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Understated Cognitive Impairment Assessed with the Clock-Drawing Test in Community-Dwelling Individuals Aged ≥ 50

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Brief summary - Understated cognitive impairment is frequent (23.6%) among community-dwelling individuals aged ≥ 50 , and is associated with factors known to be linked to a higher risk of cognitive decline and dementia

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ABSTRACT (298 words)

1 **Objectives:** To estimate the prevalence of understated cognitive impairment by administering
2 the Clock-Drawing Test (CDT) to community-dwelling individuals aged ≥ 50 , and to
3 investigate the associated clinical phenotype.

4 **Design:** A cross-sectional analysis of baseline data on community-dwelling individuals
5 assessed at an outpatient clinic in the Paris region of France.

6 **Setting and Participants:** Participants aged ≥ 50 (n=488, median age: 62.1) prospectively
7 included in the SUCCEED survey between 2010 and 2014.

8 **Methods:** A multidimensional geriatric assessment, including cognition (7-point CDT,
9 MMSE, the 5-word screening test (5-WT), and the Frontal Assessment Battery (FAB)), gait
10 speed in dual tasks, mood (the Geriatric Depression Scale (GDS)), balance, physical
11 functions (gait speed and handgrip strength), nutrition, bone density, and comorbidities;
12 major cardiovascular risk factors, and Scheltens and Fazekas scores on brain MRI. Baseline
13 characteristics were analyzed as a function of the CDT score (< 7 versus 7), using age-
14 adjusted logistic models.

15 **Results:** The prevalence of impairment in the CDT was 23.6% - higher than the values for
16 the MMSE (12.7%), 5-WT (2.3%) and FAB (16.6%). In age-adjusted analyses, a lower
17 educational level (odds ratio [95% confidence interval] = 0.72 [0.58-0.89]), diabetes (2.57
18 [1.14-5.79]), metabolic syndrome (1.93 [1.05-3.56]), lower gait speed in the cognitive dual
19 task (1.27 [1.05-1.53]), a poorer GDS score (1.86 [1.04-3.32]), a poorer MMSE score (2.56
20 [1.35-4.88]), a poorer FAB score (1.79 [1.01-3.16]), impaired episodic memory in the 5-WT
21 (4.11 [1.12-15.02]), and a higher Scheltens score ($P=.001$) were significantly associated with
22 CDT impairment.

23 **Conclusions and Implications:** Understated cognitive impairment is common among young
24 seniors and is associated with factors known to be linked to a higher risk of cognitive decline

25 and dementia. These findings suggest that the CDT may be of value for identifying high-risk
26 individuals who may then benefit from targeted multidomain prevention actions (diet,
27 exercise, cognitive training and vascular risk factor management).

Keywords

Understated cognitive impairment, Clock-Drawing Test, screening, middle-aged, elderly

1 Introduction

2

3 Cognitive decline is a common feature of ageing and is associated with an elevated
4 risk of dementia and disability.¹ A transitional state between intact cognitive functioning and
5 clinical dementia has been described as mild cognitive impairment (MCI), defined as (i) the
6 reporting of cognitive complaints and objective cognitive impairment in one or more
7 cognitive domains and (ii) the preservation of functional abilities.² However, recent results
8 from the SHARE study suggest that even subtle, understated cognitive impairment (defined
9 as impairment in one cognitive test score in an individual without cognitive complaints) is
10 predictive of an increased risk of adverse health outcomes and impaired functional capacity
11 in individuals aged ≥ 50 .³ However, there are few published data on the prevalence of
12 understated cognitive impairment. In a subgroup analysis of the SUCCEED survey, we found
13 that 34% of asymptomatic individuals (free of dementia or cognitive complaints) aged ≥ 50
14 had understated cognitive impairment, as assessed by poor performance in the Clock-
15 Drawing Test (CDT).⁴

16 The CDT has become one of the most commonly used cognitive screening
17 instruments. The test involves a diverse range of high-level cognitive abilities, such as
18 executive control, visuospatial and visuoconstructive functions, semantic memory, and
19 language skills. Impairments in these abilities may not be readily detected by other
20 commonly used cognitive screening tests, such as the Mini-Mental State Examination
21 (MMSE).⁵ Impairments in these cognitive abilities reflect possible frontal and
22 temporoparietal disturbances. The CDT has robust psychometric properties, including speed
23 of administration, easy scoring, patient acceptability, test-retest reliability, inter-rater
24 reliability, and high levels of sensitivity and specificity for identifying cognitive decline.⁶ The
25 literature data suggest that use of the CDT can readily detect early cognitive impairment in

26 elderly people.⁵ Therefore, we hypothesized that an impairment in the CDT might be a useful
27 indicator of understated cognitive impairment (before the appearance of the first clinical
28 symptoms) in asymptomatic, community-dwelling, young seniors.

