Excess mortality after hip fracture in elderly persons from Europe and the USA: the CHANCES project

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ABSTRACT

Background: Hip fractures are associated with diminished quality of life and survival especially amongst the elderly.

Objective: All-cause mortality after hip fracture was investigated to assess its magnitude.

Methods: A total of 122,808 participants from 8 cohorts in Europe and USA were followed-up for a mean of 12.6 years, accumulating 4,273 incident hip fractures and 27,999 deaths. Incident hip fractures were assessed through telephone interviews/questionnaires or national inpatient/fracture registries and causes of death were verified with death certificates. Cox proportional hazards models and the time-dependent variable methodology were used in order to assess the association between hip fracture and mortality and its magnitude at different time intervals after the injury

in each cohort. We obtained the effect estimates through a random-effects meta-analysis.

Results: Hip fracture was positively associated with increased all-cause mortality; the hazard ratio (HR) in the fully adjusted model was 2.12, 95% confidence interval (CI) 1.76-2.57, after adjusting for potential confounders. This association was stronger among men [HR:2.39, 95% CI:1.72-3.31] than among women [HR:1.92, 95% CI:1.54-2.39], although this difference was not significant. Mortality was higher during the first year after the hip fracture [HR:2.78, 95% CI:2.12-3.64] but it remained elevated without major fluctuations after longer time since hip fracture [HR (95% CI): 1.89 (1.50-2.37) after 1-4 years; 2.15 (1.81-2.55) after 4-8 years; 1.79 (1.57-2.05) after 8 or more years].

Conclusion: In this large population-based sample of older persons across 8 cohorts, hip fracture was associated with excess short and long-term all-cause mortality in both sexes.

Introduction

As the population ages, bone fractures are becoming an increasingly important health problem among the elderly with substantial burden for the individual and society. Hip fractures are the most relevant fractures in terms of severity, functional dependence, social and economic cost and fatality [1–3].

Despite a well-known increase in mortality shortly after hip fracture [3–5], the evidence on the long-term mortality following a hip fracture is not consistent [6–11]. Some studies have demonstrated a persistent increase in all-cause mortality in the

long term after the injury [6–9], whereas others report from low to no elevated long term mortality after hip fracture [10, 11]. The higher mortality rates were mostly observed in elderly, ill or impaired populations [6, 7]. A recent meta-analysis exploring the magnitude and duration of excess mortality risk after hip fracture found the highest risk in the first 3 months after the fracture (5- to 8-fold increase), and mortality remained elevated, compared to age-matched controls, even after 10 years. The excess risk increased with age and, at any given age, was higher for men than for women [12].

The aim of the present study was to investigate both short- and long-term mortality after hip fracture in a large cohort of community dwellers, aged 60 years and older, from Europe and the USA who were followed up prospectively.

Materials and methods

The CHANCES project

The Consortium on Health and Ageing: Network of Cohorts in Europe and United States (CHANCES) project is a large collaboration, funded by the European Commission within the Seventh Framework Programme, combining 14 major cohorts/studies from Europe and the USA, in order to provide evidence on ageing-related health characteristics and determinants of healthy ageing. The study protocol of each individual cohort/study has been approved by local ethics committees and all

participants have given written informed consent before enrolment. All procedures have been carried out in accordance with the Declaration of Helsinki. Variables harmonized across the cohorts were created following predetermined standardized procedures. The study design and population characteristics of the cohorts included in the CHANCES project have been described in detail elsewhere [13].

Eight cohorts with available information on hip fractures during follow-up as well as mortality were included in the present analysis: EPIC-Elderly Greece and EPIC-Elderly Umea, Sweden [14]; the ESTHER (Epidemiological Study on the Chances of Prevention, Early Recognition and Optimised Treatment of Chronic Diseases in the Older Population) Study from Germany [15]; the Tromsø study from Norway [16]; the Swedish Mammography Cohort (SMC) and the Cohort Of Swedish Men (COSM) studies [17]; the Nurses' Health Study (NHS) from the USA [18] and the Health, Alcohol and Psychosocial factors in Eastern Europe (HAPPIE) study with data from the Czech Republic [19]. Further details about the participating cohorts are available in the Appendix.

Information on incident hip fractures

Information on incident hip fractures was collected through telephone interviews or questionnaires to elicit self-reported data in EPIC-Elderly Greece, ESTHER and NHS and through national inpatient registries or fracture registries in EPIC-Elderly Umea, the Tromsø study, COSM, SMC and the Czech HAPIEE cohort [16, 20]. In order to verify self-reported hip fractures, validation studies were conducted for EPIC-Elderly Greece and ESTHER in the context of the CHANCES project. The rate of verification ranged from 52% to 86%. A validation study was also conducted as part of the NHS

in which all self-reported hip fractures were confirmed by medical records [21], while COSM, SMC and the Tromsø study had shown high validity of incident hip fracture diagnosis using the Swedish National Inpatient Register [20, 22]. Hip fractures identified as International Classification of Diseases and Related Health Problems 10th Revision (ICD-10) codes S72.0–S72.2 were included in the analyses.

Information on all-cause mortality

Vital status of the participants was assessed either by contacting relatives or household members, or through record linkage with nationwide or local death registries. All causes of death were verified through death certificates, whereas ICD coding was used across the cohorts.

Statistical analysis

Individual cohorts. In order to describe the socioeconomic, lifestyle, medical and anthropometric characteristics of the participants, the distribution of the corresponding variables, separately for men and women in every cohort, is presented. Cox regression was applied for the cohort-specific analyses to calculate hazard ratios (HRs) and 95% confidence intervals (95% CIs) for mortality following the occurrence of a hip fracture event. The survival time was calculated from the date of enrolment in the study until the date of death (for those who died during follow-up) or the date of last follow-up (for those who were alive at that time). Once the exposure of interest in this study was the hip fracture event, which occurred during follow-up, we treated hip fracture as a time-dependent variable in order to capture the association between hip fracture and mortality. The same methodology was used in order to assess the

aforementioned association at different time intervals from the beginning of the hip fracture event.

Models were run with three levels of adjustment with an increasing number of confounders. Specifically, model 1 was only adjusted for age (in years; continuous variable) and sex. Model 2 was additionally adjusted for the continuous variables body mass index (BMI) (in kg/m^2), height (in m), daily energy intake (in kcal/day) and alcohol intake (in g/day) and the categorical variables vigorous physical activity (yes/no), educational level (none/less than primary/vocational or technical secondary/secondary, not vocational and not technical/college or university), living alone (yes; for single, widowed, separated or divorced/ no; for married or living together), employment status (full-time or part-time employment and not of pensionable age/self-employment/housewife and not of pensionable age/pensionable age and still working/pensionable age and not working/stopped working before retirement age due to poor health/unemployed and not of pensionable age) and smoking status (never/former/current smoker). Finally, model 3 was additionally adjusted for hypertension (yes/no) and chronic diseases (cardiovascular disease, diabetes or cancer; yes/no).

After following a consistent harmonization procedure [13], minor differences in the definition of variables used were observed, whereas the variables that were not common in all cohorts and were used later in our analysis are the following: alcohol intake (many missing values in the Tromsø study), energy intake (not available in the Tromsø study and ESTHER), education (all participants in NHS educated to the same level), prevalent cancers (excluded in COSM at baseline), living alone (not available

in SMC), vigorous physical activity (not available in EPIC-Sweden) and prevalent hip fractures (not available in EPIC-Greece and EPIC-Sweden).

