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Association of socioeconomic status with prognosis in hypertensive patients over age 65: A cohort study in the community setting

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ABSTRACT:

Objective:

To examine whether socioeconomic status is associated with prognosis after the diagnosis of HTN, in a population older than 65 years, in the community setting.

Design:

Retrospective cohort study.

Setting:

All the Primary Care Centres (PCC) of the Community of Madrid (n=392).

Participants:

All patients (> 65 years) with a new diagnosis of HTN (ICP-2 K86 code) in 2007- 2008, without previous kidney or cardiovascular (CV) events (n=21,754).

Interventions:

Patient records from primary care Electronic Health Records (HER) and Spanish mortality database were analyzed from January 2007 through December 2018. Sociodemographic data such as age, sex and deprivation index of the area (MEDEA index in quintiles), and characteristics, such as smoking, type 2 diabetes mellitus and hypercholesterolemia, were collected at the time of enrolment.

Primary and secondary outcome measures:

The occurrence of kidney or CV events (including mortality from these causes) and total mortality were evaluated using Cox regression.

Results:

Patients had a mean age of 73.5 (SD 6.5) years, and 63.5% were women. The median follow-up was 128.7 months (IQR: 110.6-136.7 months). There were 10,648 first kidney or cardiovascular events, including 1,508 deaths from these causes and 4,273 deaths from other causes. Adjusted for age, sex, smoking, diabetes and hypercholesterolemia, when comparing the third, fourth and last quintiles (less affluent) of the deprivation index with respect to the first quintile, the hazard of kidney or CV events increased by 14.8% (95% CI: 3.3-27.6%), 16.0% (95% CI: 6.4-26.4%) and 19.1% (95% CI: 8.9-30.2%), respectively. The deprivation index (MEDEA), was not associated with differences in adjusted total mortality.

Conclusion:

A lower socioeconomic situation was associated with the occurrence of kidney or cardiovascular events but not with total mortality in patients diagnosed with hypertension after age 65 and without previous kidney or cardiovascular events.

Keywords: hypertension; socioeconomic factors; survival; ageing; primary care

Strengths and limitations of this study

The combination of mortality regional registries and "hard events" recorded in Electronic Health Records (EHRs) can be a powerful method for monitoring outcomes.

As elderly individuals may be more likely to have stable housing situations, the identification of socioeconomic level based on area of residence may be more plausible.

In 2018, the closing date of the study, 80% of the assigned population visited their family doctor on a PCC, which enhance study generalizability.

Some potential confounders as social support or individual socioeconomic variables have not been included.

The accuracy and completeness of registries in Electronic Health Records has been only validated for hypertension and diabetes mellitus diagnosis.

INTRODUCTION

Hypertension (HTN) is one of the most prevalent cardiovascular risk factors in the community environment, and the number of diagnoses has doubled in the past 30 years(1). HTN is associated with an excess of mortality, mainly mediated by cardiovascular (CV) disease(2,3). Although the control of hypertension through pharmacological and lifestyle measures has been shown to decrease mortality from these causes(4–7), it seems that hypertensive patients have an excess risk of cardiovascular events(8,9) and overall mortality(9–13). HTN is attributed to a large disease burden, making it responsible for the loss of 143 million disability-adjusted life years (DALYs) globally in 2015(3).

However, neither the incidence of HTN nor its prognosis are homogeneous in all social groups. Almost two decades ago, potential associations between population characteristics and individual blood pressure figures began to emerge, and these figures were influenced by circumstances such as lower educational levels(14). Social deprivation in the place of residence was significantly associated with the appearance of hypertension, even after adjusting for demographic variables and lifestyles(15). Some studies showed that the probability of suffering HTN increased by up to 30% when comparing those who had spent their childhood among the most disadvantaged social classes with people who lived in advantaged areas(16). The association between socioeconomic status and HTN seems clear, and some authors proposed that it is strongly mediated by education level(17) and that the risk of HTN increases with age(18). Subsequently, it has been shown that a lower socioeconomic situation across the lifecourse was associated with a higher incidence of HTN and that both the accumulation of socioeconomic risks and the models of social mobility with more adverse socioeconomic trajectories increased the incidence rate of HTN(19,20).