29 Although older age is the strongest risk factor for cognitive impairment,
30 cardiovascular risk factors and psychosocial risk factors (e.g. educational level and isolation)
31 have been also highlighted - suggesting that cognitive decline can be prevented (at least in
32 part) by targeting modifiable risk factors.¹ With regard to the CDT, the literature data
33 evidence poorer performance among elderly patients with diabetes^{7,8} or with hypertension.⁹

34 Poor performance in the CDT is also reportedly associated with physical frailty in
35 asymptomatic adults aged ≥ 50 ¹⁰ and in older community-dwellers.^{11,12} The frailty
36 components most often associated with CDT impairment among elderly community-dwellers
37 were slow gait, low muscle strength, and decreased physical performance.^{11,13,14} Associations
38 between poor performance in the CDT on one hand and slow gait and low muscle strength on
39 the other have been also observed among younger community-dwellers.¹⁰ Furthermore, poor
40 CDT performance is reported associated with an increased risk of falls and fall-related
41 injuries¹⁵ and with all-cause mortality.¹⁶ However, these studies generally included
42 individuals aged 65 and over, and so the prevalence of impaired performance in the CDT
43 among young seniors has not previously been reported. The Lancet Neurology Commission¹
44 pointed out that observational studies in community-dwellers are needed to monitor the
45 distribution of risk factors in different age groups. Few such studies have been performed in
46 middle-aged adults and younger elderly adults.

47 The objectives of the present study were therefore to estimate the prevalence of
48 understated_cognitive impairment (as assessed by the CDT) in a cohort of asymptomatic
49 community-dwelling individuals aged 50 years and over, and to investigate the associated
50 clinical phenotype. This knowledge might enable the earlier diagnosis of high-risk

51 individuals, and then better management of their chronic comorbidities and/or frailty
52 symptoms.¹⁷

53

54 **Methods**

55

56 *Study population*

57

58 We analyzed baseline data from the SUCCEED survey¹⁸ of community-dwellers aged
59 ≥ 50 , free of dementia and cognitive complaints, and consecutively assessed at an outpatient
60 clinic in a 3000-bed university hospital in the greater Paris area of France. Individuals
61 underwent a multidimensional geriatric assessment (including evaluations of cognition,
62 mood, balance, mobility, muscle strength, nutrition, comorbidities, and bone density) and
63 brain MRI. For this cross-sectional analysis (SUCCEED-03), we included individuals
64 recruited between 2010 and 2014 and for whom CDT and MRI data were available (Figure
65 1). The study was approved by an institutional review board (*CPP Ile-de-France X*, Paris,
66 France, # 96-2019).

67

68 *Assessment*

69

70 The data were collected prospectively using a standardized questionnaire.
71 Performance tests were conducted by trained nurses, and a standardized clinical assessment
72 was performed by a geriatrician (Table 1). Comorbidities were recorded, together with the
73 main cardiovascular risk factors: male gender, age >60 (in females), hypertension, smoking
74 (current or in the previous 3 years), LDL-cholesterol >1.6 g/L, diabetes, dyslipidemia, one or
75 more first degree relatives having had a stroke before 45 years of age, sudden death, or

