INTRODUCTION

According to the 2015 World Alzheimer Report, as many as 46.8 million people worldwide were suffering from dementia in 2015, resulting in impaired quality of life and high costs in the health care system. The prevalence of dementia is growing rapidly, almost doubling every 20 years, and the prognosis for 2030 is 75 million cases and for 2050 as many as 132 million worldwide. In population-based samples from Sweden, investigated in 1976–2006, approximately 2% were estimated to have dementia at age 70% and 5% at age 75%, with the risk doubling every 5 years, resulting in a 45% rate among people 90 years and older. However, aggregated data
from Europe and North America show that the incidence rate of dementia has declined by 13% per decade over the last 25 years. Although the causes of this decline remain unknown, the findings strongly suggest that the risk of dementia is modifiable, i.e. some risk factors are preventable. The contradictory facts of declining incidence in high-income countries and increasing global prevalence may be explained by less risk factor prevention in low-income countries and increasing life expectancy and longer survival with dementia in general.

Cognitive impairment (CI) can manifest both as severe cognitive impairment (dementia) and as mild cognitive impairment (MCI). MCI is defined as a decline in cognitive functions, which goes beyond what is expected in normal ageing, but does not yet meet the criteria for dementia. MCI is a heterogeneous condition and can involve multiple cognitive domains such as language, memory, learning, attention, visuospatial functions and executive functions. Just like dementia, the risk of MCI increases with age. However, prevalence estimates in previous studies differ due to differences in MCI criteria, populations studied and methodology. Prevalence in the population aged over 65 years ranges between 10%–20%. Among persons 70–75 years old, the estimated prevalence is 20%–25%.

The single most important risk factor for developing CI is age. Several other factors are associated with an increased risk. Non-modifiable factors are sex, the ApoE ε4 allele for Alzheimer’s disease, and mutations in genes coding for proteins such as Tau, TDP-43, α-synuclein, APP or Presenilin 1 or 2. Modifiable risk factors associated with CI are lower level of education, mid-life high BMI/abdominal obesity, living alone, hypertension, high intake of alcohol, sleep disturbances, physical inactivity, mental stress and depression. Moreover, cardiovascular diseases, diabetes, hyperlipidaemia, and smoking are suggested risk factors although study results diverge. In addition, many studies conclude that frequent, mentally and socially stimulating activities, both in mid-life and later in life, are protective factors for CI.

Most of the prior studies of risk factors for cognitive impairment are retrospective and based on selected patients already being diagnosed with MCI or dementia. Prospective population-based cohort studies are scarce. Consequently, there is a need for more research on the prevalence of cognitive decline in the general population, and on early risk factors for CI.

The Study of Men Born in 1943 is a prospective cohort study in Gothenburg, Sweden, following a sample of men from the age of 50, where cognitive testing was performed at age 73. The aim of the study was to investigate the prevalence of risk factors for cardiovascular disease. Of 1462 invited men, 798 (55%) agreed to participate in the study. The participants were followed prospectively and were invited to a re-examination at age 60 (2003) and at age 71 (2014). The study has previously been described in detail elsewhere.

In April 2016, we invited all the men who participated in the 2014 examination to take part in a cognitive study. Of the 530 men still alive and residing in Sweden, 342 agreed to participate (65%) and were examined in the cognitive study (Figure 1). The cognitive examination was performed in 2016 and early 2017 when all the participants were 73 years of age. Eight participants were excluded after the cognitive examination because of poor Swedish language skills, which significantly affected their test results, and one participant due to impaired eyesight. As a result, the final cognitive study population totalled 333 (63% of those invited and still alive).

**FIGURE 1 Flowchart of study**

**2 | MATERIALS & METHODS**

**2.1 | Study population**

In 1993 a random population sample of 50% of all men born in 1943 and residing in Gothenburg, Sweden, were invited to participate in a longitudinal, prospective study, i.e. ‘The Study of Men Born in 1943’. The
All the participants have given their informed consent and the study has been approved by the Gothenburg Regional Research Ethics Board (No: 886-13 and T187-16) and complies with the Declaration of Helsinki. The study is registered at ClinicalTrials.gov, with id-number: NCT03138122.