The mechanisms that explain this association are not entirely clear. It seems that unhealthy lifestyles and other risk factors (e.g., smoking and obesity), which are more frequently found in

subjects from lower socioeconomic classes, could partly explain these relationships(16). In studies carried out in our environment, it has been observed that the differences in the prevalence of hypertension according to socioeconomic factors in an older population are small, and it is suggested that, in women, the direct effect of socioeconomic status and level of education on hypertension are negligible. However, in men education and socioeconomic status are related to hypertension without being mediated by the usual risk factors(21).

More recent studies show that a higher number of social vulnerabilities are associated with a progressively greater risk of developing HTN(22). The association of a lower socioeconomic situation and the incidence of cardiovascular disease is well described(16,23). Additionally, it is associated with higher mortality from these causes(24) and with total mortality. Inverse association between educational level and cardiovascular mortality has been found in our country and it was particularly strong among women(25). Some studies relate this inequity to worse health care received by people with low socioeconomic status(26). However, it is not clear whether patients with HTN in a setting with universal access to healthcare suffer from these potential differences in their prognosis associated with socioeconomic situation.

In this framework, the evidence of the association between socioeconomic status and risk factors for cardiovascular events was stronger in older subjects(18,24). Thus, the area-level socioeconomic status where patients live may be associated with the risk of cardiovascular events and mortality after the diagnosis of HTN, and such an association should be evaluated in a population aged 65 and older in the community setting.

Methods

This is a retrospective observational study of a cohort of all patients aged 65 years or older diagnosed with HTN without evidence of kidney or cardiovascular disease in their Electronic Health Record (EHR) in the Primary Care Centres (PCC) of the Community of Madrid from January

1, 2007 to January 31, 2008. We used the code ICP-2 K86, which has been previously validated for the HTN diagnosis(27). (Figure 1).

The follow-up lasted until December 31, 2018, or until the moment in which the patient died or was discharged from the health records of the Autonomous Community.

Variables collected

Demographic (age and sex), clinical and social variables were collected.

For the definition of clinical conditions, the records of the Primary Care (PC) clinical history were used and coded according to the International Classification of Primary Care (ICPC-2)(28).

The following diagnoses were collected: diabetes mellitus type 2 (DM, ICPC-2 T89 and T90), smoking history (any review that the patient smokes or diagnosis of active smoking- ICPC-2P17- at the time or in the year prior to inclusion), and hypercholesterolemia (ICPC-2 T93). The response variables were kidney or CV events, death from any cause and kidney or CV death. The International Classification of Diseases 10th edition (ICD-10) was used to study the causes of mortality(29).

In the follow-up, it was considered that there was a kidney or cardiovascular event at the time that one of the following diagnoses appeared: chronic kidney disease (ICPC-2 U99.1), ischaemic heart disease (acute myocardial infarction- ICPC-2 K75, angina- ICPC-2K74-, cardiac ischaemia, chronic - ICPC-2 K76, cerebrovascular disease- ICPC-2 K90, peripheral arterial disease- ICPC-2 K92, urinary microalbuminuria (yes/no), defined as a urine albumin/creatinine ratio greater than 30, existence of proteinuria (yes/no) defined as the presence of 300 mg/dl of protein in urine in at least two consecutive samples in the absence of concomitant disease.

The International Classification of Diseases 10th edition (ICD-10) was used to study the causes of mortality(29). Deaths due to chronic kidney disease (ICD10: N18), cerebrovascular accident (ICD10: G46; I60-I69), ischaemic heart disease (ICD10: I20-I25), heart failure (ICD10: I50) and

peripheral arterial disease (ICD10: I70, I71, I72, I74), were classified as kidney/cardiovascular mortality.