76 myocardial infarction before the age of 55 (for men) or 65 (for women). Hypertension was
77 defined as a mean systolic blood pressure ≥ 140 mmHg, a mean diastolic blood pressure ≥ 90
78 mmHg, or ongoing antihypertensive treatment. The body mass index was calculated as
79 weight (kg)/height² (m²). The Mini Nutritional Assessment Short-Form¹⁹ score was recorded
80 (risk of malnutrition: $< 12/14$, i.e. < 12 out of 14) along with unintentional weight loss over the
81 previous year. Waist circumference values ≥ 102 cm (for men) or ≥ 88 (for women) were
82 considered to be abnormal. Metabolic syndrome (MetS) was defined as the combination of
83 three or more of the following conditions: hypertension, abnormal waist circumference,
84 fasting blood glucose ≥ 110 mg/dL, triglycerides ≥ 150 mg/dL, and HDL cholesterol < 40
85 mg/dL (for men) or < 50 (for women). Mobility was assessed via a daily pedometer count
86 over a week (sedentary: < 7500 steps/day)²⁰ and gait speed over 10 meters (slowness: < 1
87 m/s).²¹ Muscle strength was estimated by the dynamometer-measured peak dominant-hand
88 grip strength (JAMAR®, Sammons Preston, Bolingbrook, IL, USA), and the completion time
89 in a five-time sit-to-stand test (> 11.19 s).²² Weakness was defined as grip strength (kg)
90 stratified by gender and body mass index.²³ Appendicular skeletal muscle mass was estimated
91 using dual energy X-ray absorptiometry (GE Healthcare, Lunar, Prodigy) and then used to
92 compute the appendicular lean mass index (low muscle mass: < 7.23 kg/m² (for men) or < 5.67
93 (for women)).²⁴ Sarcopenia was defined as a combination of low muscle mass and low
94 muscle strength (< 30 kg in men and < 20 kg in women) or slowness.²⁴ Osteopenia and
95 osteoporosis were defined according to the bone mineral density T-score (osteopenia:
96 between -2.5 and -1 ; osteoporosis: ≤ -2.5). Ten-meter walking test times during concurrent
97 tasks were also recorded. The one-leg standing test (< 5 s)²⁵ and sternal push test were used to
98 assess balance. Lastly, the Geriatric Depression Scale (GDS) was used to explore mood (risk
99 of depression: $\geq 11/30$, or $\geq 5/15$).²⁶ Non-accidental falls in the previous year were also
100 recorded.

101 To determine the physical frailty phenotype, we considered shrinking (>4.5 kg in the
102 last year), weakness, exhaustion (a self-reported feeling of generalized weakness over the last
103 year), slowness, and a low level of activity (<7500 steps per day and no regular physical
104 activity);²³ the number of positive items defined the individuals as frail (≥ 3), pre-frail (1-2) or
105 robust (none).

106

107 *Evaluation of cognitive functions*

108

109 All participants underwent a face-to-face neuropsychological assessment with a
110 trained geriatrician. The 7-point CDT (developed as part of the 7-Minute Screen battery)²⁷
111 was used to assess executive and visuospatial functions. This test is commonly used in
112 routine practice by geriatricians, and so was chosen because of its easy administration and
113 scoring. The patient was instructed to draw numbers and set the hands to a specific time on a
114 pre-drawn circle. The instruction was: “This circle represents a clock; place all the numbers
115 in the right place and place the hands at twenty minutes to four”. The instruction could be
116 repeated during the test, as required. The CDT was scored as follows, with 1 point for each of
117 the 7 items: all the numbers draw, all the numbers in the right place, the sequence 1 to 12
118 intact, two hands present, the minute hand longer than the hour hand, the hour hand between
119 3 and 4 o’clock, and the minute hand pointing to 8. A CDT score <7 was taken as the cut-off
120 for impaired performance.

121 Overall cognitive performance was examined by the MMSE score adjusted for age
122 and years of schooling.²⁸ The five-word screening test (5-WT) was used to assess episodic
123 memory (<10/10),²⁹ and the Frontal Assessment Battery (FAB) was used to assess frontal
124 lobe functions (<16/18).³⁰

125

126 *Brain MRI*

127

128 As reported previously, the outpatient brain MRI data routinely interpreted at each
129 center were reviewed by two geriatricians with experience of neuroimaging interpretation.
130 The severity of white matter lesions (WMLs) was rated using a revised version of the
131 Fazekas scale (0, no WMLs; 1, punctate WMLs; 2, early confluent WMLs; 3, confluent
132 WMLs)³¹. The Scheltens score (from 0, no atrophy, to 4, severe atrophy)³² was used to assess
133 hippocampal atrophy.

134

135 *Outcome measure*

136

137 The primary outcome measure was the CDT score; a score <7 was denoted as
138 understated cognitive impairment.

139

140 *Statistical analysis*

141

142 Quantitative and qualitative variables were respectively described as the median
143 [interquartile range] and the number (%). Continuous variables with a skewed distribution
144 were log-transformed prior to logistic regression analyses; their odds ratio (ORs) and 95%
145 confidence interval (CIs) are given for one standard deviation (SD) of the log-transformed
146 value.

