repiSalud
Repositorio Institucional de Salud

This is the peer reviewed version of the following article:

BLOOD CADMIUM AND PHYSICAL FUNCTION LIMITATIONS IN OLDER ADULTS

García-Esquinas E, Téllez-Plaza M, Pastor-Barriuso R, Ortolá R, Olmedo P, Gil F, López-García E, Navas-Acien A, Rodríguez-Artalejo F. Blood cadmium and physical function limitations in older adults. Environ Pollut. 2021 May 1;276:116748. doi: 10.1016/j.envpol.2021.116748. Epub 2021 Feb 16. PMID: 33639488.

which has been published in final form at:
https://doi.org/10.1016/j.envpol.2021.116748

Blood cadmium and physical function limitations in older adults

Esther Garcia-Esquinas, [1,2,3] **María Tellez-Plaza,** [1,4,5] **Roberto Pastor-Barriuso**[3,4]**,**
Rosario Ortola,[1,2,3] **Pablo Olmedo,** [6] **Fernando Gil,** [6] **Esther López-García,**[1,2,3,7] **Ana Navas-Acien ,**[8] **and Fernando Rodriguez-Artalejo.** [1,2,3,7]

1-Department of Preventive Medicine and Public Health. School of Medicine. Universidad Autónoma de Madrid, Madrid, Spain.

2-IdiPaz (Hospital Universitario La Paz-Universidad Autónoma de Madrid), Madrid. Spain

3-CIBERESP (CIBER of Epidemiology and Public Health), Madrid, Spain.

4-National Center of Epidemiology. Carlos III Health Institute, Madrid, Spain.

5-Biomedical Research Institute Hospital Clinic de Valencia (INCLIVA), Valencia, Valencia, Spain.

6- Department of Legal Medicine, Toxicology, and Physical Anthropology, School of Medicine, University of Granada, Granada, Spain.

7- IMDEA Food Institute. CEI UAM+CSIC, Madrid, Spain.

8-Department of Environmental Health Sciences, Mailman School of Public Health, Columbia University, New York, USA.

Corresponding Author: Esther García-Esquinas.
Department of Preventive Medicine and Public Health.
School of Medicine, Universidad Autónoma de Madrid. Calle del Arzobispo Morcillo 4, 28029 Madrid (SPAIN).
E-mail: esthergge@gmail.com; esther.garciag@uam.es

27 **Abstract**

28 **Background:** Cadmium (Cd) is a toxic metal found in tobacco, air and food. Recent
29 cross-sectional studies have suggested that Cd negatively impacts physical performance,
30 but the prospective association is uncertain.

31 **Methods**: We used data from 2548 older adults from the Seniors-ENRICA II cohort in
32 Madrid, Spain. Whole blood Cd levels were measured at baseline using inductively
33 coupled plasma-mass spectrometry. At baseline (2017) and follow-up (2019), overall
34 physical function was evaluated using the physical component summary (PCS) of the SF
35 12-Item Health questionnaire, lower-extremity performance with the Short Physical
36 Performance Battery (SPPB), muscle weakness with a hand dynamometer, and frailty
37 with a Deficit Accumulation index. Mobility limitations and disability in instrumental
38 activities of daily living (IADL) were ascertained with standardized questionnaires.
39 Analyses were adjusted for relevant confounders, including tobacco smoke, number of
40 cigarettes smoked per day and time since cessation in former smokers.

41 **Results:** In cross-sectional analyses, odds ratios (95% confidence interval) per two-fold
42 increase in blood Cd were 1.16 (1.03; 1.31) for low PCS scores, 1.08 (0.97; 1.20) for
43 impaired lower-extremity performance, 1.10 (0.98; 1.23) for low grip strength, 1.11 (1.02;
44 1.20) for mobility limitations, 1.16 (1.02; 1.31) for frailty, and 1.26 (1.08; 1.47) for IADL
45 disability. In longitudinal analyses, corresponding hazard ratios were 1.25 (1.03; 1.51) for
46 low PCS scores, 1.14 (1.03; 1.27) for impaired lower-extremity performance, 1.02 (0.92;
47 1.13) for low grip strength, 1.03 (0.91; 1.16) for mobility limitations, and 1.16 (1.00;
48 1.35) for frailty. All the associations where consistent when current smokers were
49 excluded from the analyses.

Conclusions: Our results support the role of Cd as a risk factor for physical function impairments in older adults.

Keywords: Cadmium, functional impairment, disability, older adults

54 **Abbreviations:**

55 BMI: Body Mass Index

56 Cd: Cadmium

57 CVD: Cardiovascular Disease

58 DA: Deficit Accumulation

59 IADL: Instrumental Activities of Daily living

60 LOD: Limit Of Detection

61 MDS: Mediterranean Diet Score

62 PCS: Physical Component Summary

63 SF-12: 12-Item Short-Form Health questionnaire

64 SPPB: Short Physical Performance Battery

INTRODUCTION

Ageing is the result of cumulative molecular and cellular damage that leads to a progressive decline in physical and cognitive function (López-Otín et al., 2013), which is more accelerated during the last stages of life (García-Esquinas et al., 2019) and increases the risk of dependence, institutionalization and death. Because the rate of functional decline is heterogeneous across individuals, a growing body of research tries to identify potential preventable factors contributing to this process. However, very few studies have examined the association between environmental toxicants and physical performance decline in older adults (García-Esquinas & Rodríguez-Artalejo, 2017).

Cadmium (Cd) is a well-known hazardous contaminant widely distributed in the environment. In the general population not exposed in the workplace, this metal is mainly absorbed via inhalation of particles from cigarette smoke or ingestion of contaminated foods (most frequently shellfish, offal and vegetables) (1). Exposure to this metal has been associated with cardiovascular endpoints in adults (Tellez-Plaza et al., 2013), including peripheral arterial disease (Navas-Acien et al., 2004), coronary heart disease, heart failure (Borné et al., 2015) or stroke (C. Chen et al., 2018); as well as with renal tubular dysfunction (Grau-Perez et al., 2017; Navas-Acien et al., 2009), fractures (Cheng et al., 2016), and cardiovascular (Tellez-Plaza et al., 2012) and cancer mortality (García-Esquinas et al., 2014; Watanabe et al., 2020).

Recent studies have suggested that Cd may negatively impact physical performance in adults (García-Esquinas et al., 2020; J. Kim et al., 2018), and increase the odds of frailty (García-Esquinas et al., 2015) and functional dependence (Chen et al., 2020) in the elderly. However, with the exception of one study showing an inverse relationship between blood Cd and walking speed (Kim et al., 2016), most of the literature

90 addressing the effects of Cd on physical function is cross-sectional and uses data from
91 the US National Health and Nutrition Examination Survey. In this context, the aim of
92 the present study was to evaluate both the cross-sectional and the longitudinal
93 association between blood Cd levels and several validated measures of physical
94 performance and disability in a population of older adults in Spain with a low
95 prevalence of tobacco consumption.

96

97 ## METHODS

98 ### Study participants and design

99 The Seniors-ENRICA-2 cohort was set up between 2015 and 2017 with 3273 individuals
100 selected by sex- and district-stratified random sampling of all community-dwelling
101 individuals aged ≥65 years holding a national healthcare card and living in the city of
102 Madrid (Spain) or four surrounding large towns (please see **Supplementary Figure S1**).
103 At baseline (2015-2017), information regarding socio-demographic, lifestyle, self-rated
104 health and morbidity was collected using a computer-assisted telephone interview. Also,
105 two home visits were conducted to perform a physical examination, obtain a diet history,
106 collect biological samples and information on prescribed medications (which were
107 checked against drug packages). From the initial sample of 3273 participants, 86.5%
108 (n=2831), 85.4% (n=2795), and 79.7% (n=2610), agreed to the physical exam, completed
109 the diet history and provided blood samples, respectively. Cd determinations were
110 available in 97.6% (n=2548) of those who provided baseline blood samples.

111 During a mean follow-up time of 2.3 (SD:0.30) years, 36 participants died, 771 were lost,
112 and 1741 agreed to be re-interviewed and re-examined at home. At follow-up, data
113 collection was done using the same protocols as at baseline. Participants lost to follow-

114 up were on average one year older and more frequently women, showed lower
115 educational level, did less physical activity, watched more TV, and had a higher
116 prevalence of chronic morbidities (i.e. obesity, hypertension, diabetes, dyslipidemia) and
117 functional limitations than those who were followed (**Supplementary Table S1**). Among
118 the 1741 participants followed, 90, 243, 280, 202 and 103 developed incident low
119 physical function, impaired lower-extremity performance, low grip strength, mobility
120 limitations, and frailty, respectively. **Supplementary Table S2** shows the cumulative
121 incidence of functional limitations by the main participant´s characteristics.

122 Participants gave informed written consent, and the Clinical Research Ethics Committee
123 of the *La Paz* University Hospital in Madrid approved the study (Protocol #HULP-PI
124 1793).

125 **Study variables**

126 *Blood Cadmium*

127 At baseline, blood samples were collected and stored at -80ºC. Baseline whole blood Cd
128 was measured using inductively coupled plasma-mass spectrometry (8900 ICP-QQQ) at
129 the Department of Legal Medicine, Toxicology, and Physical Anthropology, School of
130 Medicine, University of Granada (Spain). The limit of detection (LOD) was 0.1 µg/L and
131 the percentage of individuals with values below the LOD was 7.5% for current smokers,
132 33.8% for former smokers, and 54.7% for never smokers.

133 *Physical performance and disability*

134 Overall physical function was evaluated at baseline and follow-up using the Spanish
135 version of the physical component summary (PCS) of the 12-Item Short-Form Health
136 questionnaire (SF-12) (Vilagut et al., 2008). The PCS assesses general health, physical

functioning, role functioning difficulties caused by physical problems, and bodily pain, and uses Likert scales to analyze the intensity or frequency of each response. At baseline, individuals in the lowest (worst) decile of the distribution were classified as having important physical function limitations (McCall et al., 2019). Incident cases were participants who newly developed low PCS scores during follow-up.

Lower-extremity performance was assessed at baseline and follow-up with the Short Physical Performance Battery (SPPB), and includes three tests (Guralnik et al., 1994): 1) Balance testing: Participants were first asked to stand with their feet together, and if were able to stand for 10 seconds in this position, were tested in a *semitandem* stand position (i.e. with the heel of one foot placed to the side of the big toe of the other foot). Those who were able to stand for 10 seconds in the *semitandem* were then tested in a *full-tandem* stand (i.e. with the heel of one foot placed in front of the toes of the other foot). A score of 0 indicates the inability to stand in any of the positions, while a score of 4 indicates a full-tandem stand for 10 seconds. 2) Gait speed: Calculated as the walking distance (3 meters) divided by the time to complete the test in seconds. In this test, 0 points indicated the inability to perform the walk, and 4 being in the fastest quartile of walking speed according to sex and height. 3) *Sit-to stand* test: Participants stood up and sat down from a chair five times repeatedly, with arms crossed across the chest. A score of 0 was given to those unable to perform the five chair stands, while scores of 1, 2, 3, or 4 were assigned to those who completed five chair stands in ≥16.7, 13.7-16.6, 11.2-13.6, and ≤11.1 seconds, respectively. The total SPPB score was calculated by the sum of the components, with a range from 0 to 12 (best performance). At baseline, participants with a score <9 were deemed to have impaired lower-extremity performance (Ishiyama et al., 2017). Incident cases were defined as participants who newly developed low SPPB scores during follow-up.

162 Mobility limitations were evaluated at baseline and follow-up with three questions from
163 the *Rosow and Breslau* scale: “How much difficulty do you experience…”1) “…picking
164 up or carrying a shopping bag?”, 2) “…climbing one flight of stairs?”, 3) “…walking a
165 few hundred meters?”. Individuals who answered “some difficulty", "much difficulty",
166 or "unable to do" to any of these three questions were considered as having mobility
167 limitations. Incident cases were defined as those who newly developed mobility
168 limitations during follow-up.

169 Frailty was defined according to the Rockwood’s frailty index (Rockwood & Mitnitski,
170 2007). At baseline and follow-up, a Deficit Accumulation (DA) index was calculated
171 using a total of 52 health deficits, including impairments in physical and cognitive
172 functioning, self-reported health and vitality problems, mental health conditions, as well
173 as morbidity, polypharmacy, and health services use (García-Esquinas et al., 2019). The
174 DA index summarizes age-related vulnerability, so the more health deficits (symptoms,
175 signs, diseases, or disabilities) an individual has, the higher the risk of death,
176 institutionalization, health service use, or further deficit accumulation. At baseline,
177 participants with a DA index ≥30 were considered frail (Rodríguez-Sánchez et al., 2019).
178 Incident cases were individuals who newly developed DA index scores ≥30 during
179 follow-up.