As a classification variable of the social situation of the area, the deprivation index assigned to each census tract in the MEDEA project was used, calculated from indicators related to work (unemployment, manual and casual workers) and education (total insufficient education among young people). This index allows the detection of small areas of large cities with an unfavourable socioeconomic situation and is related to general mortality(30). The index was categorized into quintiles, with the first being the most favoured and the fifth the least favoured.

The data sources linked using a matching algorithm were the EHR of PC and the registry of mortality by specific cause of the National Institute of Statistics. This study followed the guidelines for cohort studies, described in the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline and the RECORD statement.

Analysis

The database construction involved several steps to enhance data quality (see figure 1).

The distribution of the independent variables of the subject, the mean area of residence and the follow-up times were described.

Cox proportional hazards models were adjusted to study the risks associated with the context in which the subjects lived(31). The proportional hazards assumption in a Cox proportional hazards model was not met when using conventional tests, but hazard ratios over time were assessed and were found to be stable enough to proceed with the analysis. Additionally, other concerns such as influential outliers, missing data, or significant model misspecification were considered. The 95% confidence intervals for the Cox regression coefficients were estimated using bootstrap resampling. This approach has been suggested in large sample sizes or complex clinical scenarios(32).

The models were adjusted for the demographic and clinical variables of the patients. Independent models were constructed for the occurrence of kidney or cardiovascular events, including mortality from these causes, and for total mortality. The final models were also built separately for men and women. We estimated an expected size for the cohort about 20,000 subjects. It would allow finding differences in event occurrences of 2% at 10 years in each of the quintiles of the deprivation index (between 12% and 20%) even in the presence of very high variance inflation factors(33).

Patient involvement

Patients with hypertension diagnosis were not involved in setting the research question or the outcome measures. We will use these results in an ongoing research which aims to study how hypertension impact on health perception by means of focal groups.

Results

We included 21,754 patients over age 65 with new diagnoses of uncomplicated HTN in 392 centres and clinics: 12,334 in 2007 and 9,419 in 2008 (Figure 1).

Table 1 shows the characteristics of the studied cohort, in which women predominate (63.5%), with a mean age at inclusion of 73.5 years (SD 6.5 years, range 65-101 years; median 72 years, interquartile range 68-78 years). The prevalence of smokers is lower than in the general population, while the levels of DM and hypercholesterolemia are high.

The median follow-up of the cohort was 128.7 months (IQR 110.6-136.7 months).

Table 1. Characteristics of the studied cohort (n = 21,754)

Medea Index	1st Q	2nd Q	3rd Q	4th Q	5th Q	Total*
Age						
65 to 74 years	2,562 (57.2%)	2,571 (59.2%)	2,655 (62.6%)	2,828 (64.7%)	2,797 (64.9%)	13,413 (61.7%)
75 to 84 years	1,503 (33.5%)	1,433 (33.0%)	1,301 (30.7%)	1,302 (29.8%)	1,304 (30.3%)	6,843 (31.5%)
≥ 85	417 (9.3%)	340 (7.8%)	283 (6.7%)	240 (5.5%)	207 (4.8%)	1,487 (6.8%)
Median (IQR)	73 (69-79)	73 (68-78)	72 (68-77)	72 (68-77)	72 (68-77)	72 (68-78)
Woman	3,000 (63.9%)	2,811 (64.7%)	2,666 (62.9%)	2,726 (62.4%)	2,598 (60.3%)	13,801 (63.5%)
Smokers	296 (6.6%)	272 (6.3%)	254 (6.0%)	268 (6.1%)	295 (6.9%)	1,385 (6.4%)
Diabetes mellitus	518 (11.6%)	569 (13.1%)	585 (13.8%)	685 (15.8%)	673 (15.6%)	3,030 (13.9%)
Hypercholesterolemia	1.221 (27.2%)	1.150 (26.51%)	1.168 (27.6%)	1.264 (28.9%)	1.240 (28.8%)	6043 (27.8%)

*It was not possible to assign the MEDEA index to 11 subjects.