147 We compared participants with CDT results <7 vs. =7 using a Mann-Whitney, chi-
148 squared or Fisher's test, as appropriate. Odds Ratios [95% CIs] were estimated using
149 asymptotic or exact logistic regression analyses for variables that yielded *P* values ≤.15. Age-
150 adjusted ORs were also estimated. Analyses of cognitive test performances were

151 systematically adjusted for GDS results and educational level. When over 5% of the values
152 were missing, we estimated the ORs by applying a multiple-multivariate-imputations-by-
153 chained-equations procedure with the missing-at-random assumption.³³ The threshold for
154 statistical significance was set to $P \leq .05$, and P values between .05 and .10 were denoted as
155 indicating a trend. Analyses were performed using STATA, version 14.1 (StataCorp, College
156 Station, TX, US).

157

158 **Results**

159

160 A total of 488 participants were included in the analysis; the median (range) age was
161 62.1 (50-87), 20.9% had obtained a university degree, and the most prevalent cardiovascular
162 risk factors were dyslipidemia (in 34% of the participants) and hypertension (30.7%) (Table
163 1). About 68% of the participants were pre-frail and 5.5% were frail, according to the
164 physical frailty phenotype. Almost a quarter of the participants ($n=115$) had a CDT score <7 ,
165 yielding a prevalence of 23.6% [95% CI: 19.8-27.3%]. About 15% of the participants had an
166 impaired MMSE or FAB score but very few (2.3%) had abnormal 5-WT.

167 Individuals with an impaired CDT score were significantly older, were more likely to
168 smoke, to be obese, or to have diabetes or MetS, had more cardiovascular risk factors, and a
169 significantly slower gait speed in the single and dual tasks, relative to individuals with a
170 normal CDT score (Table 2). A non-significant trend was observed for a lower educational
171 level and hypertension. Individuals with impaired CDT performance were more likely to
172 have depressive symptoms and performed less well in the MMSE, 5-WT and FAB. Lastly,
173 participants with an impaired CDT score had significantly higher Scheltens scores. We did
174 not observe significant associations between the CDT score on one hand and the physical
175 frailty phenotype, history of non-accidental falls, or Fazekas score on the other.

176 In age-adjusted analyses, a lower educational level ($P=.003$), diabetes ($P=.023$), MetS
177 ($P=.034$), lower gait speed in the cognitive dual task ($P=.012$), and depressive symptoms
178 ($P=.037$) were still significantly associated with a CDT score <7 . A non-significant trend was
179 observed for smoking and obesity. Poorer cognitive performance in the MMSE ($P=.004$), 5-
180 WT ($P=.033$) and FAB ($P=.046$), and a higher Scheltens score ($P=.015$) were also
181 significantly associated with a CDT score <7 after adjustment for age. A non-significant trend
182 was observed for the association between 5-WT performance and the Scheltens score
183 ($P=.058$).

184

185 **Discussion**

186

187 In a population of asymptomatic middle-aged and elderly community-dwellers
188 (median age: 62), the prevalence of understated cognitive impairment was 23.6%. In age-
189 adjusted analyses, the factors significantly associated with impaired CDT performance were a
190 lower educational level, diabetes, MetS, depressive symptoms, a lower gait speed in the
191 cognitive dual task, poorer performance in the MMSE, 5-WT, and FAB tests, and a higher
192 Scheltens score. In our study population, the CDT score was not associated with physical
193 frailty or the Fazekas score.

194 To the best of our knowledge, the present study is the first to have investigated the
195 prevalence of understated cognitive impairment (as assessed by the CDT) and the associated
196 clinical phenotype among asymptomatic community-dwellers aged 50 and over. The CDT
197 and the MMSE are good screening tests for impairments in overall cognition.⁶ Compared
198 with the MMSE, the CDT is better able to detect impairments in visuoconstructive and
199 executive abilities.^{5,6} Given that a decline of executive control in normal aging may be
200 predictive of a change in functional status,³⁴ the detection of a mild impairment in executive

201 function in relatively young seniors may be of value in preventing dementia or delaying its
202 onset through multidomain interventions and better overall management (e.g. diet, exercise,
203 cognitive training, and the treatment of vascular risk factors).³⁵

204 The prevalence of impaired CDT performance in the present study was 23.6%; this is
205 within the range from 20.1 to 32.2% reported for MCI in community-dwellers ≥ 65 years.¹⁶
206 However, another study reported a rate of 60.6% for adults aged ≥ 65 .¹¹ The only study that
207 investigated community-dwellers aged ≥ 50 reported mean CDT scores but not a prevalence
208 rate.¹⁰ As expected, we found that individuals with an impaired CDT score were significantly
209 older and had a lower educational level.^{6,36}

210 In line with reports on older populations, individuals with an impaired CDT score
211 were more likely to have cardiovascular risk factors such as diabetes and MetS.^{7,8,37} In
212 contrast, other components of the MetS (hypertension, abdominal obesity, and dyslipidemia)
213 were not significantly associated with impaired CDT performance. However, it has been
214 reported that the association between MetS and decline in cognitive function (as assessed by
215 CDT) was not attributable to its individual altered components.³⁷ Therefore, we can assume
216 that the negative effect of MetS on cognitive functions is greater than the cumulative effect of
217 its components. However, further studies are needed to better characterize the role of MetS in
218 age-related cognitive impairment.