180 Disability in Instrumental Activities of Daily living (IADL) was defined according to
181 the Lawton-Brody index, which evaluates the individual´s ability to use the telephone,
182 go shopping, prepare meals, do the housework, do the laundry, use different means of
183 transportation, take medication, and manage finances. Due to cultural issues, the
184 questions on meal preparation, housework and laundry were excluded in men. Because
185 the incidence of IADL disability was low and did not allow for meaningful
186 comparisons, prospective analyses using this outcome were not performed.

Other variables

Information was also collected on age and sex; education (< high school, high school and > high school); smoking (never, ex-smoker, current smoker); smoking intensity (number of cigarettes smoked per day); time since smoking cessation (in former smokers); alcohol drinking (heavy drinking, moderate drinking, former drinker, never drinker); leisure-time and household physical activity (METS-h/week); diet quality (estimated with the Mediterranean Diet Score (MDS) (Ortolá et al., 2019; Trichopoulou et al., 2003); and history of physician-diagnosed chronic conditions. Cardiovascular disease (CVD) was defined as a self-reported diagnosis of coronary heart disease, congestive heart failure, heart attack or angina. A history of hypertension was based on a self-reported physician diagnosis, current use of anti-hypertensive medication, or a clinical blood pressure reading 140/90 mmHg taken under standardized conditions. Fasting serum glucose, creatinine, total cholesterol, HDL-cholesterol and triglycerides were measured with colorimetric enzymatic methods using Atellica Solution® (Siemens Healthineers), and LDL-cholesterol was calculated with the Friedewald formula (LDL = total cholesterol – triglycerides/5 – HDL). Definition of type 2 diabetes mellitus was based on a self-reported physician diagnosis, fasting glucose ≥126 mg/dL, or current use of anti-diabetic medication. Dyslipidemia was defined as total cholesterol >5.2 mmol/L or use of lipid-lowering medication. Depression was ascertained with the 10-item Geriatric Depression Scale (GDS-10), a self-report of clinically diagnosed depression, or being on anti-depressant medication (Yesavage et al., 1982). Weight and height were measured according to standardized procedures, and the body mass index (BMI) calculated as measured weight in kg divided by squared height in m.

Statistical analyses

211 Baseline blood Cd concentrations below the LOD (n=1078) were imputed as the median
212 of each subject-specific posterior distribution of predicted levels obtained from a
213 Marcov chain Monte Carlo by Gibbs sampling nested linear model, implemented with
214 WinBUGS software (Lunn et al., 2000) following previously described methods
215 (Tellez-Plaza et al., 2010). This consisted of a predictive model based on blood Cd
216 determinants including sex, age, education, and baseline smoking status, alcohol intake,
217 BMI, chronic comorbidities, and frequency of consumption of certain foods (i.e. dairy
218 products, whole grain products, meat, fruits, shellfish) associated with Cd
219 concentrations in the study sample (**Supplementary Appendix**).

220 The geometric mean (95% confidence interval) of the participants' imputed blood Cd
221 levels was 0.14 μg/L (interquartile range: 0.13–0.15). The corresponding levels in the
222 subset of the population with vales above the LOD was 0.24 μg/L (interquartile range:
223 0.16-0.43).Baseline blood Cd levels were right-skewed and log-transformed to achieve
224 normality.

225 The cross-sectional association between blood Cd and prevalence of functional
226 limitations was assessed with logistic regression models, while the prospective
227 association between baseline Cd levels and incidence of functional limitations was
228 assessed using Cox proportional hazard models with age as time scale and individual
229 starting follow-up times treated as staggered entries. The assumption of hazards
230 proportionality was evaluated with scaled Schoenfeld residuals, with no major
231 departures from proportionality. In both cross-sectional and prospective analyses, Cd
232 levels were modeled in three different ways: 1) Using a categorical variable that
233 classified individuals with Cd concentrations below the LOD into a reference category,
234 and those with concentrations above the LOD into four equally sized groups (i.e.

235 quartiles); 2) Using continuous log-transformed Cd concentrations (including both
236 observed and imputed blood Cd values), with results expressed per 2-fold increase; 3)
237 Using restricted quadratic splines with knots at the 10th, 50th, and 90th percentiles of
238 log-transformed Cd to evaluate potential nonlinear relationships (Harrell, 2001).
239 Departures from linearity in the restricted cubic spline models were evaluated using the
240 Wald test.

241 All models were performed with progressive levels of adjustment. Model 1 adjusted for
242 age, sex, and smoking status; model 2 further included education, smoking intensity
243 (cigarettes/day), diet quality (sex-specific tertiles of the MDS), alcohol drinking (never,
244 ex-, moderate and heavy drinker), physical activity (sex-specific tertiles), passive
245 sedentary time (TV viewing time categorized into sex-specific tertiles), BMI (kg/m^2),
246 hypertension (yes/no), CVD (yes/no), diabetes (yes/no), dyslipidemia (yes/no),
247 osteoarthritis (yes/no) and depression (yes/no).

248 To evaluate the consistency of the findings, we conducted analyses for log2 transformed
249 Cd and functional limitations stratified by the main participant's subgroups: age (≤70,
250 >70 years), sex (male, female), education (≤high school, >high school years), diet
251 quality (tertiles), alcohol drinking (never, former, current), physical activity (tertiles of
252 METs hours/week), BMI (<30, ≥30 kg/m^2) and each of the studied chronic morbidities.
253 Statistical interactions were tested with likelihood ratio tests that compared models with
254 and without interaction terms defined as the product of Cd by the subgroup variables.
255 Also, because smoking is a major source of Cd and adjustment for self-reported
256 smoking status might be insufficient to eliminate residual confounding by smoking, we
257 repeated all the analyses excluding current smokers, and we adjusted for years since
258 smoking cessation in former smokers. Moreover, we repeated all cross-sectional

259 analyses in the subsample of 1741 participants with follow-up information. Finally, Cd
260 concentrations including both imputed and observed Cd concentrations were also
261 modeled as quintiles.

262 Analyses were performed with R Version 2.5.1 using the package R2WinBUGS, and
263 with Stata version 14.1.

264 **Results**

265 **Table 1** shows the distribution of participant´s characteristics by blood Cd
266 concentrations. Participants with higher Cd levels were younger, more likely to be male,
267 smokers or heavy drinkers, less likely to suffer from obesity, diabetes or osteoarthritis,
268 and showed a higher prevalence of dyslipidemia than those with lower concentrations.

269 **Supplementary figure S2** presents the age, sex and smoking-adjusted prevalence of
270 functional impairments by Cd concentrations and suggest an increase in the frequency
271 of all of them with increasing Cd levels. **Table 2** shows the cross-sectional association
272 between blood Cd concentrations and limitations in physical function in the overall
273 sample of participants, as well as in non-smokers. In multivariate adjusted models,
274 individuals in the highest quartile of the observed (i.e. not imputed) Cd concentrations
275 showed a higher prevalence of low PCS scores, mobility limitations, frailty and IADL
276 disability than those with Cd concentrations below the LOD. The odds ratios (95%CI)
277 of each studied limitation per log2-increase in Cd concentrations were: 1.16 (1.03; 1.31)
278 for low PCS score, 1.08 (0.97; 1.20) for impaired lower-extremity performance, 1.10
279 (0.98; 1.23) for low grip strength, 1.11 (1.02; 1.20) for mobility limitations, 1.16 (1.02;
280 1.33) for frailty, and 1.26 (1.08; 1.47) for IADL disability. These associations where

281 consistent when smokers were excluded from the analyses (**Table 2**), and after
282 adjustment for years since tobacco cessation in former smokers (data not shown).

283 In spline regression models (**Figure 1**), the observed dose-response relationships were
284 progressive over the range of Cd concentrations for low PCS scores (p-value for linear
285 and non-linear trend: 0.05 and 0.35, respectively), low grip strength (corresponding p-
286 values: 0.04 and 0.31), mobility limitations (p-values: 0.03 and 0.42), frailty (p-values:
287 0.02 and 0.73) and IADL disability (p-values: 0.01 and 0.67), with no significant
288 departures from linearity. However, no clear dose-response association was observed
289 for impaired lower-extremity performance in the overall sample including smokers (p-
290 value for linear and non-linear trends: 0.16 and 0.19, respectively).

291 In sensitivity analyses, cross-sectional findings were similar after exclusion of
292 participants without follow-up information, and showed no overall effect modification
293 by age, education, tobacco or alcohol consumption, diet quality, physical activity,
294 sedentary time, obesity, diabetes, dyslipidemia or depression (**Figure 2**). However,
295 associations tended to be stronger among men and participants with no CVD (**Figure 2**
296 **and Supplementary Table S3**), while the association between Cd and low grip strength
297 was limited to participants with no osteoarthritis (**Figure 2**).

298 **Table 3** presents the results from multivariate models for the association between Cd
299 concentrations and incidence of functional limitations. Compared to individuals with Cd
300 concentrations below the LOD, those in the highest quartile of the observed
301 concentrations showed a higher incidence of low PCS scores, impaired lower-extremity
302 performance, and frailty. The Hazard Ratios (95%CI) per log2-increase of Cd
303 concentrations were: 1.25 (1.03; 1.51) for low PCS score, 1.14 (1.03; 1.27) for
304 impaired lower-extremity performance, 1.02 (0.92; 1.13) for low grip strength, 1.03

305 (0.91; 1.16) for mobility limitations, and 1.16 (1.00; 1.35) for frailty. Similar findings
306 were observed when excluding smokers from the analyses (**Table 3**), as well as when
307 modeling imputed Cd values as quintiles (**Supplementary Table S4**). When modeling
308 the dose–response relationship using restricted cubic splines, we found an increased
309 incidence with increasing Cd concentrations for impaired lower-extremity performance
310 (p-values for linear and non-linear trends: 0.01 and 0.10, respectively) and frailty
311 (corresponding p-values 0.05 and 0.97, respectively) (**Figure 3**); as well as a borderline
312 significant trend towards low PCS scores (corresponding p-values: 0.07 and 0.74).
313 Results were similar when modeling imputed blood cadmium concentrations as
314 quintiles (**Supplementary Table S4**) and showed no overall effect modification by age,
315 tobacco or alcohol consumption, diet quality, physical activity, sedentary time,
316 hypertension, obesity, diabetes, dyslipidemia, osteoarthritis, or depression, although,
317 again, associations tended to be stronger among participants with no previous history of
318 CVD (**Figure 4**).

319 **Discussion**

320 Our findings support previous cross-sectional studies showing an association between
321 biomarkers of Cd exposure and measures of functional impairment in adults, while
322 provide new evidence on the prospective association between exposure to low-to-
323 moderate Cd levels and higher risk of physical function decline in the elderly.

324 Using data from the NHANES, our group had previously reported a dose-response
325 relationship between blood, but not urine, Cd concentrations and slow walking speed, a
326 component of the SPPB, in middle-aged and older adults (Kim et al., 2018).
327 Longitudinal data from 983 old individuals in Korea also supported a link between
328 blood Cd and low grip strength (Kim et al., 2016). We now present the first evidence for

329 a potential association between Cd exposure and low SPPB scores, which is more
330 clinically relevant than the evidence for gait speed because the SPPB is a better
331 predictor of future hospitalizations and mortality than gait speed alone (Puthoff, 2008).
332 Moreover, the present study illustrates for the first time a dose-response relationship
333 between blood Cd concentrations and low PCS scores, also an important predictor of
334 mortality and hospitalizations in community-dwelling seniors (Dorr et al., 2006). In an
335 earlier report using NHANES data, our group encountered an inverse dose-response
336 relationship between blood and creatinine-corrected urine Cd concentrations and grip
337 strength in US adults (García-Esquinas et al., 2020). However, as in the present study,
338 we did not find a clear link between Cd and low grip strength in analyses of NHANES
339 older adults (García-Esquinas et al., 2015). It is interest to note, though, that the present
340 cross-sectional findings were modified by the presence of hand osteoarthritis, as this is a
341 disease that negatively impacts grip strength (Bagis et al., 2003) and may limit the
342 validity of the test (Ziv et al., 2008). Unfortunately, due to a low sample size, we could
343 not run prospective models further excluding patients with osteoarthritis at follow-up,
344 which would have helped further explore this hypothesis. Regarding frailty, we
345 previously showed the first evidence of an association with urine Cd, as defined using
346 Fried´s phenotypic criteria in participants from NHANES III (García-Esquinas et al.,
347 2015). The present findings corroborate that Cd exposure may increase the risk of
348 frailty, now defined using the Rockwood criteria. Concerning mobility, we observed a
349 dose-response cross-sectional association between blood Cd and self-reported mobility
350 limitations, and this was somewhat stronger in individuals with higher education levels.
351 Although we cannot discard the possibility that this was a chance finding, it is of note
352 that blood Cd concentrations were prospectively associated with the risk of mobility
353 limitations in participants with higher education. However, because information on

354 mobility problems was self-reported, an influence of educational status on individual's
355 risk perception is possible. Finally, this is the first study that shows a link between
356 blood Cd concentrations and IADL disability, and this finding is in line with that of a
357 study on NHANES 2001-2006 in which whole blood Cd was associated with limitations
358 in activities of daily living (ADL) (Chen et al., 2020).