Participants aged ≥60 years at enrolment without a prevalent hip fracture event were included in the present analysis. Model 3 was chosen as the main (fully adjusted) model. We excluded from our analyses those participants without information either during follow-up or in this model's variables. We performed three further subanalyses restricted to (i) men, (ii) women and (iii) subjects aged ≥70 years at enrolment.

We also tried to assess interaction on an additive scale between hip fractures and other risk factors using the relative excess risk due to interaction (RERI) index [23]:

$RERI = (\lambda_{11} - \lambda_{10} - \lambda_{01} + \lambda_{00})/\lambda_{00}$, where

λ_{11}=hazard rate when hip fracture and the other risk factor are present;

λ_{10}=hazard rate when hip fracture is present and the other risk factor is absent;

λ_{01}=hazard rate when hip fracture is absent and the other risk factor is present;

λ_{00}=hazard rate when hip fracture and the other risk factor are absent.

In other words:

$RERI = HR_{11} - HR_{10} - HR_{01} + 1$, where

HR_{11}=hazard ratio when hip fracture and the other risk factor are present;

HR_{10}=hazard ratio when hip fracture is present and the other risk factor is absent;

HR_{01}=hazard ratio when hip fracture is absent and the other risk factor is present.

All cohort-specific analyses were carried out using Stata statistical software versions 10–13 (STATA Corp LP).

Meta-analysis. All meta-analyses of cohort-specific estimates were performed using the DerSimonian–Laird method with random effects [24]. We estimated the HRs and 95% CIs for mortality following hip fracture events, after combining all results from each cohort separately. The heterogeneity between cohorts was measured using the I^2 statistic and tested for statistical significance with the chi-squared test from Cochran's Q statistic [25]. Moreover, we tested effect modification with a meta-analysis of all available estimates from different strata by calculating the chi-squared test for heterogeneity.

For the meta-analysis of interaction on an additive scale, we applied the index-based approach for meta-analyses; that is, we calculated the RERI (index of interest) in all cohorts and then performed a meta-analysis including these indices.

For all meta-analyses we used Stata, version 11. All tests were two-sided and *P*-values less than 0.05 were considered statistically significant.

Results

The study population consisted of 122,808 participants from eight cohorts (seven from Europe and one from the USA); during a mean follow-up time of 12.6 years (range 7.9–13.7 years) there were 4273 incident hip fractures. Participants were mostly recruited during the 1990s, and a total of 27,999 participants died during follow-up (Table 1). The rate of hip fracture varied from 1.2% to 10.3%. Once all participants were at least 60 years old, small age differences were observed among the cohorts. The percentage of participants with one or more missing values for any of the variables included in the analysis varied from 8% to 44% across the cohorts; however, the distribution of the variables in each cohort before and after exclusions were

essentially the same (see Online Resource 1). The baseline characteristics of the study participants are presented by sex and cohort in Tables 2A and 2B.

Table 3 and Fig. 1 show that the occurrence of hip fracture was positively associated with all-cause mortality (in model 3: HR 2.12, 95% CI 1.76–2.57) after adjusting for all available potential confounders. After excluding HAPIEE from the analysis due to the exceptionally high HR, overall associations decreased but remained statistically significant (in model 3: HR 1.98, 95% CI 1.65–2.38). The association between hip fracture and mortality slightly decreased after adjusting for increasing number of confounders (i.e. from model 1 to model 3). Model 3 showed that this relationship was somewhat stronger among men (HR 2.39, 95% CI 1.72–3.31) than women (HR 1.92 (95% CI 1.54–2.39), and was weaker but still significant among participants aged ≥70 years old (HR 1.84, 95% CI 1.46–2.33), as the underlying risk of these (more elderly) participants is higher. When a sensitivity analysis was applied restricting the analysis to cohorts that included both sexes, the differences remained largely unchanged and statistically significant (in model 3: HR 2.37 and 1.94 for men and women respectively). By contrast, when the association among participants aged ≥70 years was compared with the association in the primary analysis of participants ≥60 years, after excluding EPIC-Sweden, NHS and HAPIEE which do not contribute to the HR of subjects aged ≥70 years old (because they have very few or no participants in this age group at baseline), the difference was small [in model 3: HR 1.91 and 1.84 for all participants (≥60 years old) and those ≥70 years old respectively]. Although the heterogeneity of the associations was high in all these comparisons (in general: $70\% \leq I \leq 90\%$), the relationship between hip fracture and mortality was positive in all countries, but differed in magnitude (Fig. 1).

Although the proportionality assumption was not violated in any of the cohorts, we also estimated the time-dependent effect of hip fracture on mortality (Table 4). We found that the short-term effect of hip fractures was higher than the mid- and long-term effects. Specifically, the HR in the first year after hip fracture was 2.78 (95% CI 2.12–3.64), whereas in the longer term hip fractures were associated with an almost 2-fold increase in mortality (1–4 years after hip fracture: HR 1.89, 95% CI 1.50–2.37; 4–8 years after hip fracture: HR 2.15, 95% CI 1.81–2.55; and ≥8 years after hip fracture: HR 1.79, 95% CI 1.57–2.05). In this time-dependent analysis, we considered the effects of all cohorts for all time periods (except HAPIEE, which does not contribute to the overall HR for ≥8 years). However, the conclusions were unchanged when we excluded the HAPIEE cohort from this analysis (data not shown).

Finally, we found that the associations between the combination of hip fracture and prevalent chronic disease and mortality were super-additive (RERI >0), as evidenced by a 42% (95% CI 10–75%) excess risk of mortality due to the joint presence of hip fracture and chronic disease (Fig. 2). When we investigated any possible excess risk due to the interaction between hip fracture and obesity and living alone, we found no significant deviation from additivity.

Discussion

In this large sample of individuals, aged 60 years and older from Europe and the USA, there was evidence that hip fracture is associated with excess short- and long-term all-cause mortality in both sexes. Participants who had experienced a hip fracture during follow-up had the highest risk of dying during the first year after the fracture,

and an almost 2-fold increase in mortality persisted even 8 years or more after the injury. Small differences were observed according to sex, with the magnitude of the increase in all-cause mortality somewhat larger among men. Associations were significant even after controlling for chronic comorbidities and lifestyle factors. Furthermore, prevalence of chronic diseases at baseline was found to have a super-additive effect with hip fractures on mortality (as tested using the RERI index), implying that individuals with chronic diseases need particularly careful management following a hip fracture.

Our results with respect to short-term excess all-cause mortality confirm those of other studies and the most recent meta-analysis (almost 3-fold increase in the present study compared to 3- to 5-fold increase during the first 6 months in the recent meta-analysis) [5, 9, 12]. To the best of our knowledge, excess short-term mortality following hip fracture, especially during the first 3–6 months, was observed in all previously published studies. Factors that contribute the most to this finding are linked to postoperative complications after surgery such as cardiac and pulmonary complications, infections (i.e. pneumonia and septicaemia) and increased risk of thromboembolism [26, 27]. Other factors, such as multiple comorbid conditions have also been implicated [12, 25].

A difference in excess all-cause mortality after hip fracture among men and women, and specifically a higher excess mortality among men, although minimal in this study, has been a consistent finding in previous studies [5, 12, 27–29]. It seems that although hip fracture incidence in men is substantially lower compared to women, mortality after hip fracture is higher in men [29]. Efforts to explore further the causes of this

gender difference have shown, in most instances, that such differences remained even after controlling for chronic comorbidities and medications [28].

