our study sample consisted of a cohort with a fixed age of 70 years, we decided a priori to do all analyses stratified by sex. The current study thus aimed to investigate the association between serum urate and biomarkers of preclinical AD pathology using CSF data from cognitively unimpaired individuals from a representative population-based sample of 70-year-olds in Sweden by sex. The association was further evaluated for any possible interaction between serum urate and the presence of the AD risk allele APOE ϵ 4.

2 | METHODS

2.1 | Study participants

We used the baseline data from the Gothenburg H70 Birth Cohort Study 2014 to 2016. The data for individuals living in private households as well as in residential care was used.²⁹ More details on the study design, data recruitment, and health examinations are provided elsewhere.³⁰ Briefly, all men and women, born 1944 on specific dates (dates ending with 0, 2, 5, or 8), and registered as residents in Gothenburg, Sweden, were invited for a health examination between 2014 and 2016 (mean age = 70.9, standard deviation [SD] = 0.35). With a response rate of 72.2%, a total of 1203 (559 men and 644 women) individuals participated. A detailed neuropsychiatric examination was performed in 1196 individuals, and 430 (response rate 35.7%) consented to lumbar puncture (LP) for CSF sampling. Of these, 108 had pharmacological contraindications (e.g., anticoagulants and cancer therapies), leaving 322 participants.^{29,30} For this study, a subset of cognitively

HIGHLIGHTS

- Urate is suggested to reduce the risk of neurodegenerative disease by virtue of its antioxidative properties.
- The relationship between urate and Alzheimer's disease (AD) pathophysiology, examined by cerebrospinal fluid (CSF) biomarkers, has not been investigated.
- A positive association between serum urate and CSF amyloid beta (A β)₄₂ concentration in cognitively healthy men was observed, which strengthened in those possessing the apolipoprotein E ϵ 4 allele.
- The results suggest a protective effect of urate against the deposition of amyloid protein in the brain parenchyma, and in the longer term, maybe against AD dementia.

RESEARCH IN CONTEXT

1. **Systematic Review:** The literature (traditional web sources, meeting abstracts, and presentations) regarding associations between urate and Alzheimer's disease (AD) and other dementia subtypes was reviewed. Urate levels have epidemiologically been suggested to reduce the risk of neurodegenerative diseases, possibly by antioxidative properties, but an association between urate and biomarkers of preclinical AD has not been studied.
2. **Interpretation:** Using the cerebrospinal fluid (CSF) data from a cross-sectional, Gothenburg-based, birth cohort of 70-year-olds, we report that levels of serum urate are positively associated with amyloid beta (A β)₄₂ in males, and significantly stronger so in the presence of the apolipoprotein E ϵ 4 allele. This is compatible with the idea that serum urate may protect against depositions of A β ₄₂ in brain, years before the manifestation of AD symptoms.
3. **Future Directions:** Confirmation of our findings in larger datasets, and in particular in longitudinal settings, are needed. If confirmed, urate may be a modifiable risk factor that can be used to alter the course of AD.

unimpaired individuals was defined based on a Clinical Dementia Rating (CDR) score of 0.³¹ All participants (n = 63) with a CDR score of > 0 were excluded from this subset, leaving 259 (130 men and 129 women) as the study sample.

The Regional Ethics Review Board in Gothenburg provided the approval for this study. Written informed consent was obtained from all participants and/or their close relatives prior to the study.

2.2 | Assessment of CDR score and dementia

For all study participants ($n = 1196$, response rate 99.4%), a detailed neuropsychiatric assessment was performed by experienced psychiatric research nurses at Sahlgrenska University Hospital in Gothenburg or at home. The CDR score was recorded during the examinations, but the final rating scores were assigned by a geriatric psychiatrist and neurologist.²⁹ Dementia was diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) III-R criteria.³⁰ These criteria have been used in the Gothenburg studies for > 30 years.²⁹

2.3 | Urate and CSF biomarker measurements

For this study, measurements for serum urate and CSF biomarkers, $A\beta_{42}$, $A\beta_{40}$, $A\beta_{42}/A\beta_{40}$ ratio, t-tau, p-tau, and NfL were used for the cognitively unimpaired study sample ($n = 259$).

Blood sampling was performed in 1192 participants at the Neuropsychiatric Outpatient Department at the Sahlgrenska University Hospital during the 2014 to 2016 examinations. Samples were collected for each study participant after an overnight fasting. All serum samples were frozen at -80°C within approximately 1 hour of collection to be saved in a biobank for future analyses according to the Swedish Biobank Law (2002:297).³⁰ Following the standard routine clinical laboratory procedures, these samples were used to determine serum urate. The serum urate measurements were done during February and March 2018.