2.2 | Examination at age 50

The physical examinations at baseline in 1993 were performed in the morning after an overnight fast and included height, weight, waist circumference, blood pressure, and venous blood sampling. Details of the examination are given in supplementary material A. Examinations of extrapyramidal symptoms were performed according to the Simpson-Angus Scale. The selected tests were: Gait, Shoulder Shaking, Elbow Rigidity, Wrist Rigidity, Leg Pendulousness, Tremor and Cogwheel Rigidity. The participants’ performances were graded from 0 to 4. For further description of the method see Supplementary Material A. The participants were video-filmed while performing these tests and assessment of Gait was retrospectively done by two physicians, one specialist in psychiatry and one specialist in internal medicine, by analysing the video-film.

Prior to the examination, the participants completed a questionnaire addressing education, marital status, smoking habits, alcohol use, coffee consumption, physical activity during leisure time, cardiovascular diseases diagnosed by a physician, sleeping habits, stress and psychosocial factors (Supplementary Material A).

2.3 | Cognitive testing at age 73

The test battery consisted of 11 tests (Table 1), out of which six constitute the Cognitive Assessment Battery (CAB), an established test battery for distinguishing between persons with no CI, MCI and dementia. The tests followed a strict manual that described precisely in which order and how each test should be introduced, performed and graded. Test leaders, trained by an experienced psychologist specializing in cognitive decline, administered the tests. A test session lasted 40–60 min. The participants signed an informed consent before the session. For a detailed description of the tests, see Supplementary Material B.

2.4 | Definitions of mild and severe cognitive impairment

For the complete test battery (11 tests); fewer than four failed tests were considered normal, four to seven failed tests were defined as MCI, and more than seven failed tests were regarded as severe cognitive impairment. These cut-off levels correspond well to the CAB cut-offs, where MCI is defined as two to three failed tests (of six), and severe cognitive impairment/dementia as more than three failed tests.

2.5 | Statistical methods

Descriptive statistics were used to present the main characteristics of the study population. To measure the association of the risk factors with the outcome variable, cognitive impairment (mild or severe), odds ratios were calculated by logistic regression. Since education had a strong association with CI, an adjustment for education was made in the subsequent analyses. Thus, multiple logistic regression models were used with an adjustment for education as a potential confounder and for stepwise multivariable analysis.

### Table 1: Cognitive tests included in ‘The Study of Men Born in 1943’, and the results from each test

| Tests (in order of performance) | Cognitive domain       | Min-max | Cut-off | Mean | Median | Fail†, n (%)† |
|--------------------------------|------------------------|---------|---------|------|--------|---------------|
| Text recall (immediate vs delayed) | Memory & Learning | (-21)–21 | <0      | 1    | 1      | 69 (21)       |
| SDMT                            | Speed & Attention      | 0–110   | <25 p   | 35   | 35     | 36 (11)       |
| Naming test                     | Language               | 0–30    | <25 p   | 27   | 27     | 56 (17)       |
| Clox & Cube                     | Visuospatial           | 0–12    | <11 p   | 11   | 12     | 81 (25)       |
| Token test                      | Language               | 0–6     | <5 p    | 5    | 5      | 71 (21)       |
| Stroop III                      | Executive functions    | 0-no max | >49 sec | 34   | 31     | 26 (8)        |
| ROCF Copying                    | Visuospatial           | 0–36    | <27 p   | 30   | 29     | 87 (26)       |
| FAS                             | Language               | 0-no max | <24 p   | 34   | 33     | 78 (23)       |
| ROCF Recall                     | Memory & Learning      | 0–36    | <7.5 p  | 15.5† | 14.5‡  | 38 (11)       |
| PaSMO A-1                       | Executive functions    | 0-no max | >93 sec | 81‡  | 75‡    | 155 (47)      |
| Trailmaking A                   | Speed & Attention      | 0-no max | >55 sec | 46   | 44     | 74 (22)       |

Abbreviations: CAB, Cognitive Assessment Battery; F-A-S, Verbal fluency test letters F, A and S; PaSMO, Parallel Serial Mental Operations; ROCF, Ray-Osterrieth Complex Figure; SDMT, Symbol Digit Modalities Test.