Q: quintile

IQR: Interquartile range

Occurrence of kidney or CV events included death from these causes

During follow-up, 10,648 first kidney/CV events occurred (including 1,508 deaths due to these causes without a previous event). A total of 1,937,655 person-months were observed, and the incidence rate of these events was 54/10,000 person-months. The median time of occurrence of the event was 62.6 months (IQR 33.6-92.3 months).

Table 2 shows the results of the best model explaining the association between the deprivation index and the occurrence of kidney/CV events (including death from these causes).

Table 2. Cox model for kidney or cardiovascular events, including mortality from these causes, adjusted for the covariates shown.

Variable	HR	HR CI 95%	p> z
Age			
75-84 vs. 65-74 years	1,767	1,686- 1,851	<0.001
≥ 85 vs. 65-74 years	2,980	2,731- 3,25	<0.001
Female vs. male	0,966	0,927- 1,006	0.097
Diabetes mellitus	1,357	1,283- 1,435	<0.001
Baseline smoking	1,208	1,122- 1,301	<0.001
Hypercholesterolemia	1,066	1,023- 1,111	0.002
Socioeconomic group		0- 0	<0.001
2nd vs. 1st quintile	1,009	0,916- 1,112	0.849
3rd vs. 1st quintile	1,148	1,033- 1,276	0.010
4th vs. 1st quintile	1,160	1,064- 1,264	0.001
5th vs. 1st quintile	1,191	1,089- 1,302	<0.001
Included subjects = 21,743, number of clusters (centres): 392, Number of events: 10,648			

HR = Hazard ratio; CI = Confidence interval

Adjusted for age, sex, smoking, diabetes mellitus and hypercholesterolemia, an association is observed between greater deprivation and the greater occurrence of kidney or CV events, starting from the third quintile of the MEDEA Index. This association increases slightly in intensity as the deprivation index worsens; the more unfavourable this index is, the stronger the association.

Figure 2 shows the cumulative hazard function by quintiles adjusted for the variables (at means) shown in the model in Table 2. The second quintile is not clearly different from the first, but there is an evident increase in cumulative hazard in the third, fourth and fifth quintiles, with respect to the first, after adjusting for the aforementioned variables.

The best model was run separately for men and women but no significant difference were found with the overall model (see Additional file 1, Supplementary Tables).

Occurrence of mortality from any cause

During follow-up, 5,781 deaths occurred from any cause, 1,508 deaths from kidney/CV causes and 4,273 from other causes. A total of 2,513,273 person-months was observed, and the incidence rate of these events was 23/10,000 person-months. The median time to death in those who died during the study period was 85.4 months (IQR 55.4–109.5 months).

Table 3 shows the model that studies the association between the deprivation index and mortality.

In this case, there is no association between this index and all-cause mortality. Regarding the adjustment variables, the association of age with mortality was very strong; female sex was associated with lower mortality, smoking and DM were associated with higher mortality. Hypercholesterolemia and total mortality appeared to be inversely related in this model.

Again, the best model for total mortality was run separately for men and women and no relevant differences were found with the overall model (see Additional file 1, Supplementary Tables)

Table 3. Cox model to explain all-cause mortality, adjusted for the covariates shown.