All LPs were performed in the morning to collect CSF samples from the L3/L4 or L4/L5 interspace, as previously described.^{29,30} Standard laboratory procedures for CSF sample collection and storage at suitable temperature are detailed elsewhere.^{29,30} The analysis of CSF $A\beta_{42}$, t-tau, and p-tau was done using sandwich enzyme-linked immunosorbent assay (ELISA) methods. To measure $A\beta_{42}$ in CSF, an ELISA was specifically constructed to measure $A\beta$ peptides from amino acid 1 to 42³² (INNOTEST β -amyloid1-42, Fujirebio). CSF t-tau and tau phosphorylated at threonine 181 (p-tau) were also determined using sandwich ELISAs (INNOTEST htau Ag and PHOSPHO_TAU [181P], Fujirebio), as detailed previously.^{29,33,34} For the measurement of $A\beta_{40}$ and $A\beta_{42}/A\beta_{40}$ ratio, a V-PLEX $A\beta$ Peptide Panel 1 (6E10) Kit (Meso Scale Discovery) was used.³⁵ CSF NfL concentration was measured using an in-house sandwich ELISA with capture and detection antibodies that are directed against the central rod domain of the protein (NfL21 and NfL23, respectively).³⁶

2.4 | APOE genotyping

DNA extraction was performed following the standard procedures at LGC Genomics in Berlin (Germany). The samples were genotyped using the KASPar PCR SNP genotyping system (LGC Genomics).³⁰ The genotype information for two single nucleotide polymorphisms (SNPs), *rs7412* and *rs429358*, in APOE, were used to define epsilon ($\epsilon 2$, $\epsilon 3$, and $\epsilon 4$) alleles.²⁹ Both homozygotes ($\epsilon 4/\epsilon 4$) and heterozygotes ($\epsilon 2/\epsilon 4$ and

$\epsilon 3/\epsilon 4$) for the APOE $\epsilon 4$ allele were considered to define the term "APOE $\epsilon 4$ carrier" (or APOE $\epsilon 4+$). For 5 out of 259 individuals in the study sample, genotype information for APOE SNPs could not be determined.

2.5 | Statistical analyses

Data are expressed as mean \pm SD for continuous variables, and as frequencies and percentages for all categorical variables. Student's t-test was used to compare the average levels of serum urate and CSF biomarkers between men and women. To evaluate the association between serum urate and each of the CSF biomarkers ($A\beta_{42}$, $A\beta_{40}$, $A\beta_{42}/A\beta_{40}$ ratio, p-tau, t-tau, and NfL), separate multiple linear regressions, fitted for overall and sex-adjusted models, were performed. The analyses were further stratified for sex and a "serum urate \times APOE $\epsilon 4$ allele" interaction term was included in the linear regression models to test for its significance. The association analyses were also stratified for the presence of the APOE $\epsilon 4$ allele in overall and male and female groups. A $P \leq .05$ was designated as significant and all analyses were performed in statistical software R v3.5.2. Values are presented for per unit ($\mu\text{mol/L}$) increase in serum urate for per unit (pg/mL) increase and/or decrease in any CSF biomarker.

3 | RESULTS

The overall study population comprised 259 participants (130 males and 129 females). The average serum urate concentration for the subset was 321.5 (75.8 SD) $\mu\text{mol/L}$, with a significant difference between men and women (352.3 vs. 290.1 $\mu\text{mol/L}$, $P = 7.6\text{E-}12$). The levels of CSF $A\beta_{42}$, $A\beta_{40}$, p-tau, t-tau, NfL, and $A\beta_{42}/A\beta_{40}$ ratio were not significantly different between men and women, although $A\beta_{42}$ tended to be (non-significantly) lower in men ($P = .13$). There were 33.8% of the individuals who were APOE $\epsilon 4$ carriers, with a higher percentage of carriers among men (38.8%) than among women (28.8%; Table 1). The overall APOE $\epsilon 4$ allele frequency (calculated based on the total number of alleles in the sample) was 18%.

There was no significant difference in mean serum urate levels between APOE $\epsilon 4$ carriers and non-carriers in the total sample (325.5 vs. 319.4 $\mu\text{mol/L}$, $P = .54$) or in sex-stratified groups (men: 345.6 vs. 356.5 $\mu\text{mol/L}$, $P = .40$; women: 297.6 vs. 286.2 $\mu\text{mol/L}$, $P = .42$; Table S1 in supporting information).