219 In contrast to the literature data on elderly individuals, we did not observe an
220 association between impaired CDT performance and physical frailty or physical functions
221 impairment. This may be due in part to the low prevalence of frail subjects (5.5%) in our
222 population of young seniors. Furthermore, it has been shown that a decline in executive
223 function predicts (and therefore precedes) the onset of physical frailty.³⁸ However, we
224 observed a significant association between CDT impairment and the time needed to walk 10
225 meters in the cognitive dual task. This relationship suggests that (i) the cognitive dual task

226 can tax various cognitive resources to varying degrees, and (ii) executive function is one of
227 the key determinants of dual-task ability.³⁹ Lastly, walking and gait disturbances might also
228 be predictors of cognitive impairment and dementia.⁴⁰

229 In line with the literature data, individuals with impaired CDT performance were
230 more likely to have depressive symptoms.⁴¹ After adjustment for factors known to affect
231 scores in cognitive tests (age, educational level, and depressive symptoms), impaired CDT
232 performance was still significantly associated with impairment in screening tests for global
233 cognitive alterations (MMSE), episodic memory performance (5-WT), and executive
234 functions (FAB); again, this agrees with the literature data.^{5,42} These findings support the
235 hypothesis whereby the CDT assesses a broad range of cognitive abilities and may probe the
236 integration of several cognitive domains required for task performance.

237 Regarding the MRI results, we did not observe an association between impaired CDT
238 performance and the Fazekas score. However, this type of association was expected because
239 according to the literature data, the presence of white matter hyperintensities is associated
240 with lower CDT scores.⁴³ It may be that the low prevalence of severe WMLs in our study
241 population prevented us from observing an association. Conversely, we confirmed that
242 impaired CDT performance is associated with a higher Scheltens score, a hallmark of
243 hippocampal atrophy⁴⁴ usually associated with poor episodic memory, especially in
244 Alzheimer's disease.⁴⁵ Importantly, hippocampal atrophy is also associated with other
245 neurodegenerative disorders, such as hippocampal sclerosis, Lewy-related pathologies, and
246 argyrophilic grain disease.⁴⁶ It is noteworthy that in our study, poor performance in the 5-WT
247 (an episodic memory test associated with impaired CDT performance here and in the
248 literature⁶) was associated (albeit non-significantly; $P = .058$) with hippocampal atrophy.
249 However, the prevalence of impaired 5-WT performance in our population of young seniors
250 was only 2.3% - much less than the value of 23.6% for impaired CDT performance. Given

251 that the CDT is a multidomain test (rather than an episodic memory test), we suggest that it
252 might be better than the 5-WT for screening for understated cognitive impairment associated
253 with hippocampal atrophy in relatively young populations.

254 The main strengths of our study were the prospective recruitment of participants, and
255 the use of validated measurement tools that comply with international guidelines. The CDT is
256 a validated instrument with solid psychometric properties for identifying cognitive decline.
257 Although there is a lack of a consensus on the most appropriate scoring system for CDT, our
258 application of the same scoring system to all participants in the SUCCEED survey precludes
259 differential bias. Furthermore, we routinely adjusted our analyses for potential confounders
260 such as age, educational level and depressive symptoms. Other potential limitations include
261 the single-center, cross-sectional design; this limits external validity and cannot provide
262 information on the temporal relationship between impaired CDT performance and other study
263 variables.

264

265 **Conclusions and implications**

266

267 Almost a quarter of asymptomatic middle-aged and elderly community-dwellers had
268 understated cognitive impairment (as assessed by the CDT). The clinical phenotype
269 associated with CDT impairment included cardiovascular risk factors, depressive symptoms,
270 a lower educational level, worse cognitive performance in dual tasks and in memory or
271 executive tasks, and a higher degree of hippocampal atrophy. These factors (some of which
272 are modifiable) are known to be related to a higher risk of cognitive decline and dementia.
273 Conversely, impaired CDT performance was not associated with physical frailty in this
274 population of young seniors. The CDT may be of value in detecting understated cognitive

275 impairment in younger seniors, better managing their risk factors for dementia, and thus
276 preventing or at least delaying functional decline and dementia.