†Participants with a test result indicating cognitive impairment.
‡Includes only participants able to finish the test.
The final multiple regression model built for the multivariable analysis included variables according to the following two steps: Step 1 included variables significantly related to the outcome, after adjustment for education. The variables were analysed in separate groups according to the type of variable (i.e. anthropometrics, co-morbidity, lifestyle, sleep, extrapyramidal symptoms). Seven variables did not belong to a specific group and were excluded from the Step 1 analysis. Step 2 included all the variables still significantly associated with the outcome after Step 1, as well as the seven variables excluded from Step 1. A p-value of <0.05 was considered statistically significant.

The statistical analyses were conducted using the SAS statistical software package, version 9.4; SAS Institute Inc.

3 | RESULTS

Of the 333 men participating in the cognitive study, 80 (24.0%) performed at a level corresponding to MCI and four (1.2%) at a level consistent with a severe cognitive impairment. The results from each test are shown in Table 1.

The prevalence of CI was significantly lower among participants with a higher level of education (Table 2). Men with more than 12 years of education (university studies) had an odds ratio of 0.23 (95% CI 0.12–0.46, p < .001) for CI, when compared with participants with fewer than 10 years of study. Due to this strong association with CI, adjustment for education was made in the subsequent analyses.

A number of variables, at baseline, such as: living alone, higher body weight, larger waist circumference, BMI ≥30, hypertension, higher fasting p-glucose, and diabetes were associated with having CI at age 73, after an adjustment for education (Table 2). In addition, heavy smoking, high alcohol consumption, poorer quality of sleep, difficulty falling asleep, financial stress, bad family situation, hidden irritability, worse mood, less endurance, rarely being busy, and poorer quick-thinking ability were also more frequently associated to CI at age 73, after an adjustment for education (Table 3).

### TABLE 2 Comparison between participants with Cognitive impairment (CI) at age 73 and controls with regard to demographics, anthropometrics, co-morbidity and extrapyramidal remarks at baseline (age 50)