Long-term mortality after hip fracture was significantly elevated, not only for the first 8 years, but also after that period. The excess long-term risk of death after hip fracture has been found in the majority but not all relevant studies, however the mechanisms underlying this excess risk remain unclear [6–11]. One explanation has been the co-existence of chronic disease, but excess mortality remained in the studies that collected and had the ability to adjust for such data [4, 6, 7, 12]. On the other hand, hip fracture is associated with increased functional decline and disability in the elderly [30]. Recently, hip fracture occurrence has also been associated with an exaggerated persistent inflammatory response, while, in parallel, chronic inflammation might play a role in the functional decline and the onset or acceleration of frailty [31–33]. These mechanisms could provide a possible explanation of the observed decline in health and the increased long-term mortality after hip fracture. In addition, the detrimental effect of long-standing pain and diminished quality of life, especially when followed by loss of independence, should not be underestimated [34].

The strengths of our study include the large, population-based sample of more than 100,000 elderly participants from Europe and the USA, the prospective design, the use of harmonized variables across the cohorts and the implementation of a common statistical analysis with individual data. The analysis of harmonized individual data possibly reduced the potential heterogeneity, which generally occurs when performing a meta-analysis of published data. Moreover, by analysing results from different cohorts without knowing *a priori* the associations that would be estimated, we have

overcome the problem of publication bias [35] that may be present in other meta-analyses of previous publications [12].

A limitation of this study is the different periods of enrolment of the participants in the cohorts as both life expectancy and some aspects of hip fracture treatment have changed during these years. Although the majority of participants entered the studies during the 1990s, subjects were also recruited during the late 1980s to the NHS and during the 2000s to the NHS, ESTHER and HAPIEE-Czech. Nevertheless, although heterogeneity was observed between cohorts (perhaps partially explained by the different periods of recruitment of the participants in the cohorts along with the fact that participants had different characteristics across cohorts; see Tables 1, 2A and 2B), the association between hip fracture and subsequent mortality, showed the same positive direction in all cohorts. Moreover, heterogeneity decreased according to the period after hip fracture, possibly due to the decreased number of events (deaths) over time. Furthermore, we could not determine the cause of hip fracture; more specifically, we were not able to differentiate between high-energy (e.g. traffic accidents) and low-energy trauma (e.g. falls from standing height), although the majority of hip fractures in older subjects (≥60 years of age) are low-energy fractures. The different methods of hip fracture and mortality ascertainment used across the participating cohorts could potentially have resulted in differing degrees of under- and over-reporting of hip fracture cases and deaths that could further influence the association under study. Also, although extensive harmonization was undertaken in the context of the CHANCES project, different methods of data collection were used, and not all covariates were assessed in all cohorts. Residual confounding may also exist because of the inability to control for other parameters such as medication (e.g.

bisphosphonates), supplement use and access to healthcare across the cohorts. Additionally, covariates such as BMI, alcohol intake, physical activity and comorbidities were assessed at baseline and not updated during follow-up. It is unlikely, however, that such changes in the covariates would have had a major impact on the results. Information on nursing home status at the time of hip fracture was not available and thus we could not differentiate between nursing home residents and community-dwelling participants in our analyses. Nursing home residents have been shown to experience higher mortality in comparison to community dwellers both among individuals with hip fracture, especially in the immediate post-injury period, and among those without hip fracture [36]. The magnitude of missing data could have affected our findings. However, the extent would be small as there was no significant difference in the characteristics of the available participants and of those included in the analysis (see Online Resource 1). Finally, the findings of this study cannot be extrapolated to populations other than white men and women aged ≥60 years with similar sociodemographic characteristics to those of the study participants.

Conclusions

In conclusion, our study confirms that elderly individuals who have suffered a hip fracture are at increased risk of dying, compared to those who have not, in the short term after the fracture but also years later. Appropriate measures need to be implemented for primary and secondary prevention of hip fracture in order to ensure better quality of life and survival in the elderly.

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Conflict of interest statement

Michail Katsoulis, Vassiliki Benetou, Tina Karapetyan, Diane Feskanich, Francine Grodstein, Ulrika Pettersson-Kymmer, Sture Eriksson, Tom Wilsgaard, Lone Jørgensen, Ahmed Luai, Ben Schöttker, Hermann Brenner, Andrea Bellavia, Alicja Wolk, Ruzena Kubinova, Bernardine Stegeman, Martin Bobak, Paolo Boffetta and Antonia Trichopoulou declare that they have no conflicts of interest.

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APPENDIX

The participating cohorts

EPIC–Elderly (European Prospective Investigation into Cancer and Nutrition)

EPIC-Elderly cohort consists of approximately 100000 participants (aged 60 years and older at recruitment) recruited initially in the EPIC Study [1]. EPIC is an on–going, multi–centre, prospective cohort study aiming to investigate the role of biological, dietary, lifestyle, and environmental factors in the aetiology of cancer and other chronic diseases. Twenty three research centres from 10 European countries participate in EPIC (Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden, and the United Kingdom). Recruitment took place from 1992 to 2000 via administration of baseline questionnaires and interviews. After enrolment, participants were followed–up at regular intervals every 3–4 years [2].

EPIC-GREECE

Below, we present the descriptive characteristics for categorical and continuous variables for all participants and those finally analyzed (after excluding missing values)

Continuous variables

All participants (Initial Sample)

Variable name	n	mean	sd
BMI (kg/m^2)	9818	29.3	4.6
Height (m)	9826	1.58	0.09
Alcohol intake (gr/d)	9838	7.5	16.3
Energy intake (Kcal/d)	9838	1806.4	584.5
Age at recruitment (years)	9863	67.3	4.5
Age at exit from follow-up (years)	9863	77.3	5.2

All participants (excluding missing values)

Variable name	n	mean	sd
BMI (kg/m^2)	9037	29.3	4.6
Height (m)	9037	1.58	0.09
Alcohol intake (gr/d)	9037	7.5	16.4
Energy intake (Kcal/d)	9037	1805.5	580.7
Age at recruitment (years)	9037	67.3	4.5
Age at exit from follow-up (years)	9037	77.6	4.9

Categorical variables

Descriptive statistics for categorical variables (overall)

		all		excluding missing	
		n	**%**	**n**	**%**
Vigorous Physical activity	no	7678	79.3	7172	79.4
	yes	2008	20.7	1865	20.6
Education	none or less than primary	4765	48.6	4404	48.7
	primary	4179	42.7	3869	42.8
	vocational or technical secondary	78	0.8	66	0.7
	secondary not vocational/technical	469	4.8	423	4.7
	college or university	306	3.1	275	3.0
Living alone	no	7815	79.5	7207	79.7
	yes	2016	20.5	1830	20.3
Employment status	employed, not of pensionable age	1804	18.4	1649	18.2
	self-employed	0	0.0	0	0.0
	housewife	2793	28.4	2583	28.6
	pensionable age, working	0	0.0	0	0.0
	pensionable age, not working	5169	52.6	4742	52.5
	not working due to poor health	0	0.0	0	0.0
	unemployed-not of pensionable age	65	0.7	63	0.7
Smoking status	never	6658	69.5	6282	69.5
	former	1781	18.6	1687	18.7
	current	1134	11.8	1068	11.8
Hypertension	no	5361	54.4	4895	54.2
	yes	4502	45.6	4142	45.8
Prevalent cancer	no	9521	96.5	8717	96.5
	yes	342	3.5	320	3.5
Prevalent diabetes	no	8403	85.5	7720	85.4
	yes	1420	14.5	1317	14.6
Prevalent cvd	no	9230	93.6	8444	93.4
	yes	633	6.4	593	6.6
Mortality Status	alive	7844	79.5	7130	78.9
	dead	2019	20.5	1907	21.1
Incident Hip Fractures	no	9647	97.8	8828	97.7
	yes	216	2.2	209	2.3

EPIC - SWEDEN

Below, we present the descriptive characteristics for categorical and continuous variables for all participants and those finally analyzed (after excluding missing values)