359 Cd exposure can affect several physiological processes that are crucial for physical
360 function preservation. For example, in vitro exposure to Cd modifies the presynaptic
361 function (Tsentsevitsky et al., 2020) and affects the expression of essential synaptic
362 proteins and synaptic transmission in the neuromuscular junction (Braga & Rowan,
363 1994; Braga & Rowan, 1992). Also, in vivo exposure to high doses of Cd produces
364 alterations of the structure of the cerebellum, which has an important role on the
365 maintenance of balance and posture, of different animal species (Mubeena Mariyath
366 et al., 2019; Stoev et al., 2003). Moreover, exposure to Cd in humans has shown to
367 negatively impact cardiorespiratory fitness (Cakmak et al., 2014; Egwuogu et al., 2009;
368 Lampe et al., 2008), age-related changes in blood pressure (Oliver-Williams et al.,
369 2018), and glucose homeostasis (Sabir et al., 2019), all of which are essential processes
370 for exercise tolerance. Also, Cd exposure increases oxidative stress (Domingo-Relloso
371 et al., 2019) and inflammation (Fagerberg et al., 2017), which are central processes in
372 functional deterioration in old age (Cesari et al., 2012; Gale et al., 2013; Inglés M et al.,
373 2014; Semba et al., 2007;Wu et al., 2009; Yao et al., 2011). Finally, exposure to Cd has
374 been related to a higher risk of several pathologic conditions that are linked to
375 functional deterioration such as cognitive decline (Li et al., 2018; Peng et al., 2020),
376 osteoporosis (Engström et al., 2011; Gallagher et al., 2008), or macular degeneration
377 (Wu et al., 2014).

Several research groups have described deleterious health effects at very low blood Cd concentrations as those observed in the present study. For example, in the Malmö Diet and Cancer Study blood Cd levels between 0.26 and 0.4999 µg/L were associated with a 1.5 increased risk of a major adverse cardiac event compared with levels below 0.17 µg/L (Barregard et al., 2016). More recently, researchers from the ELISABET survey found that a 0.1 µg/L increment in blood Cd was associated with an HbA1c increase of 0.016% among never-smokers with median blood Cd concentrations around 0.3 µg/L. (Trouiller-Gerfaux et al., 2019) Also, in NHANES, blood Cd levels in female nonsmokers have shown a U-shaped relationship with the prevalence of peripheral artery, reflecting adverse effects at blood Cd levels < 0.3 µg/L (Tellez-Plaza et al., 2010); while blood Cd levels in the range of 0.3 to 0.6 µg/L have been associated with an increased risk of death from Alzheimer´s disease (Min & Min, 2016). Given these findings, several authors have suggested that tolerable weekly intakes should be reviewed (Satarug et al., 2017), and that population risk assessment of dietary Cd intake could benefit from reliance in blood Cd concentrations because, unlike dietary intakes, the former show a good correlation with urinary Cd. Our results support these recommendations.

The main limitation of the present study is that the sample size may have not had enough power to detect some longitudinal associations or potential interactions by participants characteristics. Also, we had a high percentage of participants with Cd concentrations below the LOD of 0.1 µg/L, which was due to the high proportion of never smokers in the study population (52.6%), and the long time since smoking cessation among former smokers (median time: 20 years; IQR:10-30). We attempted to overcome this limitation by first comparing the occurrence of functional impairments in subgroups of participants defined by their observed Cd levels (i.e. values below the

403 LOD and values above the LOD divided into quartiles); and then estimating the
404 association between imputed Cd concentrations and functional limitations. In most
405 cases, both approaches gave consistent findings, supporting the validity of our
406 imputation model. Another issue is the use of a single determination of Cd, which can
407 result in measurement error due to within-individual biomarker variability.
408 Uncertainties in exposure assessment, however, are likely to be non-differential and
409 probably lead to underestimate the associations. Finally, for former and current
410 smokers, we cannot discard residual confounding by long-term, cumulative smoking
411 dose. We tried to address this issue by excluding current smokers from the analyses, and
412 also by running separate models in former smokers further adjusting for years since
413 smoking cessation, with similar findings. In any case, never smokers showed very
414 consistent results, supporting an effect of Cd on functional impairments independent
415 from smoking.

416 Our study also has some strengths. First, we used several validated measures of physical
417 function in older adults. Second, physical performance tests were conducted by trained
418 staff under standardized conditions. Third, the analyses were adjusted for many
419 potential confounders, minimizing the probability of residual confounding. Finally,
420 results were consistent in sensitivity analyses, including the exclusion of current
421 smokers.

422 In conclusion, our study showed that low blood Cd concentrations have a dose-response
423 association with several measures of physical function decline in older adults. Given
424 that this is one of the first longitudinal studies on this association, further prospective
425 research should confirm these results in other populations.

426

Author contributions:

Esther García-Esquinas conceived the study, obtained funding, performed statistical analyses, and drafted the manuscript. María Tellez Plaza and Roberto Pastor-Barriuso performed statistical analyses. Fernando Rodríguez-Artalejo obtained funding. All authors reviewed the manuscript for important intellectual content, read and approved the final manuscript. The funders of the study had no role in the study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit the article for publication. All authors have read and agreed to the published version of the manuscript.

Funding sources:

This work was supported the State Secretary of R+D+I, and FEDER/FSE [PI19/319, 18/287, 16/609 and 15/75].

Competing Interests:

The authors declare they have no actual or potential competing financial interests.

Table 1. Baseline characteristics of study participants by categories of blood cadmium (n=2548).

Characteristics	Blood cadmium (µg/L)						
		Below LOD	Quartiles of the distribution of values > the LOD				
	All	<LOD	Q1 (LOD-0.16)	Q2 (0.17-0.24)	Q3 (0.25-0.45)	Q4 (0.46-7.10)	p-val[†]
N	2548	1078	368	367	368	367	
Age,y, mean (SD)	71.6 (4.4)	72.1 (4.6)	71.3 (4.1)	71.8 (4.5)	71.2 (4.2)	70.5 (3.9)	<0.00
Male, n (%)	1199 (47.1)	515 (47.8)	152 (41.3)	164 (44.7)	159 (43.2)	209 (57.0)	<0.00
< High School education, n (%)	454 (17.8)	184 (17.1)	76 (20.7)	69 (18.8)	66 (17.9)	59 (16.1)	0.49
Tobacco exposure							
Never smokers, n (%)	1341 (52.6)	733 (68.0)	221 (60.0)	190 (51.8)	150 (40.7)	47 (12.8)	
Former smokers, n (%)	967 (38.0)	327 (30.3)	135 (36.7)	159 (43.3)	202 (54.9)	144 (39.2)	
Current smokers, n (%)	240 (9.4)	18 (1.7)	12 (3.3)	18 (4.9)	16 (4.4)	176 (48.0)	<0.00
Non-smokers exposed to SHS, n (%)[§]	185 (8.0)	77 (7.3)	32 (9.0)	27 (7.7)	26 (7.7)	23 (12.1)	0.22
Alcohol consumption							
Never	488 (19.2)	237 (22.0)	62 (16.9)	81 (22.1)	63 (17.1)	45 (12.3)	
Moderate drinker	1769 (69.4)	724 (67.2)	263 (71.5)	252 (68.7)	260 (70.7)	270 (73.6)	
Heavy drinker	127 (5.0)	37 (3.4)	17 (4.6)	11 (3.0)	24 (6.5)	38 (10.4)	
Ex-drinker	164 (6.4)	80 (7.4)	26 (7.1)	23 (6.3)	21 (5.7)	14 (3.8)	<0.00
BMI ≥30	665 (26.1)	285 (26.4)	97 (26.4)	105 (28.6)	101 (27.5)	77 (21.0)	0.16
MDS, mean (SD)	4.3 (1.6)	4.3 (1.6)	4.3 (1.6)	4.4 (1.7)	4.4 (1.6)	4.3 (1.6)	0.51
Leisure-time PA, METs-h/w mean (SD)	66.8 (36.3)	67.9 (36.2)	67.5 (36.8)	64.9 (34.7)	69.1 (37.3)	62.6 (36.4)	0.14
Television viewing time, h/w mean (SD)	22.3 (11.0)	22.3 (10.7)	21.9 (10.6)	21.9 (10.8)	22.7 (11.1)	22.4 (12.1)	0.79
Hypertension, n (%)	1739 (68.3)	735 (68.2)	252 (68.5)	250 (68.1)	241 (65.5)	261 (71.1)	0.61
Cardiovascular disease, n (%)	88 (3.5)	35 (3.3)	8 (2.1)	17 (4.6)	18 (4.9)	10 (2.7)	0.24
Diabetes mellitus, n (%)	530 (20.8)	251 (23.3)	80 (21.7)	68 (18.5)	58 (15.8)	73 (19.9)	0.02
Dyslipidemia, n (%)	1467(57.6)	591 (54.8)	208 (56.5)	224 (61.0)	229 (62.2)	215 (59.6)	0.07
Osteoarthritis, n (%)	1104 (43.6)	510 (47.6)	146 (40.0)	164 (45.2)	152 (41.3)	132 (36.1)	0.01
Depression, n (%)	328 (13.1)	146 (13.8)	37 (10.2)	53 (14.7)	46 (12.6)	46 (12.6)	0.40

Q: Quartiles; LOD: Limit of detection

[†] P-values for the null hypothesis that there are no differences in participants characteristics by Cd categories were derived from chi-square (categorical variables) or ANOVA tests (continuous outcomes).

[§]Based on 2,307 non-smokers with this information available

Table 2: Cross-sectional association between blood cadmium concentrations and measures of physical performance and disability in older adults. Results are Odds Ratios and their 95% confidence intervals.