3.1 | Association between serum urate and CSF biomarkers

A positive association between serum urate and CSF $A\beta_{42}$ was observed among men, where higher levels of serum urate were associated with higher CSF levels of $A\beta_{42}$ (β [95% CI] = 0.55 pg/mL [0.01 to 1.10], $P = .04$). There was a positive estimate also in women (β [95% CI] = 0.14 pg/mL [-0.44 to 0.73], $P = .63$), albeit not reaching statistical significance (Table 2). Serum urate was also positively associated with $A\beta_{42}/A\beta_{40}$ ratio (β [95% CI] = 4.4E-04 [7.6E-05 to 8.2E-04], $P = .02$)

TABLE 1 Numbers and biomarker levels of the individuals included in the analyses

	All	Males	Females	P-value
Total number, n (%)	259	130 (50.2)	129 (49.8)	-
Serum urate ($\mu\text{mol/L}$) ^b	321 \pm 75.8	352 \pm 72.5	290 \pm 65.6	7.6e-12
A β_{42} (pg/mL) ^b	724 \pm 225.1	703 \pm 230.4	745 \pm 218.4	.13
A β_{40} (pg/mL) ^b	6253 \pm 1445	6151 \pm 1426	6370 \pm 1458	.22
A β_{42} /A β_{40} ^c	0.87 \pm 0.21	0.85 \pm 0.22	0.90 \pm 0.19	.10
t-tau (pg/mL) ^b	332 \pm 141	338 \pm 146	325 \pm 136	.43
p-tau (pg/mL) ^b	49.4 \pm 17.9	49.8 \pm 18.2	49.1 \pm 17.6	.75
NfL (pg/mL) ^b	869 \pm 688	894 \pm 615	839 \pm 756	.52
APOE $\epsilon 4+$, n (%) ^a	86 (33.8)	50 (38.8)	36 (28.8)	-
APOE $\epsilon 4$ homozygotes, n (%)	7 (8.1)	6 (85.7)	1 (14.2)	-

Abbreviations: A β , amyloid beta; APOE $\epsilon 4+$, individuals carrying apolipoprotein E risk allele; NfL, neurofilament light chain; p-tau, tau phosphorylated at amino acid 181; t-tau, total tau.

^aThe APOE allele data were missing for 5 out of 259 individuals (one male and four females) and the percentage is calculated for 254 (129 males and 125 females).

^bValues presented as mean \pm standard deviation.

^cThe values are presented after multiplying by 10.

TABLE 2 Association of serum urate ($\mu\text{mol/L}$) with CSF biomarkers (pg/mL) overall and stratified by sex

CSF marker	Unadjusted ^a		Adjusted ^b		Males		Females	
	β (95% CI)	P	β (95% CI)	P	β (95% CI)	P	β (95% CI)	P
A β_{42}	0.18 (-0.18 to 0.55)	.32	0.36 (-0.03 to 0.76)	.07	0.55 (0.01 to 1.10)	.04	0.14 (-0.44 to 0.73)	.63
A β_{40}	-0.72 (-3.08 to 1.63)	.54	-0.25 (-2.83 to 2.33)	.84	-0.25 (-3.73 to 3.21)	.88	-0.24 (-4.16 to 3.68)	.90
A β_{42} /A β_{40}	2.4e-04 (-1.0e-04 to 5.8e-04)	.16	4.4e-04 (7.6e-05 to 8.2e-04)	.02	5.2e-04 (-2.2e-05 to 1.0e-03)	.06	3.5e-04 (-1.5e-04 to 8.6e-04)	.16
p-tau	-0.003 (-0.03 to 0.03)	.82	-0.01 (-0.04 to 0.02)	.66	-0.02 (-0.06 to 0.02)	.34	0.01 (0.03 to 0.05)	.66
t-tau	-0.02 (-0.25 to 0.21)	.87	-0.07 (-0.33 to 0.17)	.53	-0.13 (-0.48 to 0.22)	.46	-0.01 (-0.38 to 0.35)	.94
NfL	-0.46 (-1.59 to 0.66)	.42	-0.76 (-2.01 to 0.47)	.23	-0.99 (-2.48 to 0.48)	.18	-0.46 (-2.53 to 1.61)	.66

Note: All β -values are presented as pg/mL for all CSF biomarkers, except A β_{42} /A β_{40} , which is a ratio.