Continuous variables

All participants (Initial Sample)

Variable name	n	mean	sd
BMI (kg/m^2)	3344	25.9	4.1
Height (m)	3351	1.68	0.09
Alcohol intake (gr/d)	3364	2.8	4.1
Energy intake (Kcal/d)	3364	1635.9	592.3
Age at recruitment (years)	3364	60.4	1.2
Age at exit from follow-up (years)	3364	73.6	3.1

All participants (excluding missing values)

Variable name	n	mean	sd
BMI (kg/m^2)	3108	25.9	4.0
Height (m)	3108	1.68	0.09
Alcohol intake (gr/d)	3108	2.8	4.0
Energy intake (Kcal/d)	3108	1640.1	594.5
Age at recruitment (years)	3108	60.3	1.1
Age at exit from follow-up (years)	3108	73.6	3.1

Categorical variables

Descriptive statistics for categorical variables (overall)

		all		excluding missing	
		n	%	n	%
Education	none or less than primary	0	0.0	0	0.0
	primary	1839	55.1	1695	54.5
	vocational or technical secondary	839	25.2	787	25.3
	secondary not vocational/technical	267	8.0	259	8.3
	college or university	390	11.7	367	11.8
Living alone	no	2612	78.7	2449	78.8
	yes	706	21.3	659	21.2
Employment status	employed, not of pensionable age	1818	54.0	1705	54.9
	self-employed	288	8.6	265	8.5
	housewife	124	3.7	110	3.5
	pensionable age, working	0	0.0	0	0.0
	pensionable age, not working	882	26.2	816	26.3
	not working due to poor health	0	0.0	0	0.0
	unemployed-not of pensionable age	252	7.5	212	6.8
Smoking status	never	2007	61.2	1891	60.8
	former	719	21.9	686	22.1
	current	552	16.8	531	17.1
Hypertension	no	2298	68.3	2127	68.4
	yes	1066	31.7	981	31.6
Prevalent cancer	no	3175	94.4	2932	94.3
	yes	189	5.6	176	5.7
Prevalent diabetes	no	3233	97.0	3013	96.9
	yes	101	3.0	95	3.1
Prevalent CVD	no	3268	97.1	3016	97.0
	yes	96	2.9	92	3.0
Mortality Status	alive	2862	85.1	2648	85.2
	dead	502	14.9	460	14.8
Incident Hip Fractures	no	3295	97.9	3044	97.9
	yes	69	2.1	64	2.1

The Nurses' Health Study (NHS)

The NHS started in 1976 when 121701 married female registered nurses, aged 30–55 years, residents in 11 US states, responded to initial mailed questionnaire collecting information on lifestyle practices, medical history, and risk factors related to cancer and other health outcomes [3]. Follow-up questionnaires were sent every 2 years in order to update individual characteristics and to identify incident diseases. The NHS was approved by the Institutional Review Board of the Brigham and Women's Hospital.

Below, we present the descriptive characteristics for categorical and continuous variables for all participants and those finally analyzed (after excluding missing values)

Continuous variables

All participants (Initial Sample)

Variable name	n	mean	sd
BMI (kg/m^2)	103282	26.7	5.3
Height (m)	121326	1.64	0.06
Alcohol intake (gr/d)	94478	5.9	10.4
Energy intake (Kcal/d)	94478	1734.2	533.1
Age at recruitment (years)	121550	61.0	0.7
Age at exit from follow-up (years)	116308	75.2	7.0

All participants (excluding missing values)

Variable name	n	mean	sd
BMI (kg/m^2)	68468	26.8	5.4
Height (m)	68468	1.64	0.06
Alcohol intake (gr/d)	68468	5.8	10.1
Energy intake (Kcal/d)	68468	1757.5	529.2
Age at recruitment (years)	68468	61.0	0.6
Age at exit from follow-up (years)	68468	74.1	6.1

Categorical variables

Descriptive statistics for categorical variables (overall)

		all		excluding missing	
		n	%	n	%
Vigorous Physical Activity	no	81850	77.6	47469	69.3
	yes	23581	22.4	20999	30.7
Living alone	no	81430	67.0	59194	86.5
	yes	40120	33.0	9274	13.5
Employment Status	employed, not of pensionable age	56548	64.4	44538	65.0
	self-employed	0	0.0	0	0.0
	housewife	20202	23.0	13992	20.4
	pensionable age, working	0	0.0	0	0.0
	pensionable age, not working	11011	12.5	9938	14.5
	not working due to poor health	0	0.0	0	0.0
	unemployed-not of pensionable age	0	0.0	0	0.0
Smoking status	never	49971	44.6	29894	43.7
	former	44965	40.1	29486	43.1
	current	17164	15.3	9088	13.3
Hypertension	no	74194	61.0	40653	59.4
	yes	47356	39.0	27815	40.6
Mortality Status	alive	91943	79.1	58342	85.2
	dead	24365	20.8	10126	14.8
Prevalent Diabetes	no	112822	92.8	63726	93.1
	yes	8728	7.2	4742	6.9
Prevalent CVD	no	116922	96.2	65984	96.4
	yes	4628	3.8	2484	3.6
Prevalent Cancer	no	107166	88.2	60497	88.4
	yes	14384	11.8	7971	11.6
Incident Hip Fractures	no	118883	97.8	67208	98.2
	yes	2667	2.2	1260	1.8

The Tromsø Study

The Tromsø Study is a repeated population-based health survey of inhabitants in the municipality of Tromsø in Norway [4]. The examinations were repeated in 1974 (Tromsø 1), 1979–80 (Tromsø 2), 1986–87 (Tromsø 3), 1994–95 (Tromsø 4), 2001 (Tromsø 5) and 2007–08 (Tromsø 6). In all surveys, the participants completed self-administered questionnaires covering a wide range of variables of interest.Mortality was assessed until the end of 2009 for this study, via record linkage to Statistics Norway [5,6]. Since Tromsø 4 and thereafter, the fracture registry was initiated.

Below, we present the descriptive characteristics for categorical and continuous variables for all participants and those finally analyzed (after excluding missing values)

Continuous variables

All participants (Initial Sample)

Variable name	n	mean	sd
BMI (kg/m^2)	5825	26.1	4.2
Height (m)	5826	1.66	0.10
Age at recruitment (years)	5851	69.9	7.0
Age at exit from follow-up (years)	5851	81.7	6.4

All participants (excluding missing values)

Variable name	n	mean	sd
BMI (kg/m^2)	5373	26.2	4.2
Height (m)	5373	1.66	0.10
Age at recruitment (years)	5373	69.6	6.9
Age at exit from follow-up (years)	5373	81.6	6.4

Categorical variables

		all		excluding missing	
		n	%	n	%
Vigorous Physical activity	no	4436	76.9	4102	76.3
	yes	1332	23.1	1271	23.7
Education	primary or less	3760	64.8	3456	64.3
	high school/ lyceum	1473	25.4	1379	25.7
	college or university	570	9.8	538	10.0
Living alone	no	3490	59.7	3241	60.3
	yes	2354	40.3	2132	39.7
Employment status	employed, not of pensionable age	947	16.2	908	16.9
	self-employed	0	0.0	0	0.0
	housewife	473	8.1	441	8.2
	pensionable age, working	62	1.1	60	1.1
	pensionable age, not working	3313	56.6	2976	55.4
	not working due to poor health	578	9.9	535	10.0
	unemployed-not of pensionable age	478	8.2	453	8.4
Smoking status	never	2111	36.1	1923	35.8
	former	2184	37.4	2030	37.8
	current	1550	26.5	1420	26.4
Hypertension	no	4376	75.2	4017	75.2
	yes	1442	24.8	1327	24.8
Prevalent Cancer	no	5372	91.8	4941	92.0
	yes	479	8.2	432	8.0
Prevalent Diabetes	no	5512	94.7	5105	95.0
	yes	309	5.3	268	5.0
Prevalent CVD	no	4977	85.1	4571	85.1
	yes	874	14.9	802	14.9
Mortality Status	alive	2704	46.2	2556	47.6
	dead	3147	53.8	2817	52.4
Incident Hip Fractures	no	5325	91.0	4995	93.0
	yes	526	9.0	378	7.0