Cd (μg/L)	LowPCS			Low SPPB			Low grip strength			Mobility limitations			Frailty			IADL disability		
	n/ total	**OR (95%CI) M1**	**M2**	**n/ total**	**OR (95%CI) M1**	**M2**	**n/ total**	**OR (95%CI) M1**	**M2**	**n/ total**	**OR (95%CI) M1**	**M2**	**n/ total**	**OR (95%CI) M1**	**M2**	**n/ total**	**OR (95%CI) M1**	**M2**
Overall sample																		
< LOD	97/ 981	Ref.	Ref.	152/ 997	Ref.	Ref.	128/ 997	Ref.	Ref.	366/ 989	Ref.	Ref.	87/ 1000	Ref.	Ref.	66/ 995	Ref	Ref
LOD-0.16	28/ 340	0.89 (0.57;1.39)	1.07 (0.66;1.72)	48/ 339	1.06 (0.74;1.54)	1.18 (0.81;1.73)	40/ 342	1.04 (0.70;1.53)	1.17 (0.78;1.75)	121/ 341	0.90 (0.69;1.19)	1.00 (0.74;1.33)	31/ 343	1.18 (0.71;1.97)	1.07 (0.65;1.79)	22/ 340	1.15 (0.68;1.93)	1.39 (0.78;2.38)
0.17-0.24	33/ 338	1.03 (0.68;1.58)	1.17 (0.74;1.83)	59/ 342	1.28 (0.90;1.82)	1.35 (0.94;1.95)	41/ 346	0.97 (0.66;1.44)	0.97 (0.65;1.45)	135/ 341	1.12 (0.85;1.48)	1.14 (0.85;1.53)	33/ 346	1.44 (0.87;2.36)	1.24 (0.76;2.03)	29/ 345	1.46 (0.91;2.36)	1.46 (0.87;2.45)
0.25-0.45	34/ 340	1.13 (0.74;1.72)	1.38 (0.87;2.19)	44 /342	1.03 (0.70;1.51)	1.21 (0.81;1.80)	43/ 341	1.22 (0.82;1.81)	1.34 (0.89;2.01)	133/ 341	1.11 (0.84;1.46)	1.28 (0.96;1.72)	30/ 342	1.31 (0.77;2.21)	1.30 (0.78;2.16)	22/ 342	1.32 (0.78;2.25)	1.82 (1.08;3.32)
0.46-7.10	32/ 327	1.39 (0.84;2.29)	1.86 (1.08;3.21)	35/ 331	1.09 (0.67;1.76)	1.34 (0.82;2.19)	29/ 332	1.03 (0.62;1.74)	1.20 (0.71;2.04)	115/ 331	1.27 (0.91;1.78)	1.51 (1.06;2.15)	31/ 333	2.26 (1.19;4.40)	1.88 (1.00;3.53)	19/ 331	1.59 (0.81;3.11)	2.37 (1.15;4.86)
***p-trend*†**		0.16	0.02		0.74	0.23		0.56	0.27		0.10	0.01		0.02	0.05		0.08	<0.01
Per log2	224/ 2326	1.08 (0.96;1.21)	1.16 (1.03;1.31)	338/ 2351	1.02 (0.92;1.13)	1.08 (0.97;1.20)	281/ 2358	1.07 (0.96;1.19)	1.10 (0.98;1.23)	870/ 2343	1.06 (0.99;1.15)	1.11 (1.02;1.20)	212/ 2364	1.19 (1.03;1.37)	1.16 (1.02;1.33)	158/ 2353	1.14 (0.99;1.31)	1.26 (1.08;1.47)
Excluding smokers																		
< LOD	97/ 964	Ref.	Ref.	150/ 980	Ref.	Ref.	128/ 980	Ref.	Ref.	364/ 972	Ref.	Ref.	87/ 983	Ref.	Ref.	66/ 978	Ref	Ref
LOD-0.16	27/ 328	0.87 (0.56;1.37)	1.03 (0.63;1.69)	47/ 327	1.08 (0.75;1.57)	1.22 (0.83;1.79)	39/ 330	1.02 (0.69;1.52)	1.16 (0.77;1.75)	119/ 329	0.90 (0.68; 1.18)	1.00 (0.75;1.34)	31/ 331	1.24 (0.74;2.07)	1.13 (0.68;1.88)	22/ 328	1.19 (0.71;2.01)	1.50 (0.85;2.63)
0.17-0.24	33/ 326	1.05 (0.69;1.60)	1.17 (0.74;1.85)	57/ 327	1.28 (0.90;1.82)	1.39 (0.96;2.01)	40/ 331	0.96 (0.65;1.542)	0.97 (0.65;1.46)	132/ 327	1.11 (0.85; 1.45)	1.13 (0.85;1.52)	33/ 331	1.47 (0.90;2.42)	1.27 (0.81;2.26)	28/ 330	1.44 (0.89;2.35)	1.46 (0.86;2.49)
0.25-0.45	33/ 324	1.12 (0.77;1.72)	1.37 (0.86;2.20)	43/ 326	1.05 (0.71;1.54)	1.25 (0.84;1.87)	43/ 325	1.24 (0.84;1.84)	1.37 (0.91;2.06)	128/ 325	1.11 (0.84;1.46)	1.28 (0.93;1.71)	30/ 326	1.34 (0.79;2.27)	1.33 (0.77;2.09)	21/ 326	1.31 (0.77;2.25)	2.00 (1.12;3.56)
0.46-2.97	20/ 176	1.31 (0.79;2.19)	1.84 (1.03;3.29)	21/ 178	1.10 (0.65;1.85)	1.35 (0.79;2.30)	14/ 178	0.80 (0.43;1.46)	0.95 (0.51;1.76)	66 /178	1.32 (0.95; 1.85)	1.48 (1.00;2.17)	13/ 179	1.63 (0.78;3.39)	1.35 (0.65;2.73)	9/ 178	1.41 (0.66;3.03)	2.34 (1.05;5.48)
***p-trend*†**		0.26	0.03		0.68	0.20		0.88	0.48		0.09	0.02		0.09	0.10		0.14	<0.01
Per log2	210/ 2118	1.05 (0.93;1.18)	1.14 (1.00;1.30)	318/ 2138	1.04 (0.94;1.16)	1.11 (1.00;1.25)	264/ 2144	1.03 (0.92;1.16)	1.07 (0.95;1.21)	809/ 2131	1.07 (1.00;1.16)	1.09 (1.00;1.19)	194/ 2150	1.14 (0.99;1.32)	1.12 (0.96;1.28)	146/ 2140	1.10 (0.95;1.28)	1.25 (1.06;1.48)

PCS: Physical Component Summary; SPPB: Short Physical Performance Battery; IADL: Instrumental Activities of Daily Living.
Model 1 (M1) was adjusted for sex and smoking status (never, former, current). Model 2 (M2) was further adjusted for smoking intensity (cigarettes/day), educational level (<high school, high school, >high school), diet quality (sex-specific tertiles of the MDS), alcohol drinking (never, ex-, moderate and heavy drinker), total recreational and household physical activity (sex-specific tertiles), television viewing time (sex-specific tertiles), body mass index (kg/m^2), hypertension (yes/no), cardiovascular disease (yes/no), diabetes (yes/no), dyslipidemia (yes/no), osteoarthritis (yes/no), and depression (yes/no). Cutoff values for sex-specific tertiles of physical activity in men and women were, respectively: 40-68 METS-h/wk and 56-86 METS-h/wk. Corresponding values for sex-specific tertiles of television viewing time were 14-25 hours/week and 20-28 hours/week.

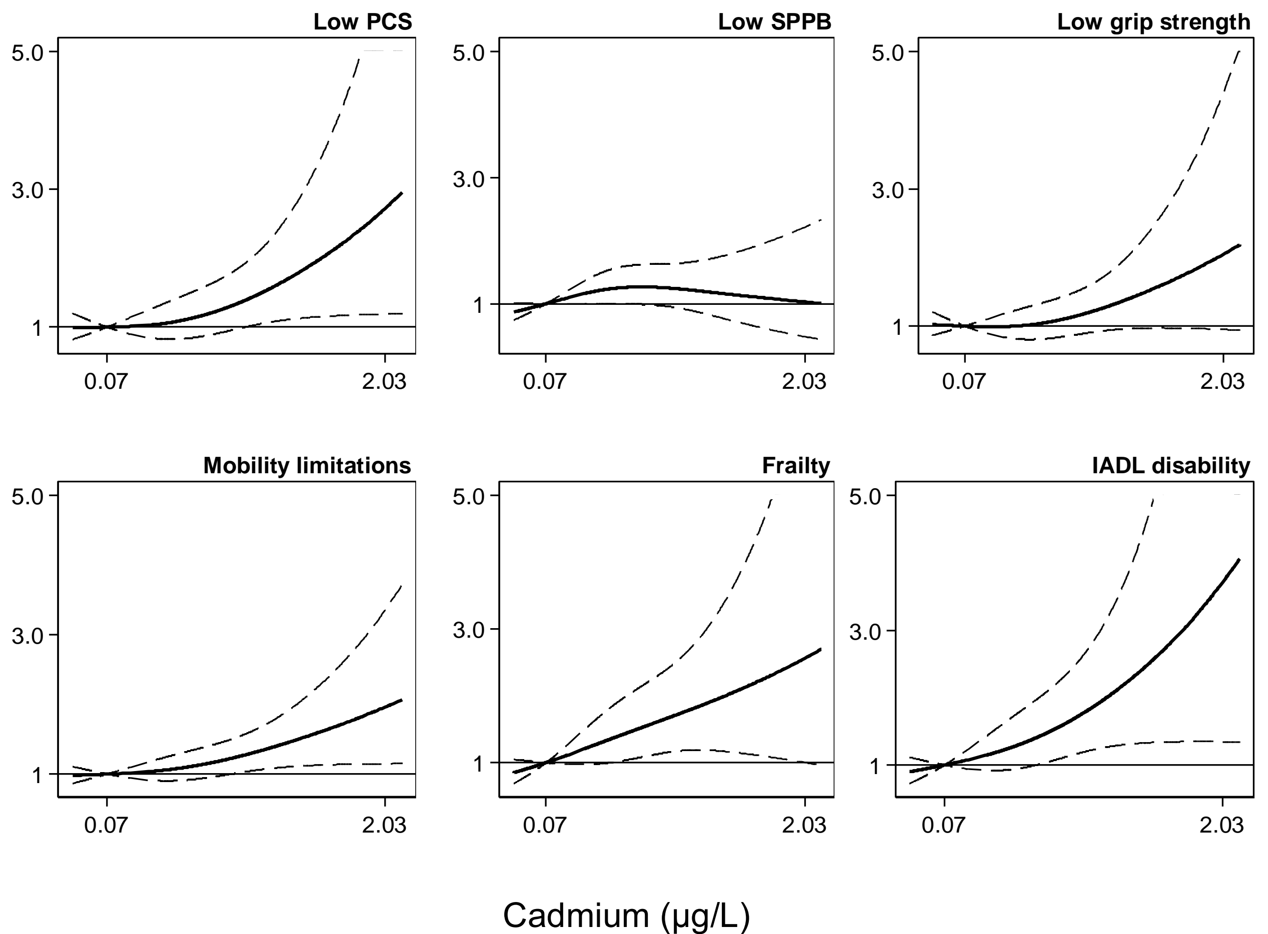
Table 3: Prospective association between blood cadmium concentrations and measures of physical performance and disability in older adults. Results are Hazard Ratios (HR) and their 95% confidence intervals (95%CI).

Cd (µg/L)	Low PCS			Low SPPB			Low grip strength			Mobility Limitations			Frailty		
	cases/ individuals at risk	HR (95%CI) M1	M2	cases/ individuals at risk	HR (95%CI) M1	M2	cases/ individuals at risk	HR (95%CI) M1	M2	cases/ individuals at risk	HR (95%CI) M1	M2	cases/ individuals at risk	HR (95%CI) M1	M2†
Overall sample															
< LOD	37/884	Ref.	Ref.	87/717	Ref	Ref	113/869	Ref.	Ref	87/623	Ref.	Ref.	40/913	Ref.	Ref.
LOD-0.16	10/312	1.22	1.18	40/255	1.55	1.56	46/302	1.23	1.23	28/220	0.86	0.88	12/312	1.11	1.85
		(0.59;2.52)	(0.55;2.54)		(1.06;2.28)	(1.06;2.29)		(0.87;1.74)	(0.87;1.75)		(0.56;1.32)	(0.57;1.36)		(0.58;2.15)	(0.44;2.15)
0.17-0.24	15/305	1.40	1.40	45/249	1.68	1.64	45/305	1.16	1.11	23/206	0.83	0.92	20/313	1.50	1.23
		(0.70;2.80)	(0.70;2.81)		(1.16;2.42)	(1.14;2.40)		(0.81;1.64)	(0.78;1.58)		(0.52;1.32)	(0.58;1.47)		(0.85;2.64)	(0.71;2.64)
0.25-0.45	15/306	1.90	2.15	33/263	1.23	1.31	43/298	1.15	1.16	36/212	1.24	1.31	18/312	1.79	1.42
		(0.99;3.67)	(1.10;5.18)		(0.82; 1.86)	(0.86; 1.98)		(0.80;1.65)	(0.80;1.67)		(0.83;1.85)	(0.87;2.00)		(1.00;3.19)	(0.82;3.19)
0.46-7.10	13/295	2.10	2.15	38/265	1.45	1.58	33/303	0.87	0.87	27/208	0.85	0.92	13/302	1.88	1.73
		(0.96;4.61)	(0.96;4.81)		(0.91; 2.29)	(1.10; 2.53)		(0.55;1.39)	(0.54;1.39)		(0.50;1.44)	(0.53;1.60)		(1.00;3.91)	(0.86;3.91)
***p-trend*†**		0.02	0.01		0.06	0.03		0.93	0.96		0.95	0.62		0.02	0.07
Per log2	90/2102	1.23	1.25	243/1749	1.12	1.14	280/2077	1.02	1.02	202/1473	1.00	1.03	103/2152	1.21	1.16
		(1.02;1.48)	(1.03;1.51)		(1.01; 1.24)	(1.03; 1.27)		(0.93;1.13)	(0.92;1.13)		(0.89;1.13)	(0.91;1.16)		(1.03;1.42)	(1.00;1.35)
Excluding smokers															
< LOD	37/867	Ref.	Ref.	86/706	Ref	Ref	113/852	Ref	Ref	82/608	Ref.	Ref.	40/896	Ref	Ref
LOD-0.16	9/301	1.10	1.18	39/245	1.57	1.56	43/291	1.18	1.19	26/210	0.89	0.91	11/300	0.94	0.81
		(0.52;2.34)	(0.55;2.53)		(1.07;2.31)	(1.06;2.31)		(0.82;1.67)	(0.83;1.69)		(0.57;1.39)	(0.58;1.43)		(0.48;1.85)	(0.42;1.58)
0.17-0.24	15/293	1.43	1.47	41/236	1.62	1.61	42/291	1.11	1.04	23/195	0.89	0.94	19/298	1.44	1.21
		(0.71;2.84)	(0.73;2.96)		(1.11;2.37)	(1.10;2.37)		(0.78;1.59)	(0.73;1.50)		(0.55;1.44)	(0.58;1.53)		(0.82;2.53)	(0.69;2.10)
0.25-0.45	15/291	1.94	2.27	31/251	1.19	1.25	41/282	1.15	1.17	34/195	1.33	1.42	17/296	1.47	1.41
		(1.01;3.75)	(1.16;4.46)		(0.80; 1.81)	(0.81; 1.92)		(0.80;1.67)	(0.80;1.69)		(0.88;2.03)	(0.92;2.17)		(0.82;2.65)	(0.80;2.49)
0.46-2.97	8/156	2.08	2.33	21/142	1.48	1.65	17/164	0.85	0.90	14/197	1.04	1.16	9/166	1.67	1.90
		(0.91;4.73)	(1.;5.41)		(0.90; 2.42)	(1.00; 2.73)		(0.50;1.43)	(0.53;1.52)		(0.58;1.87)	(0.64;2.10)		(0.79;3.53)	(0.96;3.92)
***p-trend*†**		0.02	<0.01		0.08	0.04		0.90	0.84		0.42	0.24		0.07	0.06
Per log2	84/1908	1.22	1.27	218/1580	1.12	1.14	256/1880	1.01	1.02	179/1322	1.05	1.08	96/1956	1.16	1.16
		(1.00;1.47)	(1.04;1.54)		(1.00; 1.25)	(1.02; 1.28)		(0.91;1.13)	(0.91;1.13)		(0.92;1.19)	(0.95;1.23)		(0.98;1.37)	(0.99;1.37)