| Variable                        | No CI | CI   | Univariate OR (95% CI) | p      | Adjusted for education OR (95% CI) | p      |
|---------------------------------|-------|------|------------------------|--------|-----------------------------------|--------|
| Education, n %                  |       |      |                        |        |                                   |        |
| <10 years                       | 77 (30.9) | 50 (59.5) | 1.00                  |        | 2.80 (1.40–5.63) | .004   |
| 10–12 years                     | 86 (34.5) | 21 (25.0) | 0.38 (0.21–0.68) | .001  | 1.02 (1.00–1.05) | .04    |
| >12 years                       | 86 (34.5) | 13 (15.5) | 0.23 (0.12–0.46) | <.0001 | 1.04 (1.01–1.08) | .006   |
| Living alone, n %               | 24 (9.6) | 19 (22.6) | 2.74 (1.41–5.31) | .002   | 2.80 (1.40–5.63) | .004   |
| Height (m), mean (SD)           | 1.79 (0.07) | 1.80 (0.07) | n.s.                  |        | 1.84 (1.02–3.33) | .04    |
| Weight (kg), mean (SD)          | 82.5 (10.5) | 85.7 (11.8) | 1.03 (1.00–1.05) | .03    | 1.09 (1.01–1.08) | .04    |
| Waist (cm), mean (SD)           | 93.5 (8.3) | 96.9 (8.7) | 1.05 (1.02–1.08) | .05    | 1.04 (1.01–1.08) | .006   |
| BMI (kg/m²), mean (SD)          | 25.7 (3.0) | 26.5 (3.3) | n.s.                  |        | n.s.                             |        |
| BMI ≥30, n %                    | 17 (6.8) | 12 (14.3) | 2.27 (1.04–4.99) | .04    | n.s.                             |        |
| Myocardial infarction, n %      | 4 (1.6) | 0 (0.0) | n.s.                  |        | n.s.                             |        |
| Heart failure, n %              | 0 (0.0) | 2 (2.4) | 15.12 (0.71–318.19) | .01    | n.s.                             |        |
| Atrial fibrillation, n %        | 1 (0.4) | 1 (1.2) | n.s.                  |        | n.s.                             |        |
| Stroke, n %                     | 1 (0.4) | 0 (0.0) | n.s.                  |        | n.s.                             |        |
| Hypertension, n %               | 44 (17.7) | 25 (29.8) | 1.97 (1.12–3.50) | .02    | 1.84 (1.02–3.33) | .04    |
| Diabetes: prev. diag. or Fp-gluc ≥6, n % | 3 (1.2) | 4 (4.8) | 4.16 (0.91–18.95) | .05    | 5.09 (1.04–24.96) | .04    |
| Fp-glucose (mmol/L), mean (SD)  | 4.47 (0.60) | 4.63 (0.88) | n.s.                  |        | 1.44 (1.01–2.04) | .04    |
| S-cholesterol (mmol/L), mean (SD) | 5.78 (1.05) | 5.82 (1.00) | 1.04 (0.82–1.32) | .04    | n.s.                             |        |
| S-triglycerides (mmol/L), mean (SD) | 1.51 (0.84) | 1.69 (1.14) | n.s.                  |        | n.s.                             |        |
| Shoulder shaking remark, n %    | 7 (3.0) | 11 (13.6) | 5.16 (1.93–13.82) | .0004  | 5.70 (2.01–16.19) | .001   |
| Elbow rigidity remark, n %      | 15 (6.3) | 11 (13.6) | 2.33 (1.02–5.30) | .04    | 2.61 (1.10–6.23) | .03    |
| Leg pendulousness remark, n %   | 3 (1.3) | 11 (13.6) | 12.26 (3.37–45.17) | <.0001 | 13.84 (3.56–53.80) | .0001  |
| Cogwheel remark, n %            | 1 (0.4) | 4 (4.9) | 12.26 (3.37–45.17) | <.0001 | 17.18 (3.37–45.17) | .02    |
| EPS remarks (tot. remarks >1)   | 6 (2.5) | 12 (15.0) | 6.79 (2.46–18.78) | <.0001 | 8.20 (2.76–24.33) | .0001  |

Note: n.s.=not significant, used for p values >.05.

Abbreviation: EPS, Extrapyramidal symptoms.
Four of the seven extrapyramidal symptoms (EPS), graded 0–4, were significantly more common in the CI group at the base line evaluation (i.e. shoulder shaking, elbow rigidity, leg pendulousness, and cogwheel rigidity). When analysing the symptoms dichotomously, comparing any symptom (graded >0) with no symptoms, i.e. regarded as having an extrapyramidal remark (yes/no), there was a strong statistically significant difference even after adjusting for education for all four variables (Table 2). The largest difference was found for leg pendulousness (OR 13.84, 95% CI 3.56–56.80, \( p = .0001 \)). All four variables had high specificity for the development of CI (shoulder shaking 97.0%, elbow rigidity 93.7%, leg pendulousness 98.7%, cogwheel rigidity 99.6%) and the combined variable EPS remarks, defined as the total sum of remarks exceeding 1, had a specificity of 97.5% for predicting CI. Leg pendulousness and cogwheel rigidity had positive predictive values (PPV) for CI of 78.6% and 80.0% respectively, during follow-up. Conversely, sensitivity was low (EPS remarks 14.8%, shoulder shaking 13.6%, elbow rigidity 13.6%, leg pendulousness 13.6%, and cogwheel rigidity 4.9%).

One of the participants was diagnosed with Parkinson’s disease after the examination at age 50 and prior to the cognitive testing at age 73. His cognitive test results showed severe cognitive impairment. This participant had remarks on tremor, leg pendulousness...
and shoulder shaking at the 1993 examination. No other participant had been diagnosed with Parkinson's disease or other neurodegenerative diseases prior to the testing in 2016/17.