ESTHER (Epidemiological Study on the Chances of Prevention, Early Recognition at Optimised Treatment of Chronic Diseases in the Older Population)

ESTHER Study is a population-based cohort study comprising of 9949 adults, aged 50–74 years, who were recruited during 2000–2002 from the entire federal state of Saarland in Germany [7,8]. Participants were approached during a general health check-up at their general practitioner's office where they completed a detailed self-administered questionnaire and provided biological samples (blood, stool, urine). Until 2012, three re-contacts took place (two, five and eight years after baseline) where all participants completed a standardized questionnaire, similar to that at baseline. In addition, detailed medical data were obtained from the general practitioners, and a comprehensive follow-up with respect to overall and cause-specific mortality and cancer incidence was conducted through record linkage with data from population registries, public health offices and the Saarland Cancer Registry.

Below, we present the descriptive characteristics for categorical and continuous variables for all participants and those finally analyzed (after excluding missing values)

Continuous variables

All participants (Initial Sample)

Variable name	n	mean	sd
BMI (kg/m^2)	6536	27.7	4.1
Height (m)	6540	1.67	0.08
Alcohol intake (gr/d)	5848	6.6	9.5
Age at recruitment (years)	6545	66.1	4.1
Age at exit from follow-up (years)	6544	76.9	4.5

All participants (excluding missing values)

Variable name	n	mean	sd
BMI (kg/m^2)	4957	27.7	4.1
Height (m)	4957	1.67	0.08
Alcohol intake (gr/d)	4957	6.8	9.7
Age at recruitment (years)	4957	65.9	4.1
Age at exit from follow-up (years)	4957	76.7	4.4

Categorical variables

		all		excluding missing	
		n	%	n	%
Vigorous Physical activity	no	4126	63.32	2941	59.3
	yes	2390	36.68	2016	40.7
Education	none or less than primary	232	3.658	158	3.2
	primary	4717	74.38	3588	72.4
	vocational or technical secondary	1140	17.98	991	20.0
	secondary not vocational/technical	253	3.989	220	4.4
	college or university	0	0	0	0
Living alone	no	4769	74.23	3730	75.2
	yes	1656	25.77	1227	24.8
Employment Status	employed, not of pensionable age	371	5.897	302	6.1
	self-employed	47	0.747	36	0.7
	housewife	751	11.94	574	11.6
	pensionable age, working	153	2.432	108	2.2
	pensionable age, not working	3504	55.7	2722	54.9
	not working due to poor health	1438	22.86	1190	24.0
	unemployed-not of pensionable age	27	0.429	25	0.5
Smoking status	never	3412	54	2579	52.0
	former	2104	33.3	1741	35.1
	current	803	12.71	637	12.9
Hypertension	no	2439	37.27	1789	36.1
	yes	4106	62.73	3168	63.9
Prevalent cancer	no	6063	92.64	4585	92.5
	yes	482	7.364	372	7.5
Prevalent Diabetes	no	5288	86.55	4348	87.7
	yes	822	13.45	609	12.3
Prevalent CVD	no	5628	89.62	4456	89.9
	yes	652	10.38	501	10.1
Mortality Status	alive	5229	79.89	4001	80.7
	dead	1316	20.11	956	19.3
Incident Hip Fractures	no	6456	98.6	4895	98.7
	yes	89	1.4	62	1.3

The Swedish Mammography Cohort (SMC) and the Cohort Of Swedish Men (COSM)

Two population-based prospective cohort studies provided data for the present analyses. The SMC was established between 1987 and 1990, when all women born between 1914 and 1948 and living in central Sweden received a mailed questionnaire that elicited information on diet, weight, height and education; 66651 women returned a completed questionnaire. In 1997, an expanded questionnaire that included data on various lifestyle factors and medical history was mailed to women who were still alive and residing in the study area; 39227 women (70%) completed the questionnaire. At the same time, 48850 men born between 1918 and 1952 and residing in central Sweden were enrolled in the COSM after returning a mailed questionnaire that was identical to the 1997 SMC questionnaire (except for some sex-specific questions). The studies were approved by the Regional Ethical Review Board in Stockholm [9].

COSM

Below, we present the descriptive characteristics for categorical and continuous variables for all participants and those finally analyzed (after excluding missing values)

Continuous variables

All participants (Initial Sample)

Variable name	n	mean	sd
BMI (kg/m^2)	19815	25.7	3.4
Height (m)	19955	1.76	0.07
Alcohol intake (gr/d)	19581	10.8	12.5
Energy intake (Kcal/d)	21072	2408.8	739.6
Age at recruitment (years)	21433	69.4	5.2
Age at exit from follow-up (years)	21433	81.7	5.4

All participants (excluding missing values)

Variable name	n	mean	sd
BMI (kg/m^2)	15744	25.7	3.2
Height (m)	15744	1.76	0.07
Alcohol intake (gr/d)	15744	11.1	12.4
Energy intake (Kcal/d)	15744	2466.3	692.5
Age at recruitment (years)	15744	69.0	5.2
Age at exit from follow-up (years)	15744	81.7	5.4

Categorical Variables

		all		excluding missing	
		n	%	n	%
Vigorous Physical Activity	no	1187	6.2	878	5.6
	yes	17876	93.8	14866	94.4
Education	none or less than primary	0	0.0	0	0.0
	primary	10188	47.9	6960	44.2
	vocational or technical secondary	8867	41.7	6906	43.9
	secondary not vocational/technical	593	2.8	474	3.0
	college or university	1638	7.7	1404	8.9
Living alone	no	17206	80.3	13122	83.3
	yes	4227	19.7	2622	16.7
Employment Status	Employed, not of pensionable age	2663	12.5	2201	14.0
	self-employed	7	0.0	7	0.0
	housewife	0	0.0	0	0.0
	pensionable age, working	0	0.0	0	0.0
	pensionable age, not working	17217	80.8	12497	79.4
	not working due to poor health	1027	4.8	725	4.6
	unemployed-not of pensionable age	407	1.9	314	2.0
Smoking status	never	7754	36.8	5948	37.8
	former	8469	40.2	6483	41.2
	current	4832	22.9	3313	21.0
Hypertension	no	14338	66.9	10726	68.1
	yes	7095	33.1	5018	31.9
Mortality Status	alive	10936	51.0	8601	54.6
	dead	10497	49.0	7143	45.4
Prevalent Diabetes	no	19458	90.8	14400	91.5
	yes	1975	9.2	1344	8.5
Prevalent CVD	no	17388	81.1	12932	82.1
	yes	4045	18.9	2812	17.9
Incident Hip Fractures	no	20.087	93.7	14.808	94.1
	yes	1.346	6.3	936	5.9

SMC

Below, we present the descriptive characteristics for categorical and continuous variables for all participants and those finally analyzed (after excluding missing values)

Continuous variables

All participants (Initial Sample)

Variable name	n	mean	sd
BMI (kg/m^2)	19043	25.3	4.0
Height (m)	17299	1.64	0.06
Alcohol intake (gr/d)	17158	4.0	6.2
Energy intake (Kcal/d)	19542	1665.2	557.5
Age at recruitment (years)	19591	70.0	5.9
Age at exit from follow-up (years)	19591	83.2	5.7