Abbreviations: A β , amyloid beta; CI, confidence interval; CSF, cerebrospinal fluid; NfL, neurofilament light chain; p-tau, tau phosphorylated at amino acid 181; t-tau, total tau.

^aThe associations of serum urate with CSF biomarkers were determined using linear regression models with serum urate as the independent variable.

^bThe above linear regression models were additionally adjusted for sex.

in sex-adjusted analysis (Table 2). There was a trend of positive serum urate association with A β_{42} /A β_{40} ratio in men (β [95% CI] = 5.2E-04 [-2.2E-05 to 1.0E-03], $P = .06$), but not in women (Table 2). There were no significant associations between serum urate and A β_{40} (β [95% CI] = -0.25 pg/mL [-2.83 to 2.33], $P = .84$), p-tau (β [95% CI] = -0.01 pg/mL [-0.04 to 0.02], $P = .66$), t-tau (β [95% CI] = -0.07 pg/mL [-0.33 to 0.17], $P = .53$), or NfL (β [95% CI] = -0.76 pg/mL [-2.01 to 0.47], $P = .23$) in sex-adjusted analyses in the total sample or when men and women were analyzed separately (Table 2).

3.2 | Serum urate and APOE $\epsilon 4$ interaction

There was an interaction between serum urate and APOE $\epsilon 4$ status in relation to the association between urate and A β_{42} in the sex-adjusted (β [95% CI] = 0.73 pg/mL [0.01 to 1.45], $P_{\text{interaction}} = .04$)

analysis (Table 3). In sex-stratified groups, the significant serum urate-APOE $\epsilon 4$ interaction was observed in relation to A β_{42} in males (β [95% CI] = 1.24 pg/mL [0.17 to 2.31], $P_{\text{interaction}} = .02$), but not females (β [95% CI] = 0.28 pg/mL [-0.87 to 1.43], $P_{\text{interaction}} = 0.69$; Table 3). The analysis did not indicate an interaction between serum urate and APOE $\epsilon 4$ status in relation to an association between serum urate and A β_{40} , A β_{42} /A β_{40} ratio, tau biomarkers and NfL, neither in sex-adjusted nor in sex stratified analyses (Table 3).

3.3 | Association between serum urate and CSF biomarkers in APOE $\epsilon 4$ stratified groups

In regression analyses, stratified by presence of the APOE $\epsilon 4$ allele and adjusted for sex, the positive association between serum urate and A β_{42} was only observed in APOE $\epsilon 4$ carriers (β [95% CI] = 0.88 pg/mL

TABLE 3 The level and statistical significance of an interaction term between serum urate and APOE $\epsilon 4$ status in models evaluating the association between serum urate and CSF biomarkers

CSF marker	Unadjusted ^a		Adjusted ^b		Males		Females	
	β (95% CI)	P	β (95% CI)	P	β (95% CI)	P	β (95% CI)	P
A β_{42}	0.77 (0.05 to 1.49)	.03	0.73 (0.01 to 1.45)	.04	1.24 (0.17 to 2.31)	.02	0.28 (-0.87 to 1.43)	.63
A β_{40}	1.22 (-3.84 to 6.29)	.63	1.03 (-4.04 to 6.11)	.69	4.73 (-2.62 to 12.1)	.21	-2.55 (-10.79 to -5.68)	.54
A β_{42} /A β_{40}	4.4e-04 (-2.2e-04 to 1.1e-03)	.18	3.9e-04 (-2.6e-04 to 1.05e-03)	.24	8.1e-04 (-2.2e-04 to 1.8e-03)	.12	2.4e-04 (-7.4e-04 to 1.2e-03)	.62
p-tau	-0.01 (-0.07 to 0.05)	.67	-0.01 (-0.07 to 0.03)	.68	0.01 (-0.08 to 0.10)	.81	-0.06 (-0.16 to 0.03)	.21
t-tau	0.02 (-0.46 to 0.49)	.94	0.03 (-0.45 to 0.51)	.91	0.16 (-0.55 to 0.89)	.64	-0.27 (-1.03 to 0.48)	.47
NfL	-1.43 (-3.86 to 0.99)	.24	-1.34 (-3.77 to 1.09)	.27	0.39 (-2.77 to 3.55)	.81	-3.08 (-7.4 to 1.24)	.16

Note: All β -values and their P-values are presented for interaction.