In the first step of the stepwise multivariable analysis, the following risk factors were associated with cognitive impairment: waist circumference, hypertension, heavy smoking (>14 cig/day), ever needing an 'eye-opener', financial stress, difficulty falling asleep, leg pendulousness and cogwheel rigidity (Table 4). After Step 2, waist circumference (OR 1.04, 95% CI 1.00–1.08, \( p = .04 \)), leg pendulousness (OR 41.97, 95% CI 3.27–538.62, \( p = .004 \)) and hidden irritability (OR 2.18, 95% CI 1.10–4.32, \( p = .03 \)) remained statistically significant.

| Table 4 Comparison between participants with Cognitive impairment (CI) at age 73 and controls, in stepwise multivariable analysis |
| -------- | -------- | -------- | -------- | -------- | -------- |
| Group    | Variable                                    | Step 1\(^1\) | Step 2\(^2\) |
|         |          | OR (95% CI) | \( p \)    | OR (95% CI) | \( p \)    |
| Anthropometrics | Weight (kg) | n.s. | – | – | – |
|           | Waist (cm) | 1.07 (1.01–1.13) | .02 | 1.04 (1.00–1.08) | .04 |
| Co-morbidity | Hypertension | 1.86 (1.04–3.36) | .04 | n.s. | – |
|           | Diabetes: Fp-glucose ≥6 (mmol/L) | n.s. | – | – | – |
|           | Diabetes: Fp-glucose cont. (mmol/L) | n.s. | – | – | – |
| Lifestyle | Heavy smoker (>14 cig/day) | 2.67 (1.26–5.67) | .01 | n.s. | – |
|           | Need morning 'eye-opener' | 3.37 (1.44–7.92) | .005 | n.s. | – |
|           | Current drinking problem (alcohol) | n.s. | – | – | – |
| Stress   | Financial stress | 2.13 (1.15–3.95) | .02 | n.s. | – |
|           | Bad family situation | n.s. | – | – | – |
| Sleep    | Poor quality of sleep | 2.29 | n.s. | – | – |
|           | Difficulty falling asleep | (1.10–4.76) | .03 | n.s. | – |
| EPS      | Shoulder shaking remark | n.s. | – | – | – |
|           | Elbow rigidity remark | n.s. | – | – | – |
|           | Leg pendulousness remark | 13.22 (2.48–70.45) | .002 | 41.97 (3.27–538.62) | .004 |
|           | Cogwheel remark | 13.82 (1.13–169.19) | .04 | n.s. | – |
| Other    | EPS remarks (tot. remarks >1) | n.s. | – | – | – |
|           | Living alone | n.s. | – | – | – |
|           | Busy-ness | n.s. | – | – | – |
|           | Bad mood | n.s. | – | – | – |
|           | Low mental endurance | n.s. | – | – | – |
|           | Poor quick-thinking ability | n.s. | – | – | – |
|           | Hidden irritability | 2.18 (1.10–4.32) | .03 | n.s. | – |

Note: n.s. = not significant, used for \( p \) values >.05.

\(^1\)Step 1 = includes all variables from the univariate analysis which were significantly related to CI, after adjustment for education. The variables were sorted by group (anthropometrics, co-morbidity, lifestyle, stress, sleep, and extrapyramidal symptoms). Seven variables did not belong to any group and were excluded from Step 1 and instead directly included into Step 2.

\(^2\)Step 2 = includes only the variables still significantly related to CI after Step 1 and the seven variables not belonging to any group in Step 1.

4 DISCUSSION

In this cohort study, a randomly selected sample of 50-year-old men from the general population was followed for 23 years and assessed with cognitive testing at age 73. Several factors, adjusted for education, were found to be associated with cognitive impairment during follow-up. After a stepwise multivariable analysis, abdominal obesity, hidden irritability and leg pendulousness were statistically significant as early markers of CI.