All participants (excluding missing values)

Variable name	n	mean	sd
BMI (kg/m^2)	12923	25.2	3.9
Height (m)	12923	1.64	0.06
Alcohol intake (gr/d)	12923	4.4	6.4
Energy intake (Kcal/d)	12923	1713.1	510.9
Age at recruitment (years)	12923	69.0	5.6
Age at exit from follow-up (years)	12923	82.7	5.5

Categorical variables

		Initial Sample		excluding missing	
		n	**%**	**n**	**%**
Vigorous Physical activity	no	1122	6.8	777	6.0
	yes	15337	93.2	12146	94.0
Education	none or less than primary	0	0.0	0	0.0
	primary	10802	55.8	6518	50.4
	vocational or technical secondary	7217	37.3	5279	40.8
	secondary not vocational/technical	226	1.2	169	1.3
	college or university	1124	5.8	957	7.4
Prevalent Cancer	no	18390	93.9	12172	94.2
	yes	1201	6.1	751	5.8
Employment Status	employed, not of pensionable age	2022	10.4	1638	12.7
	self-employed	0	0.0	0	0.0
	housewife	892	4.6	523	4.0
	pensionable age, working	0	0.0	0	0.0
	pensionable age, not working	15093	77.7	9752	75.5
	not working due to poor health	1190	6.1	832	6.4
	unemployed-not of pensionable age	230	1.2	178	1.4
Smoking status	never	12407	65.0	8222	63.6
	former	3331	17.4	2470	19.1
	current	3354	17.6	2231	17.3
Hypertension	no	14251	72.7	9410	72.8
	yes	5340	27.3	3513	27.2
Mortality Status	alive	12068	61.6	8732	67.6
	dead	7523	38.4	4191	32.4
Prevalent Diabetes	no	18404	93.9	12260	94.9
	yes	1187	6.1	663	5.1
Prevalent CVD	no	17836	91.0	11946	92.4
	yes	1755	9.0	977	7.6
Incident Hip Fractures	no	17319	88.4	11596	89.7
	yes	2272	11.6	1327	10.3

The Health, Alcohol and Psychosocial factors in Eastern Europe (HAPPIE) study with data from the Czech Republic

The multi-centre study HAPIEE study assessing the effects of dietary factors, alcohol consumption and psychosocial factors on health is being conducted in random samples of men and women selected in Russia, Poland, Lithuania and the Czech Republic - four countries of Central and Eastern Europe undergoing rapid social and economic transition [10]. Below, we present the descriptive characteristics for categorical and continuous variables for all participants and those finally analyzed (after excluding missing values)

Continuous variables

All participants (Initial Sample)

Variable name	n	mean	sd
BMI (kg/m^2)	3825	24.3	11.3
Height (m)	3828	1.67	0.09
Alcohol intake (gr/d)	3745	13.4	21.8
Energy intake (Kcal/d)	3810	2036.9	1020.8
Age at recruitment (years)	3833	64.8	2.9
Age at exit from follow-up (years)	3694	72.6	3.2

All participants (excluding missing values)

Variable name	n	mean	sd
BMI (kg/m^2)	3198	25.0	10.6
Height (m)	3198	1.67	0.09
Alcohol intake (gr/d)	3198	13.6	21.9
Energy intake (Kcal/d)	3198	2029.8	965.6
Age at recruitment (years)	3198	64.7	2.9
Age at exit from follow-up (years)	3198	72.6	3.2

Categorical variables

		all		excluding missing	
		n	%	n	%
Vigorous Physical activity	no	1148	31.5	990	31.0
	yes	2492	68.5	2208	69.0
Education	none or less than primary	26	0.7	19	0.6
	primary	568	14.9	456	14.3
	vocational or technical secondary	1378	36.2	1153	36.1
	secondary not vocational/technical	1328	34.9	1135	35.5
	college or university	502	13.2	435	13.6
Living alone	no	2836	74.2	2401	75.1
	yes	984	25.8	797	24.9
Employment status	employed, not of pensionable age	155	4.1	138	4.3
	self-employed	82	2.2	72	2.3
	housewife	12	0.3	10	0.3
	pensionable age, working	545	14.4	474	14.8
	pensionable age, not working	2979	78.7	2494	78.0
	not working due to poor health	1	0.0	1	0.0
	unemployed-not of pensionable age	10	0.3	8	0.3
	employed, not of pensionable age	3	0.1	1	0.0
Smoking status	never	1856	49.1	1556	48.7
	former	1219	32.3	1029	32.2
	current	704	18.6	613	19.2
Hypertension	no	1640	43.0	1390	43.5
	yes	2178	57.0	1808	56.5
Prevalent Cancer	no	3562	92.9	2979	93.2
	yes	271	7.1	219	6.8
Prevalent Diabetes	no	3157	82.7	2656	83.1
	yes	661	17.3	542	16.9
Prevalent CVD	no	3156	88.0	2822	88.2
	yes	430	12.0	376	11.8
Mortality Status	alive	3207	86.8	2799	87.5
	dead	487	13.2	399	12.5
Incident Hip Fractures	no	3789	98.9	3161	98.8
	yes	44	1.2	37	1.2

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Fig 1 Forest plot showing hazard ratios for mortality after hip fracture in model 3 (i.e. the fully adjusted model).