PCS: Physical Component Summary; SPPB: Short Physical Performance Battery.

Model 1 (M1) was adjusted for sex, age and smoking status (never, former, current). Model 2 (M2) was further adjusted for smoking intensity, educational level (<high school, high school, >high school), diet quality (sex-specific tertiles of the MDS), alcohol drinking (never, ex-, moderate and heavy drinker), physical activity (sex-specific tertiles), television viewing time (sex-specific tertiles), body mass index (kg/m2), hypertension (yes/no), cardiovascular disease (yes/no), diabetes (yes/no), dyslipidemia (yes/no), osteoarthritis (yes/no), and depression (yes/no). Cutoff values for sex-specific tertiles of physical activity in men and women were, respectively: 40-68 METS-h/wk and 56-86 METS-h/wk. Corresponding values for sex-specific tertiles of television viewing time were 14-25 hours/week and 20-28 hours/week.

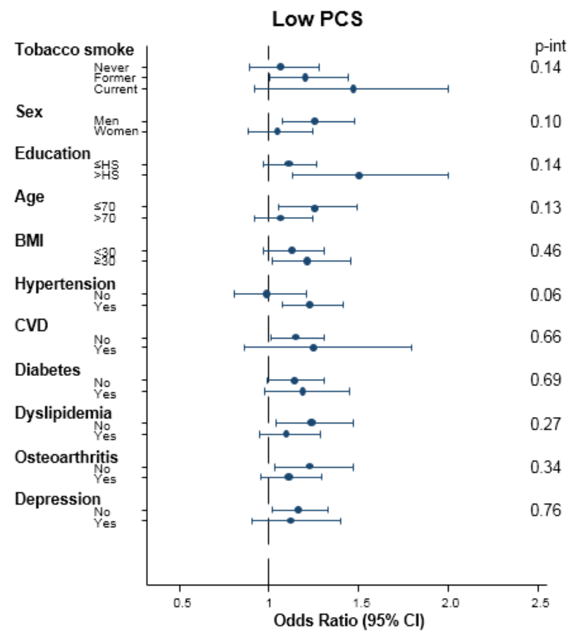
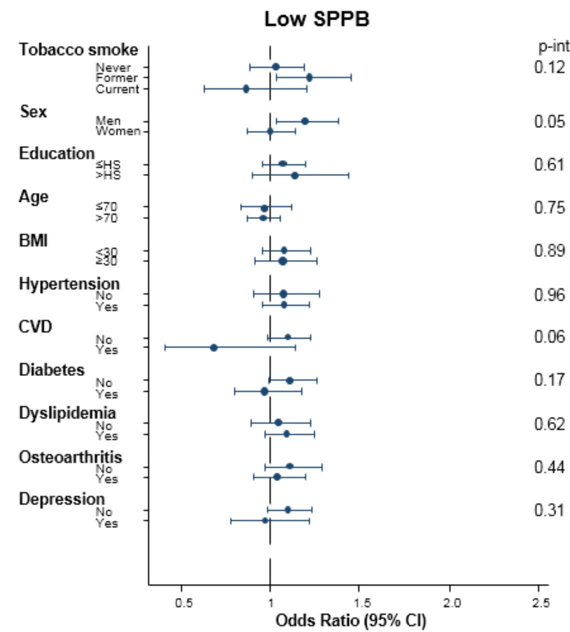
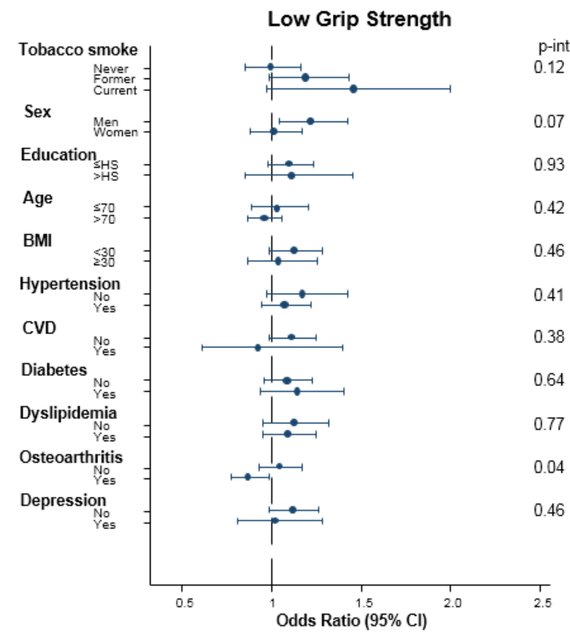
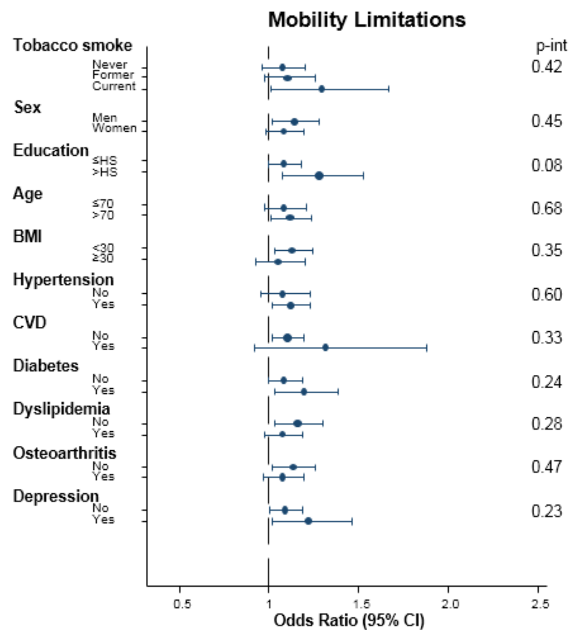
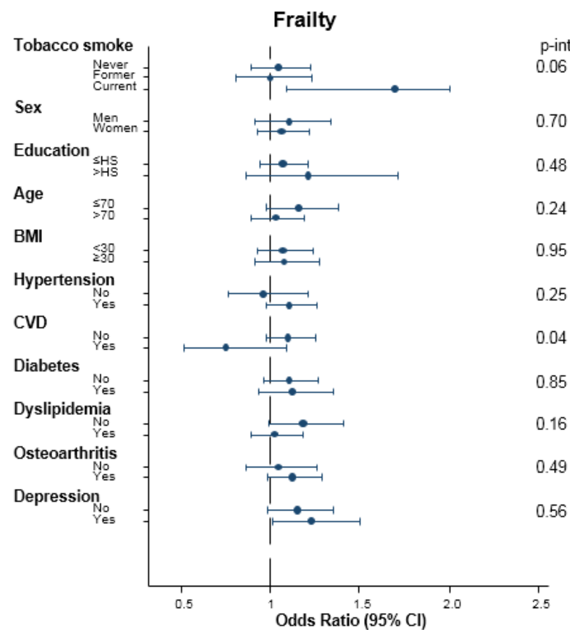
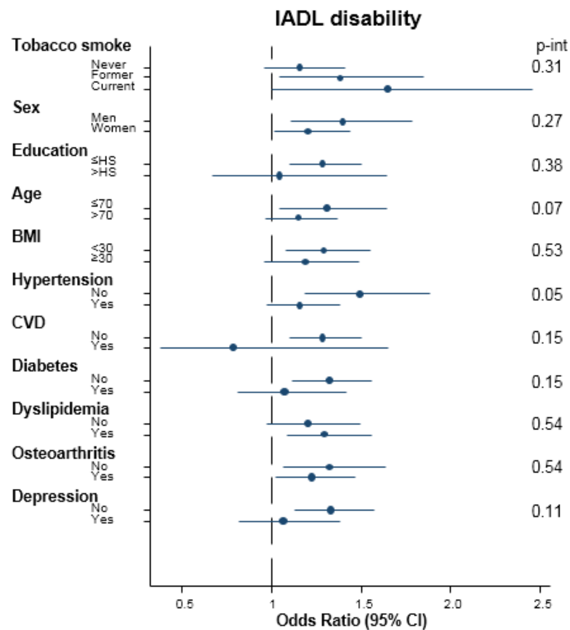
Figure 1: Dose-response association between blood cadmium concentrations (µg/L) and baseline prevalence of physical function limitations in older adults from the Seniors-ENRICA-2 cohort (n=2548)



PCS: Physical Component Summary; SPPB: Short Physical Performance Battery; IADL: Instrumental Activities of Daily Living.

Plotted values show Odds Ratios (solid curves) and 95% confidence intervals (dashed curves) for the association between blood cadmium concentrations and functional limitations. Curves are derived from logistic models using restricted cubic splines and adjust for the same variables as Model 2 in Table 2. The reference was set at the 33.3th percentile of cadmium concentrations (0.07 µg/L).