The test battery for cognitive assessment included 11 accredited and commonly used tests, covering the five cognitive domains (memory and learning, speed and attention, language, visuospatial ability, and executive functions). This enabled a thorough understanding of the participants’ cognitive abilities, providing the opportunity to distinguish between the normal cognitive ability of the age group and cognitive impairment, as well as between mild and severe CI. The percentage of cases MCI in the study, 24.0%, is in line with previous epidemiological studies. However, the prevalence of severe cognitive impairment, 1.2%, is lower than previously described in this age group, which is 2% or higher. This difference may be explained by the fact that persons with established or incipient dementia are more prone to decline participation in epidemiological studies, leading to an underestimation of the true prevalence of severe cognitive impairment in the present study.
We have used the endpoint CI, regarding MCI and dementia as different manifestations of the same disease. There are benign forms of MCI that do not progress to severe cognitive impairment/dementia, but, in more than 50% of the cases, MCI progresses to dementia within five years, implying that MCI should be regarded as a risk state for dementia. Previous studies have found that the two conditions share numerous risk factors, as well as protective factors. Due to the different types of dementia, and associated MCI subtypes, some risk factors are more specific to one type than the other. Risk factors may also vary depending on age, i.e. different risk factors in mid-life versus later in life. There is also an ongoing debate regarding whether certain factors, such as depression, are actual risk factors or prodromal features of the disease. A 28-year follow-up study from 2017 show no support for depression as a risk factor, rather that depressive symptoms are early signs of dementia, or, that dementia and depression have common causes.

As mentioned above, there are few prospective population-based cohort studies of risk factors for CI. The Gerontological and Geriatric Population Studies (H70), also conducted in Gothenburg, have studied the longitudinal risk factors for dementia. However, the participants were 70 years of age when first examined and a mid-life association with CI could therefore not be evaluated in this cohort. The Prospective Population Study of Women in Gothenburg follow participants from 1968/69 but only includes women. The CAIDE (Cardiovascular Risk Factors, Aging and Dementia) study in Finland is a prospective population-based study comprising 1511 participants. However, there was a wide age span among the participants, which reduces comparability.

Higher education is known to be a protective factor for CI. In our study, a university education showed a reduced risk of almost 80% compared with education of fewer than 10 years. This observation is most frequently explained by the cognitive reserve theory, claiming that a higher education compensates for cognitive decline through a higher number of healthy synapses and/or more efficient circuits, thereby delaying clinical symptoms. This could be interpreted as meaning that education is a protective factor delaying the onset of dementia, or, potentially, that education merely masks incipient dementia. The latter is supported by the fact that there are studies showing a faster decline in Alzheimer’s disease patients with a higher education, once clinical symptoms are manifested. Regardless of the underlying cause, a lower education is strongly associated with test results in the range of CI, which was confirmed by our study. For this reason, we adjusted for education in our analyses.

The most novel finding in the study is the strong correlation between mid-life extrapyramidal symptoms and CI later in life. Participants with any symptoms of shoulder shaking, elbow rigidity, leg pendulousness or cog wheel rigidity at age 50, had a significantly higher prevalence of cognitive impairment at age 73. In the multivariable analysis, there was a strong association between leg pendulousness and cognitive impairment. Leg pendulousness had a positive predictive value for future cognitive impairment of 79% and a specificity of just under 99%. This suggests the potential for one or more of these extrapyramidal tests to be used as indicators for the early identification of cognitive decline later in life. In spite of this, sensitivity was low, i.e. most of the CI-cases were not detected by the tests. One possible explanation for the difference between the high specificity and the low sensitivity could be that EPS is a strong predictor, but only for certain types of CI. A previous study from South Korea of 882 MCI patients with an average age of 71 years showed a six-folded relative risk of MCI patients with EPS progressing to ‘dementia other than Alzheimer’s disease’ compared with MCI patients without EPS, during a 5 years follow-up. Conversely, the relative risk of progression to Alzheimer’s disease for MCI patients with EPS was 0.7 in the same study. It is possible that Lewy Body Dementias (LBD) are the type of dementia with the strongest association, since EPS are characteristic symptoms of this type of dementia (as is REM sleep disorders, often many years prior to dementia onset, and recurrent visual hallucination). LBD is the second most common form of neurodegenerative dementia and accounts for 10%–20% of all cases, which corresponds well to the 15% of CI participants displaying EPS in our study. However, this remains conjectural and the underlying mechanisms of the association between these early extrapyramidal symptoms and subsequent cognitive decline require further investigation.