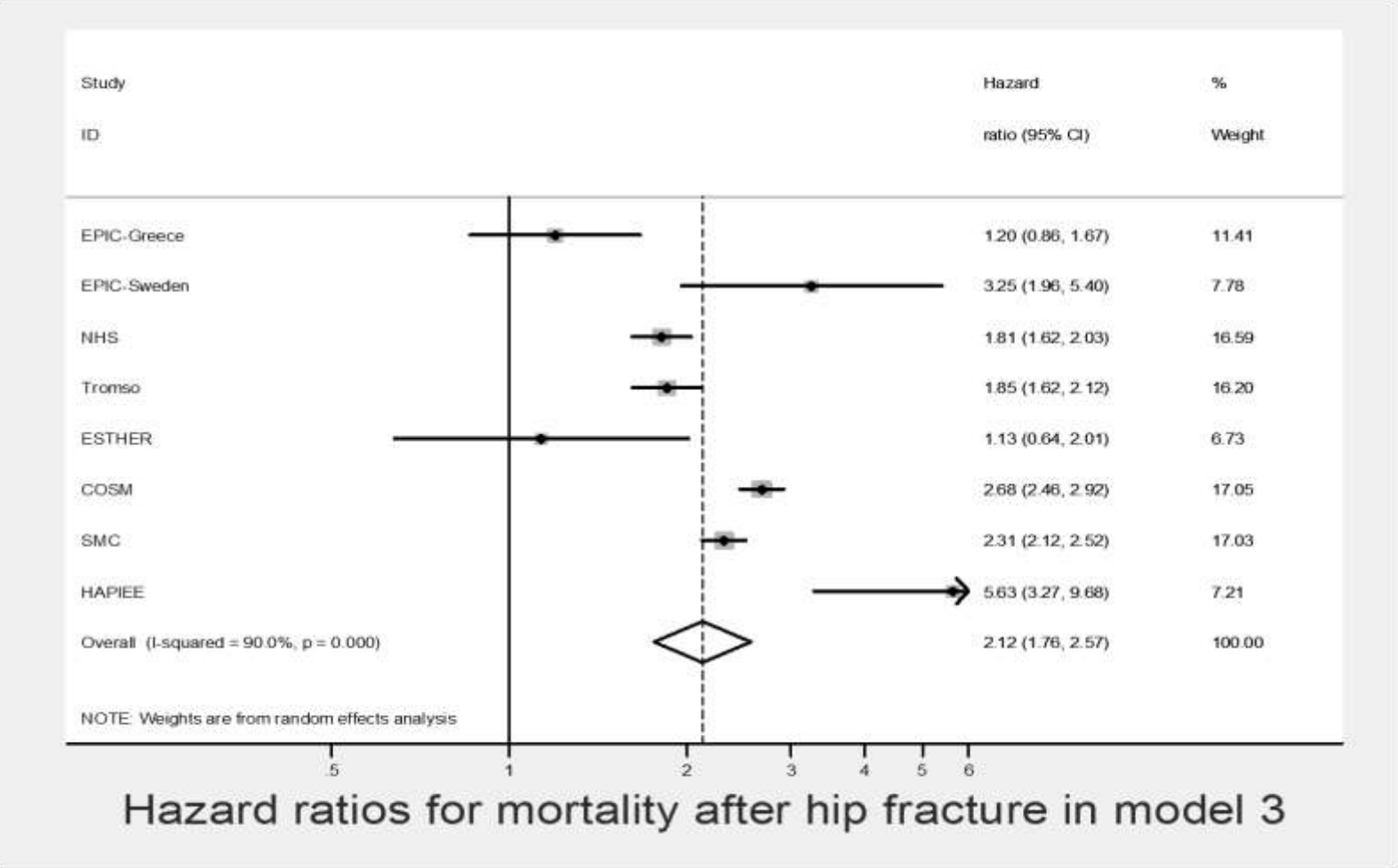

Fig. 2 Forest plot showing relative excess risk due to interaction (RERI) between hip fractures and chronic diseases for mortality in model 3 (i.e. the fully adjusted model).

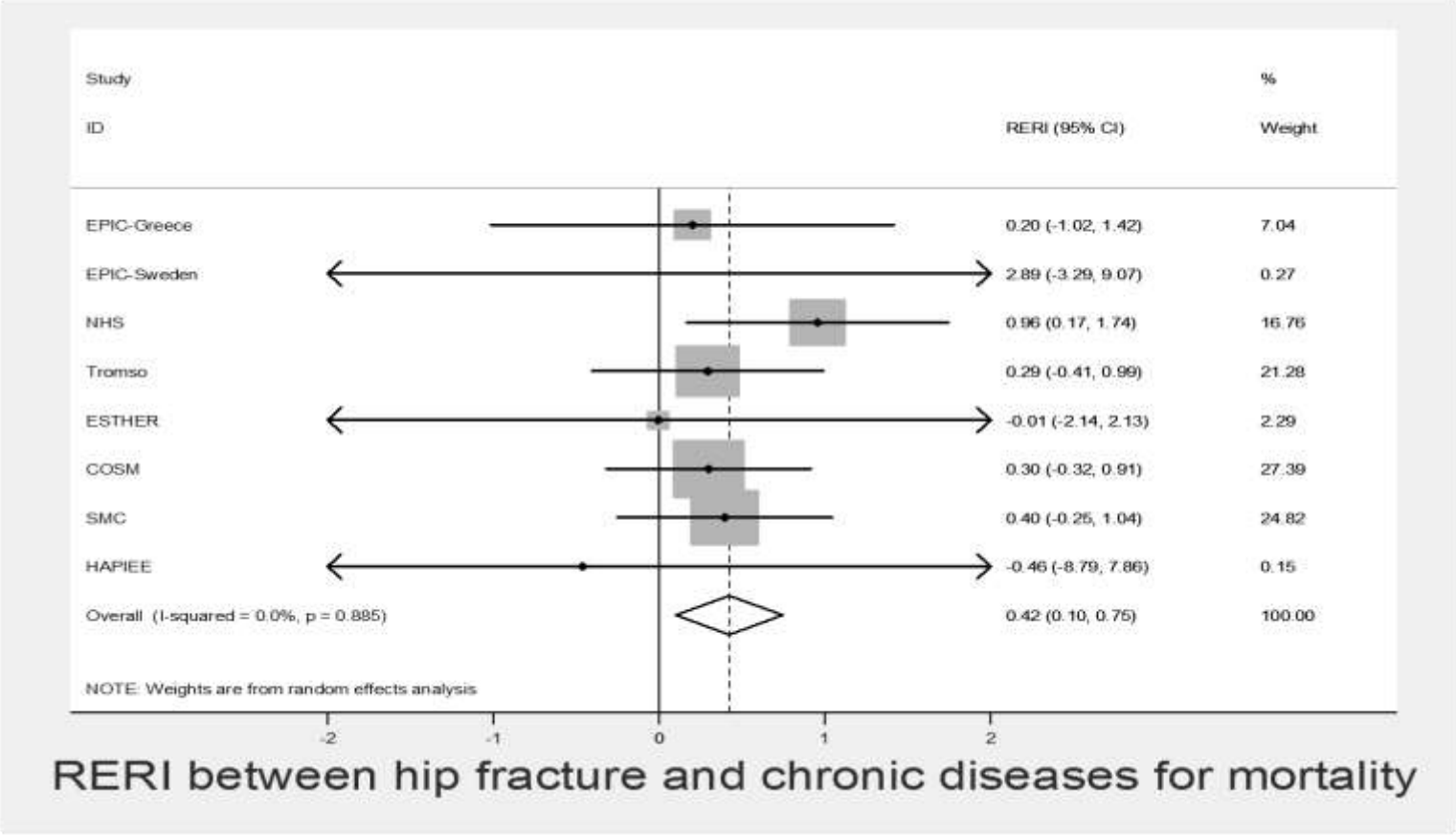

Table 1 Description of the participating cohorts

Cohort name	Country	*n*[a]	Females, *n* (%)	Hip fractures, *n* (%)	Deaths, *n* (%)	Mean age (years) at enrolment (SD)	Baseline period	Mean follow-up period (years) (SD)
EPIC-Greece	Greece	9037	5488 (61)	209 (2)	1907 (21)	67.3 (4.5)	1994–1999	10.3 (3.3)
EPIC-Sweden	Sweden	3108	1641 (53)	64 (2)	460 (15)	60.3 (1.1)	1992–1996	13.3 (3.0)
Nurses' Health Study	USA	68,468	68,468 (100)	1260 (2)	10,126 (15)	61.0 (0.6)	1986–2010	13.0 (6.1)
The Tromsø study	Norway	5373	2930 (55)	378 (7)	2817 (52)	69.6 (6.9)	1994–1995	12.0 (4.9)
ESTHER	Germany	4957	2541 (51)	62 (1)	956 (19)	65.9 (4.1)	2000–2002	10.8 (2.4)
COSM	Sweden	15,744	0 (0)	936 (6)	7143 (45)	69.0 (5.2)	1998	12.7 (4.1)
SMC	Sweden	12,923	12,923 (100)	1327 (10)	4191 (32)	69.0 (5.6)	1998	13.7 (3.5)
HAPIEE	Czech Republic	3198	1649 (52)	37 (1)	399 (13)	64.7 (2.9)	2002–2005	7.9 (1.6)

[a]Number of participants (without missing values for any confounding variable included in model 3).