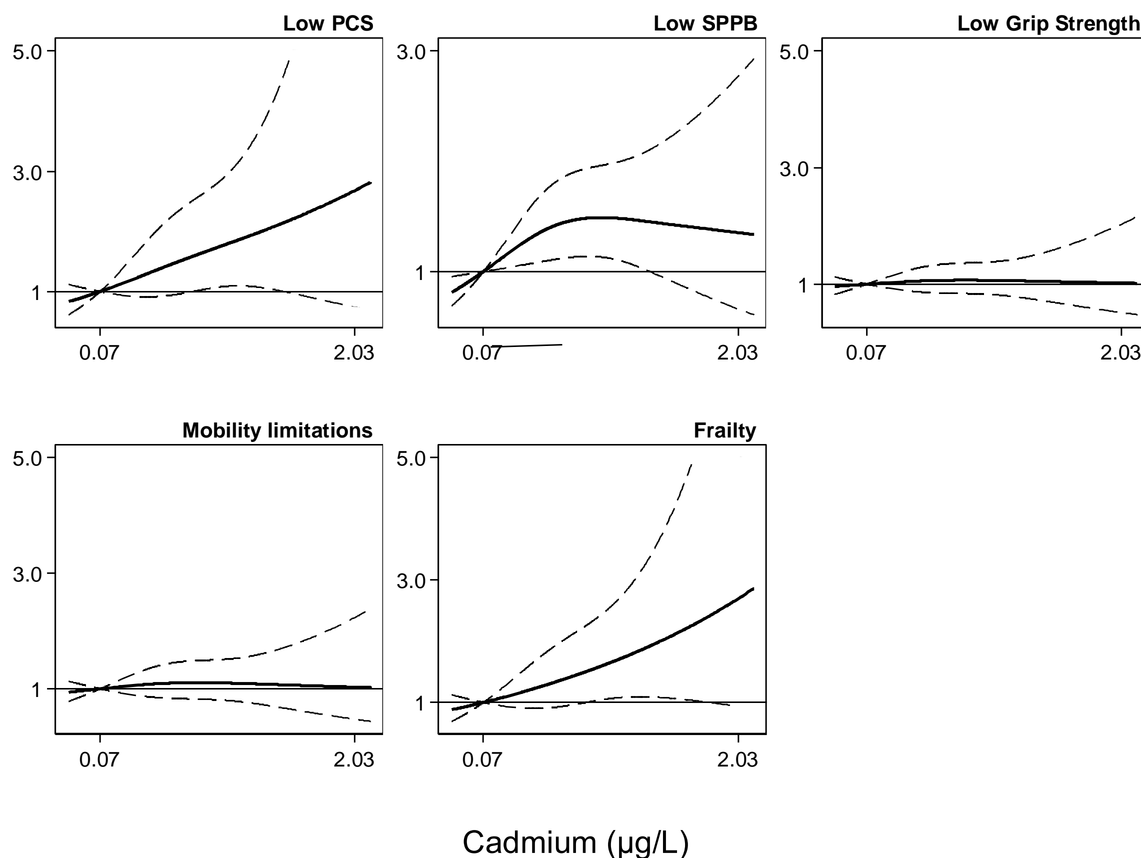
Figure 2 Cross-sectional association between blood cadmium concentrations and measures of physical performance and disability in older adults according to participants characteristics


Low PCS
Tobacco smoke
Never
Former
Current
Sex
Men
Women
Education
≤HS
>HS
Age
≤70
>70
BMI
≤30
≥30
Hypertension
No
Yes
CVD
No
Yes
Diabetes
No
Yes
Dyslipidemia
No
Yes
Osteoarthritis
No
Yes
Depression
No
Yes
p-int
0.14
0.10
0.14
0.13
0.46
0.06
0.66
0.69
0.27
0.34
0.76
0.5
1
1.5
2.0
2.5
Odds Ratio (95% CI)

Low SPPB
Tobacco smoke
Never
Former
Current
Sex
Men
Women
Education
≤HS
>HS
Age
≤70
>70
BMI
≤30
≥30
Hypertension
No
Yes
CVD
No
Yes
Diabetes
No
Yes
Dyslipidemia
No
Yes
Osteoarthritis
No
Yes
Depression
No
Yes
p-int
0.12
0.05
0.61
0.75
0.89
0.96
0.06
0.17
0.62
0.44
0.31
0.5
1
1.5
2.0
2.5
Odds Ratio (95% CI)

Low Grip Strength
Tobacco smoke
Never
Former
Current
Sex
Men
Women
Education
≤HS
>HS
Age
≤70
>70
BMI
≤30
≥30
Hypertension
No
Yes
CVD
No
Yes
Diabetes
No
Yes
Dyslipidemia
No
Yes
Osteoarthritis
No
Yes
Depression
No
Yes
p-int
0.12
0.07
0.93
0.42
0.46
0.41
0.38
0.64
0.77
0.04
0.46
0.5
1
1.5
2.0
2.5
Odds Ratio (95% CI)

Mobility Limitations
Tobacco smoke
Never
Former
Current
Sex
Men
Women
Education
≤HS
>HS
Age
≤70
>70
BMI
≤30
≥30
Hypertension
No
Yes
CVD
No
Yes
Diabetes
No
Yes
Dyslipidemia
No
Yes
Osteoarthritis
No
Yes
Depression
No
Yes
p-int
0.42
0.45
0.08
0.68
0.35
0.60
0.33
0.24
0.28
0.47
0.23
0.5
1
1.5
2.0
2.5
Odds Ratio (95% CI)

Frailty
Tobacco smoke
Never
Former
Current
Sex
Men
Women
Education
≤HS
>HS
Age
≤70
>70
BMI
≤30
≥30
Hypertension
No
Yes
CVD
No
Yes
Diabetes
No
Yes
Dyslipidemia
No
Yes
Osteoarthritis
No
Yes
Depression
No
Yes
p-int
0.06
0.70
0.48
0.24
0.95
0.25
0.04
0.85
0.16
0.49
0.56
0.5
1
1.5
2.0
2.5
Odds Ratio (95% CI)

IADL disability
Tobacco smoke
Never
Former
Current
Sex
Men
Women
Education
≤HS
>HS
Age
≤70
>70
BMI
≤30
≥30
Hypertension
No
Yes
CVD
No
Yes
Diabetes
No
Yes
Dyslipidemia
No
Yes
Osteoarthritis
No
Yes
Depression
No
Yes
p-int
0.31
0.27
0.38
0.07
0.53
0.05
0.15
0.15
0.54
0.54
0.11
0.5
1
1.5
2.0
2.5
Odds Ratio (95% CI)

PCS: Physical Component Summary; SPPB: Short Physical Performance Battery; IADL: Instrumental Activities of Daily Living.

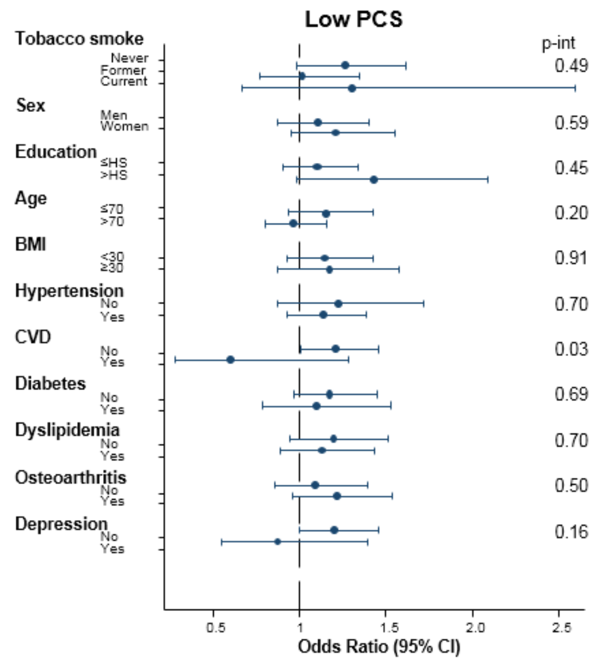
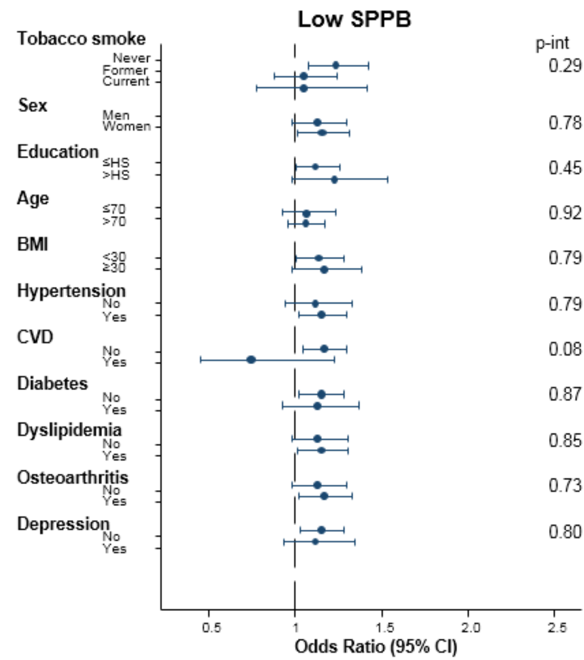
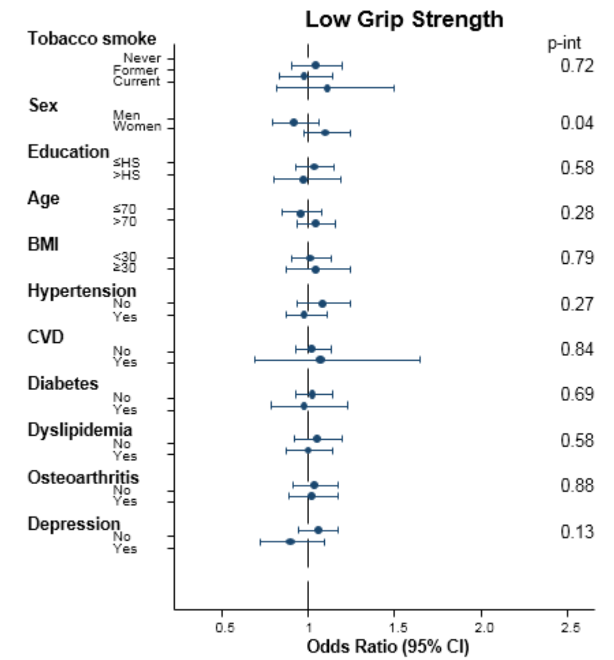
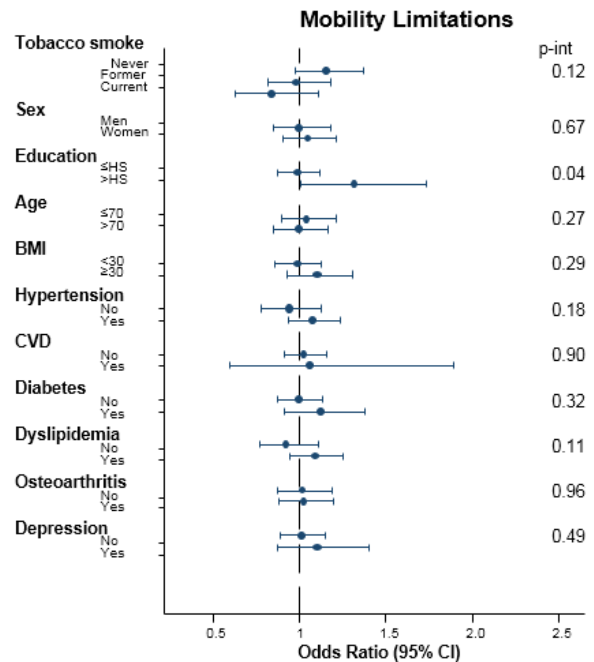
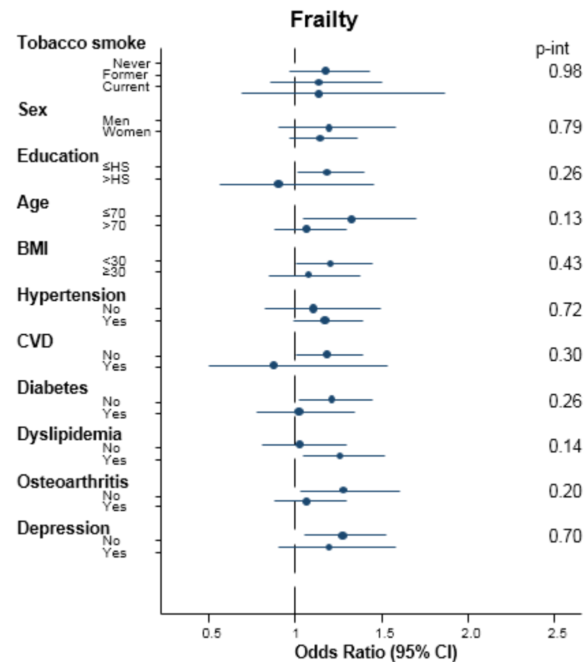
Odds ratios (points) and 95% confidence intervals (CIs, horizontal lines) were obtained from logistic regression models with interactions between log-transformed imputed cadmium concentrations and the corresponding subgroups. Models adjusted for sex, age, smoking status, smoking intensity, educational level, diet quality, alcohol drinking, physical activity, television viewing time, body mass index, hypertension, cardiovascular disease, diabetes, dyslipidemia, osteoarthritis, and depression. P-values for interaction (p-int) were calculated with likelihood ratio tests.

Figure 3: Dose-response association between blood cadmium concentrations (µg/L) and incidence of physical function limitations in older adults from the Seniors-ENRICA-2 cohort followed from baseline (2015-2017) to wave 1 (2019)



PCS: Physical Component Summary; SPPB: Short Physical Performance Battery.
Plotted values show Hazard ratios (solid curves) and 95% confidence intervals (dashed curves) for the association between blood cadmium concentrations and functional limitations. Curves are derived from Cox regression models using restricted cubic splines and adjust for the same variables as Model 2 in Table 3. The reference was set at the 33.3th percentile of cadmium concentrations (0.07 µg/L).
Note: prospective analyses for IADL disability could not be performed because of the low number of incident cases.