Neurodegenerative diseases involve the progressive loss of neurones. In general, this is a selective loss, generating either motor neurone diseases or cognitive diseases, but there is an overlap in later stages leading motor neurone diseases to cause dementia and vice versa. Our findings might indicate that this overlap begins long before any symptoms of cognitive decline. Nevertheless, we do not yet know whether the MCI cases in our study will develop dementia over time. There could be an overlap of mild extrapyramidal symptoms and mild cognitive impairment without progressing to either dementia or motor disorders. To the best of our knowledge, no similar findings of an association between mid-life EPS and late-life CI have previously been published. There are some studies showing that EPS could be a predictor of incipient dementia or MCI, and that the presence of EPS increases the risk of progressing to non-Alzheimer’s disease dementia. These studies were, however, primarily performed on elderly people and with a relatively short follow-up period, ranging between two to six years.

Hidden irritability was also significantly associated with cognitive impairment in the multivariable analysis. Whether hidden irritability is a very early sign (prodromal phase) of MCI and incipient dementia, or whether it constitutes a risk behaviour/risk personality remains to be determined. The latter would in such case mean a behavioural pattern where anger is habitually restrained and, possibly, in combination with more feelings of irritability in general.

Previous research has found an association between mid-life high BMI and CI. In our study, waist circumference was significantly associated with cognitive impairment in the multivariable analysis. This finding indicates that abdominal obesity, which has previously been associated with a higher risk, is a greater risk factor than other types of obesity. We also found associations between CI and mid-life hypertension, a high intake of alcohol, and living alone, when adjusted for education, in univariable analysis but not in
we found no association between CI and a sedentary lifestyle, or between CI and mid-life stress, apart from an association with financial stress in the univariable analysis. Cardiovascular diseases, diabetes, hyperlipidaemia, and smoking are other suggested risk factors, although the research results diverge. In our study, we found no such association. However, at baseline, only a few participants had cardiovascular diseases or diabetes and the absence of association may be due to a lack of power. As a result, no further conclusion should be drawn from this observation.

Self-assessed mid-life observations of bad mood, low mental endurance, ‘rarely being busy’, and poor quick-thinking ability were more frequently associated to CI at age 73. However, poor multitasking ability, bad memory, impatience, poor concentration, and poor attention tended to be more common among men developing CI later in life, although not statistically significant. This might be due to lack of power and would be an interesting topic for further studies.

4.1 | Strengths and limitations

The main strength of the study is the longitudinal design, with a 23 years follow-up of an homogeneous cohort. The random sample from the general population had the same age, same sex, and lived in the same geographical area. However, the all-male population is a limitation to the universality of the findings.

Another strength of the study is the extensive cognitive test battery, based on standardized, established cognitive tests. Nevertheless, cognitive tests are sensitive to language skills, settings and test leader skills.

Assuming that non-participants are less healthy, a participation rate of 55% in the initial examination in 1993 must be regarded as a limitation. The participation rate for the cognitive testing in 2016 was 65% of the participants still alive from the initial cohort of 1993. Despite the rate improvement, it can be assumed that participants with diagnosed dementia, incipient dementia or MCI are less inclined to attend a cognitive examination and therefore bias the result (underestimation of CI). Only 333 participants were included in the cognitive study; the small sample size is also a limitation of the study.

5 | CONCLUSION

Extrapyramidal symptoms, especially leg pendulousness, at age 50 may predict cognitive impairment 23 years later. Whether this knowledge can help health care providers to identify the early stages of MCI and thereby take preventive actions and reduce the risk of developing dementia remains to be studied.

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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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