Table 2A Characteristics of male participants at baseline by participating cohort (based on the number of observations in the fully adjusted model 3)

	EPIC-Greece	EPIC-Sweden	Nurses' Health Study	Tromsø study	ESTHER	COSM	SMC	HAPIEE-Czech
Men, *n* (%)	3549 (39)	1467 (47)	0 (0)	2443 (45)	2416 (49)	15,744 (100)	0 (0)	1549 (48)
Body mass index (kg/m^2), mean (SD)	28.0 (4.0)	25.9 (3.6)	-	25.8 (3.5)	27.8 (3.8)	25.7 (3.2)	-	24.6 (10.6)
Height (m), mean (SD)	1.66 (0.06)	1.75 (0.06)	-	1.74 (0.07)	1.73 (0.06)	1.76 (0.06)	-	1.74 (0.06)
Energy intake (kcal/day), mean (SD)	2049 (613)	1916 (636)	-	-	-	2466 (692)	-	2051 (964)
Alcohol intake (g/day), mean (SD)	15.2 (23.3)	4.3 (5.0)	-	-	10.2 (11.6)	11.1 (12.4)	-	23.3 (27.0)
Education (primary or less), *n* (%)	3209 (90)	789 (54)	-	1319 (54)	1744 (72)	6960 (44)	-	108 (7)
Living alone, *n* (%)	231 (7)	270 (18)	-	642 (26)	310 (13)	2622 (17)	-	202 (13)
Currently working, *n* (%)	980 (28)	884 (60)	-	540 (22)	205 (8)	2208 (14)	-	441 (29)
Never smokers, *n* (%)	1131 (32)	756 (52)	-	370 (15)	759 (31)	5948 (38)	-	519 (34)
Vigorous physical activity, *n* (%)	686 (19)	-	-	813 (33)	1159 (48)	14,866 (94)	-	1077 (70)
Hypertension, *n* (%)	1432 (40)	423 (29)	-	569 (23)	1594 (66)	5018 (32)	-	894 (58)
Prevalent cancer, *n* (%)	102 (3)	42 (3)	-	201 (8)	165 (7)	-	-	86 (6)
Prevalent diabetes, *n* (%)	551 (16)	64 (4)	-	108 (4)	346 (14)	1344 (9)	-	302 (19)
Prevalent CVD, *n* (%)	384 (11)	76 (5)	-	503 (21)	356 (15)	2812 (18)	-	255 (16)

Table 2B Characteristics of female participants at baseline by participating cohort (based on the number of observations in the fully adjusted model 3)

	EPIC-Greece	EPIC-Sweden	Nurses' Health Study	Tromsø study	ESTHER	COSM	SMC	HAPIEE-Czech
Women; *n* (%)	5488 (61)	1641 (53)	68,468 (100)	2930 (55)	2541 (51)	0 (0)	12,923 (100)	1649 (52)
Body mass index (kg/m^2), mean (SD)	30.1 (4.8)	25.9 (4.4)	26.8 (5.4)	26.5 (4.7)	27.5 (4.3)	-	25.2 (3.9)	25.3 (10.7)
Height (m), mean (SD)	1.53 (0.06)	1.62 (0.06)	1.64 (0.06)	1.59 (0.06)	1.62 (0.06)	-	1.64 (0.06)	1.61 (0.06)
Energy intake (kcal/day), mean (SD)	1648 (500)	1393 (423)	1758 (529)	-	-	-	1713 (511)	2010 (967)
Alcohol intake (g/day), mean (SD)	2.5 (5.4)	1.4 (2.2)	5.8 (10.1)	-	3.5 (5.7)	-	4.4 (6.4)	4.6 (8.6)
Education (primary or less), *n* (%)	5064 (92)	906 (55)	-	2137 (73)	2002 (79)	-	6518 (50)	367 (22)
Living alone, *n* (%)	1599 (29)	389 (24)	9274 (14)	1490 (51)	917 (36)	-	-	595 (36)
Currently working, *n* (%)	669 (12)	1086 (66)	44,538 (65)	428 (15)	241 (9)	-	1638 (13)	243 (15)
Never smokers, *n* (%)	5151 (94)	1135 (69)	29,894 (44)	1553 (53)	1820 (72)	-	8222 (64)	1037 (63)
Vigorous physical activity, *n* (%)	1179 (21)	-	20,999 (31)	458 (16)	857 (34)	-	12,146 (94)	1131 (69)
Hypertension, *n* (%)	2710 (49)	558 (34)	27,815 (41)	758 (26)	1574 (62)	-	3513 (27)	914 (55)
Prevalent cancer, *n* (%)	218 (4)	134 (8)	7971 (12)	231 (8)	207 (8)	-	751 (6)	133 (8)
Prevalent diabetes, *n* (%)	766 (14)	31 (2)	4742 (7)	160 (5)	263 (10)	-	663 (5)	240 (15)
Prevalent CVD, *n* (%)	209 (4)	16 (1)	2484 (4)	299 (10)	145 (6)	-	977 (8)	121 (7)

Table 3 Hazard ratio (HR) for mortality (95% confidence interval) after hip fracture among participants in three models

	Number of cohorts	HR from model 1[a]	HR from model 2[b]	HR from model 3[c]	I^2 for model 3 (*P*-value)
Total population	8	2.39 (1.95–2.92)	2.21 (1.82–2.68)	2.12 (1.76–2.57)	90% (<0.001)
Men	6	2.87 (1.90–4.35)	2.54 (1.78–3.62)	2.39 (1.72–3.31)	78% (<0.001)
Women	7	2.07 (1.67–2.56)	1.97 (1.59–2.44)	1.92 (1.54–2.39)	84% (<0.001)
Elderly (≥70 years at baseline)	5	1.91 (1.49–2.45)	1.88 (1.49–2.38)	1.84 (1.46–2.33)	90% (<0.001)

[a]Model 1: adjusted for age (in years; continuous) and sex (male/female).

[b]Model 2: adjusted for the same variables as in model 1 and additionally for the continuous variables body mass index (in kg/m^2) , height (in m), daily energy intake (in kcal/day) and alcohol intake (in g/day), and the categorical variables vigorous physical activity (yes/no), educational level (none/less than primary/vocational or technical secondary/secondary, not vocational and not technical/college or university), living alone (yes/no), employment status (full-time or part-time employment and not of pensionable age/self-employment/housewife and not of pensionable age/pensionable age and still working/pensionable age and not working/stopped working before retirement age due to poor health/unemployed and not of pensionable age) and smoking status (never/former/current smoker).

[c]Model 3: adjusted for the same variables as in model 2 and additionally hypertension (yes/no) and chronic diseases (cardiovascular disease, diabetes or cancer; yes/no).

Table 4 Hazard ratio (HR) and 95% confidence interval (CI) for mortality after hip fracture in model 3 (i.e. the fully adjusted model) by time since fracture occurrence

Time since hip fracture	Number of cohorts	HR for model 3[a]	95% CI	I^2 for model 3 (*P*-value)
≥0 to <1 year	8	2.78	2.12–3.64	81% (<0.001)
≥1 to <4 years	8	1.89	1.50–2.37	81% (<0.001)
≥4 to <8 years	8	2.15	1.81–2.55	57% (0.021)
≥8 years	7	1.79	1.57–2.05	0% (0.918)

[a]Model 3 adjusted for sex (male/female), the continuous variables age (in years), body mass index (in kg/m^2), height (in m), daily energy intake (in kcal/day) and alcohol intake (in g/day) and the categorical variables vigorous physical activity (yes/no), educational level (none/less than primary/vocational or technical secondary/secondary, not vocational and not technical/college or university), living alone (yes/no), employment status (full-time or part-time employment and not of pensionable age/self-employment/housewife and not of pensionable age/pensionable age and still working/pensionable age and not working/stopped working before retirement age due to poor health/unemployed and not of pensionable age) and smoking status (never/former/current smoker), and hypertension (yes/no) and chronic diseases (cardiovascular disease, diabetes or cancer; yes/no).

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