Abbreviations: CSF, Cerebrospinal fluid; A β , Amyloid beta; t-tau, total tau; p-tau, tau phosphorylated at amino acid 181; NfL, neurofilament light chain; β (95% CI), Beta/effect estimate (95% confidence interval); p, P-value.

^aThe "serum urate x APOE $\epsilon 4$ " interaction term was included as an additional independent variable (along with serum urate) in the multiple linear regression models.

^bThe above linear regression models were additionally adjusted for sex.

[0.23 to 1.54], $P = .008$). Serum urate was not associated with A β_{42} in APOE $\epsilon 4$ non-carriers (β [95% CI] = 0.08 pg/mL [-0.37 to 0.54], $P = .71$) (Table 4). Similar positive association was observed between serum urate and A β_{42} /A β_{40} ratio (β [95% CI] = 7.7E-04 [7.1E-05 to 1.4E-03], $P = .03$) only in APOE $\epsilon 4$ carriers in sex-adjusted analysis (Table 4). No significant associations were found in APOE $\epsilon 4$ carriers for t-tau, p-tau and NfL (Table 4). In sex-stratified analyses, levels of serum urate were positively associated with A β_{42} in APOE $\epsilon 4$ carriers only among men (β [95% CI] = 1.28 pg/mL [0.29 to 2.27], $P = .01$), and not among women (Table 4). There was also a trend for a positive association between serum urate and A β_{42} /A β_{40} ratio (β [95% CI] = 9.4E-04 [-8.0E-05 to 1.9E-03], $P = .07$) in APOE $\epsilon 4$ -carrying men (Table 4).

4 | DISCUSSION

We found a protective effect of serum levels of urate on levels of CSF A β_{42} in cognitively unimpaired men from a representative population of 70-year-olds in Gothenburg, Sweden. The association was further strengthened in the presence of the APOE $\epsilon 4$ allele. No such associations were observed in women. Our findings indicate that higher urate is protective very early in the pathological process of AD.

Three longitudinal studies have investigated the association between urate and risk of late-life dementia, with conflicting results.²¹⁻²³ Our findings are in line with two of these studies. The Dutch Rotterdam Study showed a decreased risk of AD in individuals with higher serum urate concentration,²¹ and a recent study from our group in women from Gothenburg reported an association between higher serum urate and lower risk for dementia during 44 years follow-up, regardless of dementia subtypes.²³ These, and our present study, suggest a protective role of urate in relation to dementia development. To date, only one study has investigated the association between serum urate and in vivo pathology of dementia in non-demented individuals.²⁴ While the study did not find an association

between serum urate and cerebral A β deposition, it did report an association between urate and AD signature cerebral glucose metabolism, which, in turn, indicates a possible relationship between serum urate and AD and supports our findings. The different results to our study may partially be explained by the differences in the study populations (i.e., ethnicity, selection, age range); analysis (no sex-stratified analysis in Kim et al.²⁴); and the methods used for the detection of amyloid deposition, positron emission tomography (PET) scan in Kim et al.²⁴ and CSF markers by us, which may differ with regard to the timing, sensitivity, and specificity for the detection of A β deposition.

The positive association between serum urate and A β_{42} was only observed in men. While our finding of higher concentrations of serum urate in males compared to females is consistent with the literature,^{37,38} the reason for the sex differences for an association with A β_{42} is unclear. This might partially be due to the generally higher levels of urate in men, and that levels in women in the age group included in our study are too low to exert a protective effect. Another reason might be the higher prevalence of dementia in women aged 85 years and over than in men, for whom the prevalence remains fairly stable after 80 to 85 years.^{39,40} Other factors, such as higher life expectancy in Swedish women than men on an average of 3 years,⁴¹ which is mainly attributed to hormonal and genetic differences between the two,⁴¹ may also have contributed to our results. Difference in both hormonal and genetic factors has also been attributed to higher prevalence and incidence of dementia among women after age 80.⁴² We have previously reported that higher urate in midlife was associated with a lower incidence of late-life AD in women.²⁶ Most women in that study developed dementia around age 80. Longitudinal studies of the present cohort will help to elucidate if similar associations will occur in women at higher ages.