277

278 **Conflict of interest**

279

280 The authors disclose no conflicts of interest.

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Table 1. Characteristics of the study population (N=488)

Age, median [IQR] years	62.1 [57.4-67.1]
Female sex	328 (67.2)
Years of education from first year of primary school, median [IQR] (23/4.7)	12 [11-15]
Being retired (23/4.7)	260(53.7)
Living alone	140 (28.7)
Number of steps per day, median [IQR] (97/19.9)	7405 [5154-10211]
Sedentariness (Steps/day <7500) (97/19.9)	196 (50.1)
Low physical activity (steps/day <7500 and no regular physical activity) (33/6.7) *	194 (41.9)
Family history of sudden death or myocardial infarction (178/36.4)	15(4.8)
Smoking (current or past 3 years) (107/21.9)	31(8.1)
Obesity (body mass index \geq 30) (1/0.2)	68(14.0)
Waist circumference \geq 88 cm (female) or 102 cm (males) (5/1.0)	232 (48.0)
Hypertension [†]	150(30.7)
Diabetes (1/0.2)	27(5.5)
Personal history of cardiovascular disease (11/2.25) [‡]	25 (5.2)
Dyslipidemia (2/0.4)	165(34.0)
Metabolic syndrome (14/2.9)	55(11.6)
Number of major cardiovascular risk factors, median [IQR] [§]	1 [1-2]
0	76 (15.6)
1	179 (36.7)
2	155 (31.8)
\geq 3	78 (16.0)
One or more non-accidental falls in the year (6/1.2)	41(8.5)
Nutrition	
Risk of malnutrition/malnutrition (MNA <12) (6/1.2)	25 (5.2)
Unintentional weight loss \geq 4.5 kg in the past year (32/6.5)	15 (3.2)
Mobility and muscle strength	
Gait speed m/s, median [IQR]	1.43 [1.25-1.64]
Slowness (gait speed < 1 m/s) (1/0.2)	15(3.1)
Ten-meter walking test times during a concurrent motor task, s	7 [6.2-8]
Ten-meter walking test times during a concurrent cognitive task, s	7.7 [6.8-9]
Appendicular lean mass index, kg/m ² < 7.23 (male) or 5.67 (female)	49(10.0)
Weakness, grip strength (kg) stratified by sex and body mass index	178 (36.6)
Time to get up from a chair (5 times) >11.1 s (10/2.0)	50(10.5)

Sarcopenia	25 (5.1)
Balance	
One-leg standing test (6/1.2) < 5 s	48(10.0)
Failure to resist a sternal push (14/2.9)	29 (6.1)
Bone mineral density (15/3.1)	
Normal (T-score > -1)	206(43.6)
Osteopenia (T-score between -1 and -2.5)	191(40.4)
Osteoporosis (T-score<=-2.5)	76(16.1)
Exhaustion (122/24.6)	110 (29.4)
Physical frailty phenotype (modified CHS criteria) (6/1.2%)[†]	
Robust	125 (25.6)
Pre-frail	330 (67.6)
Frail	27 (5.5)
Depressive symptoms (GDS \geq11/30 or 5/15) (63/12.9)	65(15.3)
Cognition	
Clock drawing test <7	115 (23.6)
MMSE \leq lower quartile according to age and education (23/4.7)	62(13.3)
Five-word test score <10	11(2.3)
Frontal Assessment Battery score <16 (1/0.2)	81(16.6)
Brain MRI	
Scheltens score (86/17.6)	
0	230 (57.2)
1	143 (35.6)
2-3	29 (7.2)
Fazekas score (118/24.2)	
0-1	313 (84.6)
2-3	57 (15.4)

Variables are expressed as the n (%), unless otherwise stated; (/) indicates the number and % of missing values.

Abbreviations: IQR, interquartile range; MNA, Mini Nutritional Assessment; MMSE, Mini Mental State Examination; GDS, Geriatric Depression Scale; CHS, Cardiovascular Health Study; MRI, magnetic resonance imaging.

* Regular physical activity including walking, recreational sports and other physical activities.

[†] Hypertension, defined as a systolic blood pressure \geq 140 mmHg or a diastolic blood pressure \geq 90 mmHg or ongoing treatment for hypertension.