Figure 4: Prospective association between blood cadmium concentrations and measures of physical performance and disability in older adults according to participants characteristics.


Low PCS
Tobacco smoke
Never
Former
Current
Sex
Men
Women
Education
≤HS
>HS
Age
≤70
>70
BMI
<30
≥30
Hypertension
No
Yes
CVD
No
Yes
Diabetes
No
Yes
Dyslipidemia
No
Yes
Osteoarthritis
No
Yes
Depression
No
Yes
p-int
0.49
0.59
0.45
0.20
0.91
0.70
0.03
0.69
0.70
0.50
0.16
0.5
1
1.5
2.0
2.5
Odds Ratio (95% CI)

Low SPPB
Tobacco smoke
Never
Former
Current
Sex
Men
Women
Education
≤HS
>HS
Age
≤70
>70
BMI
<30
≥30
Hypertension
No
Yes
CVD
No
Yes
Diabetes
No
Yes
Dyslipidemia
No
Yes
Osteoarthritis
No
Yes
Depression
No
Yes
p-int
0.29
0.78
0.45
0.92
0.79
0.79
0.08
0.87
0.85
0.73
0.80
0.5
1
1.5
2.0
2.5
Odds Ratio (95% CI)

Low Grip Strength
Tobacco smoke
Never
Former
Current
Sex
Men
Women
Education
≤HS
>HS
Age
≤70
>70
BMI
<30
≥30
Hypertension
No
Yes
CVD
No
Yes
Diabetes
No
Yes
Dyslipidemia
No
Yes
Osteoarthritis
No
Yes
Depression
No
Yes
p-int
0.72
0.04
0.58
0.28
0.79
0.27
0.84
0.69
0.58
0.88
0.13
0.5
1
1.5
2.0
2.5
Odds Ratio (95% CI)

Mobility Limitations
Tobacco smoke
Never
Former
Current
Sex
Men
Women
Education
≤HS
>HS
Age
≤70
>70
BMI
<30
≥30
Hypertension
No
Yes
CVD
No
Yes
Diabetes
No
Yes
Dyslipidemia
No
Yes
Osteoarthritis
No
Yes
Depression
No
Yes
p-int
0.12
0.67
0.04
0.27
0.29
0.18
0.90
0.32
0.11
0.96
0.49
0.5
1
1.5
2.0
2.5
Odds Ratio (95% CI)

Frailty
Tobacco smoke
Never
Former
Current
Sex
Men
Women
Education
≤HS
>HS
Age
≤70
>70
BMI
<30
≥30
Hypertension
No
Yes
CVD
No
Yes
Diabetes
No
Yes
Dyslipidemia
No
Yes
Osteoarthritis
No
Yes
Depression
No
Yes
p-int
0.98
0.79
0.26
0.13
0.43
0.72
0.30
0.26
0.14
0.20
0.70
0.5
1
1.5
2.0
2.5
Odds Ratio (95% CI)

PCS: Physical Component Summary; SPPB: Short Physical Performance Battery.
Hazard ratios (points) and 95% confidence intervals (CIs, horizontal lines) were obtained from Cox regression models with interactions between log-transformed imputed blood cadmium concentrations and the corresponding subgroups. Models adjusted for sex, age, smoking status, smoking intensity, educational level, diet quality, alcohol drinking, physical activity, television viewing time, body mass index, hypertension, cardiovascular disease, diabetes, dyslipidemia, osteoarthritis, and depression. P-values for interaction (p-int) were calculated with likelihood ratio tests.

Bibliography:

ATSDR - Toxicological Profile: Cadmium. Available at: https://www.atsdr.cdc.gov/toxprofiles/tp.asp?id=48&tid=15. Last accessed: July 2020

Bagis, S., Sahin, G., Yapici, Y., Cimen, O. B., & Erdogan, C. (2003). The effect of hand osteoarthritis on grip and pinch strength and hand function in postmenopausal women. *Clinical Rheumatology*, *22*(6), 420-424. https://doi.org/10.1007/s10067-003-0792-4

Barregard, L., Sallsten, G., Fagerberg, B., Borné, Y., Persson, M., Hedblad, B., & Engström, G. (2016). Blood Cadmium Levels and Incident Cardiovascular Events during Follow-up in a Population-Based Cohort of Swedish Adults: The Malmö Diet and Cancer Study. *Environ Health Perspect*, *124*(5), 594-600. https://doi.org/10.1289/ehp.1509735

Borné, Y., Barregard, L., Persson, M., Hedblad, B., Fagerberg, B., & Engström, G. (2015). Cadmium exposure and incidence of heart failure and atrial fibrillation: A population-based prospective cohort study. *BMJ Open*, *5*(6), e007366. https://doi.org/10.1136/bmjopen-2014-007366

Braga, M. F. M., & Rowan, E. G. (1994). The pharmacological effects of cadmium on skeletal neuromuscular transmission. *General Pharmacology: The Vascular System*, *25*(8), 1729-1739. https://doi.org/10.1016/0306-3623(94)90379-4

Braga, M. F., & Rowan, E. G. (1992). Reversal by cysteine of the cadmium-induced block of skeletal neuromuscular transmission in vitro. *Br J Pharmacol*, *107*(1), 95-100. https://doi.org/10.1111/j.1476-5381.1992.tb14468.x

Cakmak, S., Dales, R., Kauri, L. M., Mahmud, M., Van Ryswyk, K., Vanos, J., Liu, L., Kumarathasan, P., Thomson, E., Vincent, R., & Weichenthal, S. (2014). Metal composition of fine particulate air pollution and acute changes in cardiorespiratory physiology. *Environ Pollut*, *189*, 208-214. https://doi.org/10.1016/j.envpol.2014.03.004

Cesari, M., Kritchevsky, S. B., Nicklas, B., Kanaya, A. M., Patrignani, P., Tacconelli, S., Tranah, G. J., Tognoni, G., Harris, T. B., Incalzi, R. A., Newman, A. B., Pahor, M., & Health ABC study. (2012). Oxidative damage, platelet activation, and inflammation to predict mobility disability and mortality in older persons: Results from the health aging and body composition study. *J Gerontol A Biol Sci Med Sci. 67*(6), 671-676. https://doi.org/10.1093/gerona/glr246

Chen, C., Xun, P., Tsinovoi, C., McClure, L. A., Brockman, J., MacDonald, L., Cushman, M., Cai, J., Kamendulis, L., Mackey, J., & He, K. (2018). Urinary cadmium concentration and the risk of ischemic stroke. *Neurology*, *91*(4), e382-e391. https://doi.org/10.1212/WNL.0000000000005856

Chen, Y.-Y., Wang, C.-C., Kao, T.-W., Wu, C.-J., Chen, Y.-J., Lai, C.-H., Zhou, Y.-C., & Chen, W.-L. (2020). The relationship between lead and cadmium levels and functional dependence among elderly participants. *Environ Sci Pollut Res Int.*, *27*(6), 5932-5940. https://doi.org/10.1007/s11356-019-07381-3

Cheng, X., Niu, Y., Ding, Q., Yin, X., Huang, G., Peng, J., & Song, J. (2016). Cadmium Exposure and Risk of Any Fracture: A PRISMA-Compliant Systematic Review and Meta-Analysis. *Medicine*, *95*(10), e2932. https://doi.org/10.1097/MD.0000000000002932

Domingo-Relloso, A., Grau-Perez, M., Galan-Chilet, I., Garrido-Martinez, M. J., Tormos, C., Navas-Acien, A., Gomez-Ariza, J. L., Monzo-Beltran, L., Saez-Tormo, G., Garcia-Barrera, T., Dueñas Laita, A., Briongos Figuero, L. S., Martin-Escudero, J. C., Chaves, F. J., Redon, J., & Tellez-Plaza, M. (2019). Urinary metals and metal mixtures and oxidative stress biomarkers in an adult population from Spain: The Hortega Study. *Environ Int 123*, 171-180. https://doi.org/10.1016/j.envint.2018.11.055

Dorr, D. A., Jones, S. S., Burns, L., Donnelly, S. M., Brunker, C. P., Wilcox, A., & Clayton, P. D. (2006). Use of health-related, quality-of-life metrics to predict mortality and hospitalizations in community-dwelling seniors. *J Am Geriatr Soc*, *54*(4), 667-673. https://doi.org/10.1111/j.1532-5415.2006.00681.x

Egwuogu, H., Shendell, D. G., Okosun, I. S., & Goodfellow, L. (2009). The effect of urinary cadmium on cardiovascular fitness as measured by VO2 max in white, black and Mexican Americans. *Environ Res*, *109*(3), 292-300. https://doi.org/10.1016/j.envres.2008.11.010

Engström, A., Michaëlsson, K., Suwazono, Y., Wolk, A., Vahter, M., & Akesson, A. (2011). Long-term cadmium exposure and the association with bone mineral density and fractures in a population-based study among women. *J Bone Miner Res.*, *26*(3), 486-495. https://doi.org/10.1002/jbmr.224

Fagerberg, B., Borné, Y., Barregard, L., Sallsten, G., Forsgard, N., Hedblad, B., Persson, M., & Engström, G. (2017). Cadmium exposure is associated with soluble urokinase plasminogen activator receptor, a circulating marker of inflammation and future cardiovascular disease. *Environ Res*, *152*, 185-191. https://doi.org/10.1016/j.envres.2016.10.019

Gale, C. R., Baylis, D., Cooper, C., & Sayer, A. A. (2013). Inflammatory markers and incident frailty in men and women: The English Longitudinal Study of Ageing. *Age*, *35*(6), 2493-2501. https://doi.org/10.1007/s11357-013-9528-9

Gallagher, C. M., Kovach, J. S., & Meliker, J. R. (2008). Urinary cadmium and osteoporosis in U.S. Women >or= 50 years of age: NHANES 1988-1994 and 1999-2004. *Environ Health Perspect. 116*(10), 1338-1343. https://doi.org/10.1289/ehp.11452

García-Esquinas, E., Carrasco-Rios, M., Navas-Acien, A., Ortolá, R., & Rodríguez-Artalejo, F. (2020). Cadmium exposure is associated with reduced grip strength in US adults. *Environ Res*, *180*, 108819. https://doi.org/10.1016/j.envres.2019.108819

García-Esquinas, Esther, Navas-Acien, A., Pérez-Gómez, B., & Artalejo, F. R. (2015). Association of lead and cadmium exposure with frailty in US older adults. *Environ Res*, *137*, 424-431. https://doi.org/10.1016/j.envres.2015.01.013

García-Esquinas, Esther, Ortolá, R., Prina, M., Stefler, D., Rodríguez-Artalejo, F., & Pastor-Barriuso, R. (2019). Trajectories of Accumulation of Health Deficits in Older Adults: Are There Variations According to Health Domains? *J Am Med Dir Assoc.* https://doi.org/10.1016/j.jamda.2018.12.023

García-Esquinas, Esther, Pollan, M., Tellez-Plaza, M., Francesconi, K. A., Goessler, W., Guallar, E., Umans, J. G., Yeh, J., Best, L. G., & Navas-Acien, A. (2014). Cadmium exposure and cancer mortality in a prospective cohort: The strong heart study. *Environ Health Perspect.. 122*(4), 363-370. https://doi.org/10.1289/ehp.1306587

García-Esquinas, Esther, & Rodríguez-Artalejo, F. (2017). Environmental Pollutants, Limitations in Physical Functioning, and Frailty in Older Adults. *Curr Environ Health Rep.*, *4*(1), 12-20. https://doi.org/10.1007/s40572-017-0128-1

Grau-Perez, M., Pichler, G., Galan-Chilet, I., Briongos-Figuero, L. S., Rentero-Garrido, P., Lopez-Izquierdo, R., Navas-Acien, A., Weaver, V., García-Barrera, T., Gomez-Ariza, J. L., Martín-Escudero, J. C., Chaves, F. J., Redon, J., & Tellez-Plaza, M. (2017). Urine cadmium levels and albuminuria in a general population from Spain: A gene-environment interaction analysis. *Environ In.t*, *106*, 27-36. https://doi.org/10.1016/j.envint.2017.05.008

Guralnik, J. M., Simonsick, E. M., Ferrucci, L., Glynn, R. J., Berkman, L. F., Blazer, D. G., Scherr, P. A., & Wallace, R. B. (1994). A Short Physical Performance Battery Assessing Lower Extremity Function: Association With Self-Reported Disability and Prediction of Mortality and Nursing Home Admission. *J Gerontol.*, *49*(2), M85-M94. https://doi.org/10.1093/geronj/49.2.M85

Harrell, FE. (2001). Regression Modeling Strategies With Applications to Linear Models, Logistic and Ordinal Regression, and Survival Analysis. Springer, New York.