We also observed that the association between serum urate and CSF A β_{42} was mainly found in men possessing the APOE $\epsilon 4$ allele. The APOE $\epsilon 4$ allele is the major genetic risk factor for late-onset AD and the frequency of this allele has been reported to be $\approx 15\%$ in the Swedish

TABLE 4 Associations of serum urate ($\mu\text{mol/L}$) with CSF biomarkers (pg/mL) in *APOE* $\epsilon 4$ -stratified groups

	Unadjusted ^a		Adjusted ^b		Males		Females	
	β (95% CI)	P	β (95% CI)	P	β (95% CI)	P	β (95% CI)	P
<i>Aβ₄₂</i>								
<i>APOE</i> $\epsilon 4+$	0.74 (0.12 to 1.37)	.02	0.88 (0.23 to 1.54)	.008	1.28 (0.29 to 2.27)	.01	0.42 (-0.39 to 1.25)	.30
<i>APOE</i> $\epsilon 4-$	-0.02 (-0.43 to 0.37)	.89	0.08 (-0.37 to 0.54)	.71	0.03 (-0.53 to 0.61)	.89	0.14 (-0.59 to 0.88)	.69
<i>Aβ₄₀</i>								
<i>APOE</i> $\epsilon 4+$	0.07 (-4.39 to 4.55)	.97	0.71 (-4.00 to 5.42)	.76	2.90 (-3.74 to 9.54)	.38	-1.81 (-8.68 to 5.06)	.59
<i>APOE</i> $\epsilon 4-$	-1.14 (-3.94 to 1.65)	.42	-0.71 (-3.86 to 2.43)	.65	-1.83 (-5.89 to 2.23)	.37	0.74 (-4.24 to 5.74)	.76
<i>Aβ₄₂/Aβ₄₀</i>								
<i>APOE</i> $\epsilon 4+$	5.7e-04 (-1.1e-04 to 1.2e-03)	.09	7.7e-04 (7.1e-05 to 1.4e-03)	.03	9.4e-04 (-8.0e-05 to 1.9e-03)	.07	5.8e-04 (-4.1e-04 to 1.5e-03)	.23
<i>APOE</i> $\epsilon 4-$	1.3e-04 (-1.9e-04 to 4.5e-04)	.43	2.2e-04 (-1.4e-04 to 5.8e-04)	.23	1.3e-04 (-3.8e-04 to 6.4e-04)	.61	3.4e-04 (-1.9e-04 to 8.8e-04)	.21
p-tau								
<i>APOE</i> $\epsilon 4+$	-0.01 (-0.07 to 0.04)	.66	-0.02 (-0.08 to 0.05)	.57	-0.01 (-0.11 to 0.08)	0.83	-0.03 (-0.12 to 0.06)	.53
<i>APOE</i> $\epsilon 4-$	-0.001 (-0.03 to 0.03)	.96	0.002 (-0.03 to 0.03)	.88	-0.02 (-0.06 to 0.02)	0.32	0.03 (-0.02 to 0.08)	.23
t-tau								
<i>APOE</i> $\epsilon 4+$	-0.02 (-0.54 to 0.49)	.93	-0.08 (-0.63 to 0.46)	.76	0.01 (-0.76 to 0.79)	.96	-0.19 (-1.01 to 0.61)	.62
<i>APOE</i> $\epsilon 4-$	-0.04 (-0.26 to 0.18)	.72	-0.05 (-0.30 to 0.19)	.68	-0.15 (-0.47 to 0.17)	.35	0.08 (-0.31 to 0.47)	.68
NfL								
<i>APOE</i> $\epsilon 4+$	-1.44 (-3.51 to 0.62)	.16	-1.53 (-3.71 to 0.65)	.16	-0.75 (-2.58 to 1.07)	.41	-2.43 (-6.89 to 2.03)	.27
<i>APOE</i> $\epsilon 4-$	-0.01 (-1.38 to 1.35)	.98	-0.37 (-1.91 to 1.17)	.63	-1.14 (-3.26 to 0.97)	.28	0.65 (-1.64 to 2.96)	.57

Note: All β -values are presented as pg/mL for all CSF biomarkers, except *A β ₄₂/A β ₄₀*, which is a ratio.

Abbreviations: *A β* , amyloid beta; *APOE* $\epsilon 4+$, individuals carrying apolipoprotein E risk allele; *APOE* $\epsilon 4-$, individuals carrying other/normal allele; CI, confidence interval; CSF, cerebrospinal fluid; NfL, neurofilament light chain; p-tau, tau phosphorylated at amino acid 181; t-tau, total tau.

^aThe associations of serum urate with CSF biomarkers were determined using linear regression models with serum urate as the independent variable.