[‡] History of cardiovascular disease, including stroke, transient ischemic attack, or coronary heart disease.

[§] Major cardiovascular risk factors include: male sex, age >60 years (female), hypertension, smoking (current or past 3 years), dyslipidemia, diabetes, and first degree relative(s) with stroke before 45 years of age, sudden death, or myocardial infarction before 55 [men] or 65 (women) years of age.

[†] The modified CHS criteria were unintentional weight loss $\geq 4.5\text{kg}$ in the year, self-reported exhaustion, poor grip strength, gait speed $<1\text{m/s}$ and low physical activity (<7500 steps/day and no regular physical activity). Individuals with ≥ 3 criteria are considered to be frail, those with 1-2 criteria are considered to be pre-frail, and those with no criteria are considered to be robust.

Table 2. Characteristics of the study participants as a function of the CDT score (univariate and age-adjusted analyses)

	Clock-Drawing Test score		Univariate analysis		Age adjusted analysis	
	7 (N=373)	<7 (N=115)	<i>P</i> value *	OR [95% CI] †	OR [95% CI] ‡	<i>P</i> value
Age, median [IQR] years	61.4 [56.6-66.0]	63.9 [59.3-70.0]	<.001	1.07 [1.04-1.11]		
Female sex	256 (68.6)	72 (62.6)	.229			
Years of full-time education from the first year of primary school, median [IQR] §	12 [11-15]	12 [11-15]	.058	0.70 [0.56-0.86]	0.72 [0.58-0.89]	.003
Living alone	104 (27.9)	36 (31.3)	.478			
Low physical activity (steps/day < 7500 and no regular physical activity) ¶ **	145 (41.7)	48 (44.4)	.61			
First-degree relatives with a history of sudden death or myocardial infarction ††	14 (6.0)	1 (1.3)	.274			
Personal history of cardiovascular disease ††	16 (4.4)	9 (8.2)	.115	1.95 [0.84-4.56]	1.30 [0.53-3.18]	.559
Smoking (current or past 3 years)	19 (6.5)	12 (13.3)	.039	1.89 [0.87-4.09]	2.17 [0.96-4.92]	.062
Obesity (body mass index ≥ 30)	45 (12.1)	23 (20.0)	.034	1.82 [1.04-3.16]	1.65 [0.94-2.92]	.083
Waist circumference ≥ 88 cm (female) or 102 cm (males)	172 (46.7)	60 (52.2)	.309			
Hypertension §§	107 (28.7)	43 (37.4)	.077	1.48 [0.96-2.30]	1.19 [0.75-1.88]	.46
Diabetes	15 (4.0)	12 (10.4)	.011	2.77 [1.26-6.11]	2.57 [1.14-5.79]	.023
Dyslipidemia	129 (34.8)	36 (31.3)	.493			
Metabolic Syndrome	34 (9.3)	21 (19.1)	.006	2.29 [1.27-4.14]	1.93 [1.05-3.56]	.034
Number of major cardiovascular risk factors ¶¶	1 [1-2]	2 [1-2]	.005	1.34 [1.09-1.65]	1.14 [0.90-1.43]	.267
0	67 (18.0)	9 (7.8)				
1	134 (35.9)	45 (39.1)	.02	2.5 [1.15-5.42]	1.49 [0.66-3.40]	.338
2	120 (32.2)	35 (30.4)	.055	2.17 [0.98-4.79]	1.07 [0.44-2.56]	.885
≥3	52 (13.9)	26 (22.6)	.002	3.72 [1.61-8.62]	1.85 [0.74-4.63]	.187
One or more non-accidental falls in the year	29 (7.9)	12 (10.5)	.376			
Risk of malnutrition/malnutrition (MNA <12) **	21 (5.7)	4 (3.5)	.355			