Inglés M, Gambini J, Carnicero JA, García-García FJ, Rodríguez-Mañas L, Olaso-González G, Dromant M, Borrás C, Viña J (2014). Oxidative stress is related to frailty, not to age or sex, in a geriatric population: lipid and protein oxidation as biomarkers of frailty. *J Am Geriatr Soc.,* 62(7):1324-8. https://onlinelibrary.wiley.com/doi/epdf/10.1111/jgs.12876

Ishiyama, D., Yamada, M., Makino, A., Iwasaki, S., Otobe, Y., Shinohara, A., Nishio, N., Kimura, Y., Itagaki, A., Koyama, S., Yagi, M., Matsunaga, Y., Mizuno, K., & Matsushita, K. (2017). The cut-off point of short physical performance battery score for sarcopenia in older cardiac inpatients. *Eur Geriatr Med.*, *8*(4), 299-303. https://doi.org/10.1016/j.eurger.2017.05.001

Kim, J., Garcia-Esquinas, E., Navas-Acien, A., & Choi, Y.-H. (2018). Blood and urine cadmium concentrations and walking speed in middle-aged and older U.S. adults. *Environ Pollut.*, *232*, 97-104. https://doi.org/10.1016/j.envpol.2017.09.022

Kim, K.-N., Lee, M.-R., Choi, Y.-H., Lee, B.-E., & Hong, Y.-C. (2016). Associations of Blood Cadmium Levels With Depression and Lower Handgrip Strength in a Community-Dwelling Elderly Population: A Repeated-Measures Panel Study. *J Gerontol A Biol Sci Med Sci*, *71*(11), 1525-1530. https://doi.org/10.1093/gerona/glw119

Lampe, B. J., Park, S. K., Robins, T., Mukherjee, B., Litonjua, A. A., Amarasiriwardena, C., Weisskopf, M., Sparrow, D., & Hu, H. (2008). Association between 24-Hour Urinary Cadmium and Pulmonary Function among Community-Exposed Men: The VA Normative Aging Study. *Environ Health Perspect.*, *116*(9), 1226-1230. https://doi.org/10.1289/ehp.11265

Lawton, M.P., Brody, E.M.(1969) Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist,9:179-86. https://doi:10.1093/geront/9.3_Part_1.179

Li, H., Wang, Z., Fu, Z., Yan, M., Wu, N., Wu, H., & Yin, P. (2018). Associations between blood cadmium levels and cognitive function in a cross-sectional study of US adults aged 60 years or older. *BMJ Open*, *8*(4), e020533. https://doi.org/10.1136/bmjopen-2017-020533

López-Otín, C., Blasco, M. A., Partridge, L., Serrano, M., & Kroemer, G. (2013). The Hallmarks of Aging. *Cell*, *153*(6), 1194-1217. https://doi.org/10.1016/j.cell.2013.05.039

Lunn, D., Thomas, A., Best, N., & Spiegelhalte. (2000). WinBUGS—a Bayesian modelling framework: Concepts, structure, and extensibility, *Stat Comput.*, *10*, 325-337.

McCall, S. J., Clark, A. B., Luben, R. N., Wareham, N. J., Khaw, K.-T., & Myint, P. K. (2019). Plasma Vitamin C Levels: Risk Factors for Deficiency and Association with Self-Reported Functional Health in the European Prospective Investigation into Cancer-Norfolk. *Nutrients*, *11*(7). https://doi.org/10.3390/nu11071552

Min, J., & Min, K. (2016). Blood cadmium levels and Alzheimer's disease mortality risk in older US adults. *Environ Health*, *15*(1), 1-6. https://doi.org/10.1186/s12940-016-0155-7

Mubeena Mariyath PM, Shahi, M. H., Tayyab, M., Farheen, S., Khanam, N., Tabassum, S., & Ali, A. (2019). Cadmium-induced neurodegeneration and activation of noncanonical sonic hedgehog pathway in rat cerebellum. *J Biochem Mol Toxicol.*, *33*(4), e22274. https://doi.org/10.1002/jbt.22274

Navas-Acien, A., Selvin, E., Sharrett, A. R., Calderon-Aranda, E., Silbergeld, E., & Guallar, E. (2004). Lead, Cadmium, Smoking, and Increased Risk of Peripheral Arterial Disease. *Circulation*, *109*(25), 3196-3201. https://doi.org/10.1161/01.CIR.0000130848.18636.B2

Navas-Acien, A., Tellez-Plaza, M., Guallar, E., Muntner, P., Silbergeld, E., Jaar, B., & Weaver, V. (2009). Blood cadmium and lead and chronic kidney disease in US adults: A joint analysis. *Am J Epidemiol.*, *170*(9), 1156-1164. https://doi.org/10.1093/aje/kwp248

Oliver-Williams, C., Howard, A. G., Navas-Acien, A., Howard, B. V., Tellez-Plaza, M., & Franceschini, N. (2018). Cadmium body burden, hypertension, and changes in blood pressure over time: Results from a prospective cohort study in American Indians. *JASH*, *12*(6), 426-437.e9. https://doi.org/10.1016/j.jash.2018.03.002

Ortolá, R., García-Esquinas, E., García-Varela, G., Struijk, E. A., Rodríguez-Artalejo, F., & López-García, E. (2019). Influence of Changes in Diet Quality on Unhealthy Aging: The Seniors-ENRICA Cohort. *Am J Med*, *132*(9), 1091-1102.e9. https://doi.org/10.1016/j.amjmed.2019.03.023

Peng, Y., Li, Z., Yang, X., Yang, L., He, M., Zhang, H., Wei, X., Qin, J., Li, X., Lu, G., Zhang, L., Yang, Y., Zhang, Z., & Zou, Y. (2020). Relation between cadmium body burden and cognitive function in older men: A cross-sectional study in China. *Chemosphere*, *250*, 126535. https://doi.org/10.1016/j.chemosphere.2020.126535

Puthoff, M. L. (2008). Outcome Measures in Cardiopulmonary Physical Therapy: Short Physical Performance Battery. *Cardiopulmon Phys Ther J*, *19*(1), 17-22.

Rockwood, K., & Mitnitski, A. (2007). Frailty in Relation to the Accumulation of Deficits. *J Gerontol A Biol Sci Med Sci*, *62*(7), 722-727. https://doi.org/10.1093/gerona/62.7.722

Rodríguez-Sánchez, I., García-Esquinas, E., Mesas, A. E., Martín-Moreno, J. M., Rodríguez-Mañas, L., & Rodríguez-Artalejo, F. (2019). Frequency, intensity and localization of pain as risk factors for frailty in older adults. *Age and Ageing*, *48*(1), 74-80. https://doi.org/10.1093/ageing/afy163

Rosow, I., Breslau, N. (1996) A Guttman health scale for the aged. J Gerontol, 2, 556-9. https://doi:10.1093/geronj/21.4.556.

Sabir, S., Akash, M. S. H., Fiayyaz, F., Saleem, U., Mehmood, M. H., & Rehman, K. (2019). Role of cadmium and arsenic as endocrine disruptors in the metabolism of carbohydrates: Inserting the

association into perspectives. *Biomed Pharmacother*, *114*, 108802. https://doi.org/10.1016/j.biopha.2019.108802

Satarug, S., Vesey, D. A., & Gobe, G. C. (2017). Health Risk Assessment of Dietary Cadmium Intake: Do Current Guidelines Indicate How Much is Safe? *Environ Health Perspec*, *125*(3), 284-288. https://doi.org/10.1289/EHP108

Semba, R. D., Ferrucci, L., Sun, K., Walston, J., Varadhan, R., Guralnik, J. M., & Fried, L. P. (2007). Oxidative stress and severe walking disability among older women. *Am J Med*, *120*(12), 1084-1089. https://doi.org/10.1016/j.amjmed.2007.07.028

Stoev, S. D., Grozeva, N., Simeonov, R., Borisov, I., Hubenov, H., Nikolov, Y., Tsaneva, M., & Lazarova, S. (2003). Experimental cadmium poisoning in sheep. *Exp Toxicol Pathol.*, *55*(4), 309-314. https://doi.org/10.1078/0940-2993-00333

Tellez-Plaza, M., Guallar, E., Howard, B. V., Umans, J. G., Francesconi, K. A., Goessler, W., Silbergeld, E. K., Devereux, R. B., & Navas-Acien, A. (2013). Cadmium Exposure and Incident Cardiovascular Disease: *Epidemiology*, *24*(3), 421-429. https://doi.org/10.1097/EDE.0b013e31828b0631

Tellez-Plaza, M., Navas-Acien, A., Crainiceanu, C. M., Sharrett, A. R., & Guallar, E. (2010). Cadmium and Peripheral Arterial Disease: Gender Differences in the 1999–2004 US National Health and Nutrition Examination Survey. *Am J Epidemiol*, *172*(6), 671-681. https://doi.org/10.1093/aje/kwq172

Tellez-Plaza, M., Navas-Acien, A., Menke, A., Crainiceanu, C. M., Pastor-Barriuso, R., & Guallar, E. (2012). Cadmium Exposure and All-Cause and Cardiovascular Mortality in the U.S. General Population. *Environ Health Perspect*, *120*(7), 1017-1022. https://doi.org/10.1289/ehp.1104352

Trichopoulou, A., Costacou, T., Bamia, C., & Trichopoulos, D. (2003). Adherence to a Mediterranean diet and survival in a Greek population. *N Engl J Med*, *348*(26), 2599-2608. https://doi.org/10.1056/NEJMoa025039

Trouiller-Gerfaux, P., Podglajen, E., Hulo, S., Richeval, C., Allorge, D., Garat, A., Matran, R., Amouyel, P., Meirhaeghe, A., & Dauchet, L. (2019). The association between blood cadmium

and glycated haemoglobin among never-, former, and current smokers: A cross-sectional study in France. *Environ Res*, *178*, 108673. https://doi.org/10.1016/j.envres.2019.108673

Tsentsevitsky, A. N., Zakyrjanova, G. F., & Petrov, A. M. (2020). Cadmium desynchronizes neurotransmitter release in the neuromuscular junction: Key role of ROS. *Free Radic Biol Med*, *155*, 19-28. https://doi.org/10.1016/j.freeradbiomed.2020.05.017

Vilagut, G., María Valderas, J., Ferrer, M., Garin, O., López-García, E., & Alonso, J. (2008). Interpretación de los cuestionarios de salud SF-36 y SF-12 en España: Componentes físico y mental. *Med Clín.*, *130*(19), 726-735. https://doi.org/10.1157/13121076

Watanabe, Y., Nogawa, K., Nishijo, M., Sakurai, M., Ishizaki, M., Morikawa, Y., Kido, T., Nakagawa, H., & Suwazono, Y. (2020). Relationship between cancer mortality and environmental cadmium exposure in the general Japanese population in cadmium non-polluted areas. *Int J Hyg Environ Health.*, *223*(1), 65-70. https://doi.org/10.1016/j.ijheh.2019.10.005

Wu, E. W., Schaumberg, D. A., & Park, S. K. (2014). Environmental cadmium and lead exposures and age-related macular degeneration in US adults: The National Health and Nutrition Examination Survey 2005 to 2008. *Environ res., 133*, 178-184. https://doi.org/10.1016/j.envres.2014.05.023

Wu, I.-C., Shiesh, S.-C., Kuo, P.-H., & Lin, X.-Z. (2009). High oxidative stress is correlated with frailty in elderly chinese. *J Am Geriatr Soc.*, *57*(9), 1666-1671. https://doi.org/10.1111/j.1532-5415.2009.02392.x

Yao, X., Li, H., & Leng, S. X. (2011). Inflammation and immune system alterations in frailty. *Clin Geriatr Med., 27*(1), 79-87. https://doi.org/10.1016/j.cger.2010.08.002

Yesavage, J. A., Brink, T. L., Rose, T. L., Lum, O., Huang, V., Adey, M., & Leirer, V. O. (s. f.). Development and validation of a geriatric depression screening scale: A preliminary report. *J Psychiatr Res.*, *17*(1), 37-49. https://doi.org/10.1016/0022-3956(82)90033-4

Ziv, E., Patish, H., & Dvir, Z. (2008). Grip and Pinch Strength in Healthy Subjects and Patients with Primary Osteoarthritis of the Hand: A Reproducibility Study. *Open Orthop J*, *2*, 86-90. https://doi.org/10.2174/1874325000802010086