^bThe above linear regression models were additionally adjusted for sex.

population.⁴³ We and others have reported that the *APOE* $\epsilon 4$ allele is a predictor for *A β ₄₂* pathology in cognitively unimpaired individuals.^{29,44} The same allele has also been reported to be associated with primary hyperuricemia in Chinese men,²⁸ a finding which we could not confirm. Nevertheless, our results suggest that the presence of the *APOE* $\epsilon 4$ allele enhances the protective effect of urate for *A β ₄₂*. Individuals with the *APOE* $\epsilon 4$ allele develop dementia earlier than other individuals,⁴⁵ and may also develop pathological *A β ₄₂* earlier. We have previously reported that levels of CSF *A β ₄₂* are lower among those with the *APOE* $\epsilon 4$ allele in this sample.²⁹ One explanation for why we only saw the protective effect in males may be the relatively higher serum urate levels compared to females. Longitudinal analyses of our and other data sets will enlighten if this is also seen in women at higher ages, if pathology in tau and other CSF biomarkers' patterns develops subsequently, and whether there is any cut-off in levels of serum urate for these effects.

It needs to be emphasized that our study was performed in cognitively unimpaired individuals; that is, before the development of dementia. Amyloid and tau pathology in CSF, indicating preclinical AD, are very common in older individuals with normal cognitive function.^{11,29} We found positive associations between serum urate and *A β ₄₂*, but no associations with CSF levels of p-tau and t-tau. It might be that urate exerts a protective role very early in the disease pro-

cess. Several studies suggest that a decrease in CSF *A β ₄₂* is the first stage in the AD process, occurring two to three decades before clinical symptoms.⁴⁶⁻⁴⁸ This change is paralleled by increased phosphorylation and secretion of tau proteins from neurons, most likely as a neuronal response to *A β* pathology.⁴⁹ Some years later, 10 to 15 years before symptoms, tau tangle pathology and neurodegeneration appear. The former can be detected using tau PET⁵⁰ and CSF tau fragments including the microtubule-binding region,^{51,52} while the latter can be monitored using longitudinal brain imaging and CSF NfL. The progress from such pathological patterns of biomarkers to dementia onset is often accompanied by oxidative damage to neuronal lipids and proteins that is mainly caused by overproduction of reactive oxygen species (ROS).¹⁶ Increased brain levels of redox-active metal ions, such as copper and iron, have been reported in brain regions with high *A β* plaque load in AD patients. When loosely bound to the plaques, these metals can efficiently catalyze the production of ROS, thus contributing to increased oxidative stress.⁵³ Urate, as the major inherent antioxidant in the human body,³² is believed to have been selected (during primate evolution) as the first-line defense mechanism to protect the cells against such oxidative insults.⁵⁴ Possible mechanisms behind the protective role of urate in AD include the ability of urate to scavenge free radicals and inhibit lipid peroxidation and protein modification,⁵⁵

which may be involved in $A\beta_{42}$ plaque formation.⁵⁶ Urate is also known to possess metal (iron and copper)–chelating properties,⁵⁷ which possibly might be another mechanism by which urate has a protective effect against $A\beta_{42}$ -induced oxidative stress. However, the positive association of serum urate with CSF $A\beta_{42}$ concentration suggests that the main effect of urate may be increasing the solubility of $A\beta_{42}$, potentially by mitigating the catalyzing effect lipids and metals may have on $A\beta_{42}$ aggregation.⁵⁸

We did not find any association between serum urate and CSF levels of $A\beta_{40}$, speaking against a primary effect of urate on amyloidogenic APP processing and secretion. Although $A\beta_{42}$ constitutes only 10% of the $A\beta$ isoforms that are synthesized as a result of proteolytic cleavage of APP, it aggregates in the brain at a much faster rate than $A\beta_{40}$.⁵⁹ Moreover, studies have reported that CSF $A\beta_{40}$ remains unchanged or increased only slightly in AD.^{60,61} Considering that a rise in CSF $A\beta_{40}$ directly reflects increased amyloidogenic APP processing, and that we did not observe an association between serum urate and CSF $A\beta_{40}$, this potential confounder has been removed. This finding is further strengthened by a positive trend for an association, similar to $A\beta_{42}$, between serum urate and $A\beta_{42}/A\beta_{40}$ ratio. As a number of studies have reported that $A\beta_{42}/A\beta_{40}$ ratio is a promising biomarker for AD,^{7,8} these results support AD-specific, and possibly $A\beta_{42}$ -dependent, protective effects of urate in cognitively unimpaired individuals. We also did not observe any association between serum urate and CSF NfL, which indicates that urate does not have an effect on unspecific neurodegeneration in AD. It has been indicated in the literature that axonal damage due to increased levels of CSF NfL occurs very late in AD, even after tau pathology have been settled; however, this change is not only less pronounced but also seems to progress with age regardless of $A\beta$ pathology.⁹ We speculate that the $A\beta_{42}$ -dependent protective effect of urate may have been the primary reason we did not find an association between serum urate and CSF NfL. Appearance of axonal damage is far later in the AD process. Nevertheless, this speculation is less supported in light of our findings.