Unintentional weight loss \geq 4.5 kg in the past year	9 (2.6)	6 (5.4)	.149	2.14 [0.74-6.15]	2.13 [0.71-6.38]	.175
Mobility and muscle strength						
Gait speed m/s, median [IQR]	1.43 [1.25-1.67]	1.37 [1.18-1.54]	.011	0.40 [0.19-0.85]	0.54 [0.26-1.15]	.109
Slowness (gait speed < 1 m/s)	10 (2.7)	5 (4.4)	.362			
Ten-meter walking test times during a concurrent task						
Motor dual task, s [§]	7 [6-8]	7.5 [6.7-8.6]	<.001	1.24 [1.03-1.50]	1.18 [0.98-1.42]	.078
Cognitive dual task, s [§]	7.3 [6.5-8.5]	8.2 [7-10]	<.001	1.33 [1.10-1.60]	1.27 [1.05-1.53]	.012
Appendicular lean mass index, kg/m ² < 7.23 (male) or 5.67 (female)	37 (9.9)	12 (10.4)	.872			
Weakness (grip), stratified by sex and body mass index	135 (36.3)	43 (37.4)	.83			
Time getting up from a chair (5 times) >11.19s	38 (10.3)	12 (10.9)	.861			
Sarcopenia	18 (4.8)	7 (6.1)	.592			
Balance						
One-leg standing test < 5 s	40 (10.9)	8 (7.0)	.23			
Failure to resist a sternal push	21 (5.8)	8 (7.1)	.625			
Bone mineral density)						
Normal (T-score > -1)	166 (45.4)	40 (37.4)				
Osteopenia (T-score between -1 and -2.5)	144 (39.3)	47 (43.9)				
Osteoporosis (T-score \leq -2.5)	56 (15.3)	20 (18.7)				
Exhaustion **	87 (29.9)	22 (28.2)	.77			
Physical frailty phenotype (modified CHS criteria) [¶]						
Robust	98 (26.4)	27 (24)				
Pre-frail	253 (68.5)	77 (68.8)	.732			
Frail	19 (5.1)	8 (7.1)	.381			
Depressive symptoms (GDS score \geq11/30 or 5/15) **	42 (12.9)	23 (23.2)	.013	1.92 [1.10-3.35]	1.86 [1.04-3.32]	.037
Cognition #						

MMSE \leq lower quartile, according to age and educational level	40 (11.1)	22 (21.0)	<.001	2.19 [1.17-4.08]	2.56 [1.35-4.88]	.004
Five-word test score <10	5 (1.3)	6 (5.2)	.025	4.45 [1.32-15.03]	4.11 [1.12-15.02]	.033
Frontal Assessment Battery score <16	50 (13.4)	31 (27.0)	.001	2.18 [1.26-3.78]	1.79 [1.01-3.16]	.046
Brain MRI **						
Scheltens score			.001			
0	190 (62.7)	40 (40.4)				
1	94 (31.0)	49 (49.5)	<.001	2.20 [1.37-3.53]	1.83 [1.13-2.99]	.015
2-3	19 (6.3)	10 (10.1)	.032	2.15 [0.95-4.90]	1.28 [0.53-3.09]	.584
Fazekas score			.55			
0-1	242 (85.2)	71 (82.6)				
2-3	42 (14.8)	15 (17.4)				

Variables are expressed as the n (%), unless otherwise stated.

Abbreviations: IQR, interquartile range; MNA, Mini Nutritional Assessment; MMSE, Mini Mental State Examination; GDS, Geriatric Depression Scale; CHS, Cardiovascular Health Study; MRI, magnetic resonance imaging.

* P value in a Mann-Whitney, Chi² or Fisher test, as appropriate; logistic regression analyses were used to estimate [†] crude and [‡] age-adjusted odds ratios, and [#] odds ratios adjusted for depressive symptoms and educational level; ** odds ratios estimated after multiple imputation (> 5% missing values).

[§] Odds ratios and confidence intervals are given for one standard deviation of the log-transformed value.

^{||} Regular physical activity, including walking, recreational sports and other physical activities.

^{††} Myocardial infarction was considered if occurred before 55 [men] or 65 (women) years of age.

^{‡‡} Personal history of cardiovascular disease includes: stroke, transient ischemic attack, and coronary heart disease.

^{§§} Hypertension, defined as a systolic blood pressure \geq 140 mmHg or a diastolic blood pressure \geq 90 mmHg or ongoing treatment for hypertension.

^{|||} Major cardiovascular risk factors, including male sex, age > 60 years (female), hypertension, smoking (current or past 3 years), dyslipidemia, diabetes, and first degree relative(s) with sudden death, or myocardial infarction before 55 [men] or 65 (women) years of age.

[¶] The modified CHS criteria were unintentional weight loss $\geq 4.5\text{kg}$ in the year, self-reported exhaustion, poor grip strength, gait speed $<1\text{m/s}$ and low physical activity (<7500 steps/day and no regular physical activity). Individuals with ≥ 3 criteria are considered to be frail, those with 1-2 criteria are considered to be pre-frail, and those with no criteria are considered to be robust.