The study has several strengths. First, it reports the association of serum urate with CSF biomarkers of preclinical AD in a representative population-based sample of healthy older people. Second, the population had a relatively high response rate for LP and a comprehensive neuropsychiatric examination that was conducted by trained nurses.²⁹ Third, the study confirms the protective role of urate in AD risk, and provides, for the first time, evidence for an interaction of *APOE* $\epsilon 4$ risk allele with serum urate for a possible contribution to the protective effect. Fourth, the exhaustive list of biomarkers examined made it possible to focus the mechanism underlying the associations on $A\beta_{42}$ solubility; no associations of serum urate concentration with markers of amyloidogenic APP processing, tau secretion and phosphorylation, or neurodegeneration were detected.

The study also has some limitations. First, selection bias might have occurred due to the lower percentage of individuals for whom the CSF data were available. However, this issue has been addressed in detail in a previous study that found trivial differences for several demographic and clinical variables between the CSF group and the rest of the population.²⁹ Second, the cross-sectional design precludes the pos-

sibility to study direction of associations. Third, our study population included only Sweden-based 70-year-olds. Our results can therefore not be generalized to other age groups and populations. Fourth, considering the cross-sectional design of the study and that we saw associations between urate and $A\beta_{42}$ only in men and not for other AD biomarkers it cannot be excluded that our findings are spurious (or “by chance”). The findings, therefore, need to be confirmed in other settings and through follow-up of the present cohort with description of how these associations translate in the other AD biomarkers and also possibly develop in women at higher ages. Fifth, as there is a difference in the risk of late-onset AD between *APOE* $\epsilon 4$ homozygotes and heterozygotes,⁴⁵ keeping them in one group may have served as another possible limitation in our study. However, as the sample size for *APOE* $\epsilon 4$ homozygotes was very small ($n = 7$), we kept these two groups together as *APOE* $\epsilon 4$ carriers while performing all analyses to avoid spurious results.

4.1 | Conclusions

In cognitively healthy 70-year-old men predisposed for AD (*APOE* $\epsilon 4$ carriers), we identified an association indicating a protective effect of serum urate against $A\beta_{42}$ deposition in the AD process. If confirmed in other settings and in longitudinal analyses, urate may thus be a modifiable risk factor, available for interventions that may alter the course of AD.

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CONFLICTS OF INTEREST

Tahzeeb Fatima, Lennart T.H. Jacobsson, Anna Zettergren, Mats Dehlin, and Ingmar Skoog declare no conflicts of interest. Silke Kern has served as a consultant, on advisory boards for Geras Solutions, unrelated to the results presented in this paper. Kaj Blennow has served as a consultant, on advisory boards, or on data monitoring committees for Abcam, Axon, Biogen, JOMDD/Shimadzu, Julius Clinical, Lilly, MagQu, Novartis, Roche Diagnostics, and Siemens Healthineers, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program, all unrelated to the results presented in this paper. Henrik Zetterberg has served on scientific advisory boards for Denali, Roche Diagnostics, Wave, Samumed, Siemens Healthineers, Pinteon Therapeutics, Nervgen, and CogRx; has given lectures in symposia sponsored by Fujirebio, Alzecure, and Biogen; and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program, all unrelated to the results presented in this paper.

AUTHOR CONTRIBUTIONS

Tahzeeb Fatima, Lennart T.H. Jacobsson, Mats Dehlin, and Ingmar Skoog designed the study, oversaw its execution, and generated and analyzed and/or interpreted the data/results. Kaj Blennow and Henrik Zetterberg performed the CSF biomarker measurements and interpreted the results. Tahzeeb Fatima wrote the first draft. Silke Kern, Anna Zettergren, Kaj Blennow, Henrik Zetterberg, and Lena Johansson helped to interpret the results. All authors revised the manuscript for important intellectual content and read and approved the final manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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