Variable	HR	HR CI 95%	p> z
Age			
75-84 vs. 65-74 years	3.446	3.255- 3.649	<0.001
≥ 85 vs. 65-74 years	13.115	12.214- 14.083	<0.001
Female vs. male	0.695	0.656- 0.736	<0.001
Diabetes mellitus	1.319	1.223- 1.422	<0.001
Baseline smoking	1.418	1.269- 1.583	<0.001
Hypercholesterolemia	0.782	0.731- 0.837	<0.001
Socioeconomic group			0.391
2nd vs. 1st quintile	0.942	0.82- 1.081	0.395
3rd vs. 1st quintile	0.913	0.798- 1.044	0.183
4th vs. 1st quintile	0.866	0.781- 1.006	0.062
5th vs. 1st quintile	0.952	0.846- 1.072	0.420
Included subjects = 21,743 Number of clusters (centres): 392, number of events: 5,781			

HR = Hazard ratio; CI = Confidence interval

Discussion

The deprivation index of the area in which one lives is associated with an increase in kidney/CV events in hypertensive patients diagnosed after age 65 and without previous cardiovascular history, in follow-up in the community environment for more than 10 years. This association remained after adjusting for other potential demographic and metabolic risk factors, such as diabetes or hypercholesterolemia, or lifestyles indicators, such as smoking. This association was not found when mortality from all causes was studied. It should also be noted that no gender differences were found when studying the aforementioned relationships between socioeconomic status and prognosis in older patients with hypertension.

In this study, an increased hazard of almost 20% of kidney/CV events (including death due to these causes) was found in patients residing in areas in the least affluent quintile compared to those who inhabited the most favoured areas. The association between the incidence of HTN

and social group is already known(15,16), also in the elderly(21). In addition, an association between a lower socioeconomic situation and an increased risk of cardiovascular and total mortality was found, and it seems that the factors that mediated this association had to do mainly with habits and inflammatory markers rather than with psychosocial risk(24). Other authors support that the role of conventional risk factors might be minor in explaining relationship between social and pshychological factors and cardiovascular disease(34). Moreover, other social situations such as being unmarried or not cohabiting have been identified as important additional risk factors for cardiovascular and total mortality(35).The association between cardiovascular mortality and socioeconomic characteristics has been described generically in our environment(25,36). However, there has been a sharp decline in cardiovascular mortality rates in the most disadvantaged socioeconomic groups in recent decades, which is attributed to better access to preventive activities and health care(37). The study of the association between socioeconomic status and mortality in hypertensive patients has been recently reported at the individual level, but it was not evident when the socioeconomic status of the area was studied(22). The association between socioeconomic status and mortality when HTN is combined with another cardiovascular risk factor, such as DM, is much stronger. Increases of almost four times the risk of mortality have been reported when DM and HTN are associated with low income levels(38), our results also go in the same direction. Furthermore, we have extended the understanding to evaluate the association of the socioeconomic level of the area with kidney or CV events, adjusted for the potential effect of other classic cardiovascular risk factors.

We found no apparent relationship between the socioeconomic status of the area and total mortality in newly diagnosed hypertensive patients over age 65 years. When the relationship between socioeconomic status and total mortality in older patients is studied, the differences in the Spanish population are lower than in the rest of Europe(39). These differences with respect to patterns of other countries have been explained by lifestyles and the existence of stronger

social networks, regardless of social class. It has been mentioned how social support can be a protective factor against cardiovascular mortality in older people(40). In our country, individuals over age 65 who lived in provinces with the most adverse socioeconomic context had the highest mortality from cardiovascular diseases and the lowest mortality from cancer and external causes(41). This may mean that the association between socioeconomic status and total mortality is not as strong as expected. In general, the trend of the past two decades is that inequalities in total mortality are reduced in all European countries and, especially, in Spain. This change is attributed more to improvements in lifestyle and access to preventive activities than to policies aimed at reducing health inequalities(42). A previous study conducted in the same region as ours, reported a differential use of more intensive PC services in those subjects with lower economic situations(43). This could indicate that there are no major problems with accessibility to health care and preventive activities and would partly explain why no association was found between the socioeconomic status of the area and total mortality in this group of patients.

One element to assess is the measurement of the socioeconomic situation. There are multiple characteristics that can define the socioeconomic situation, and this can be observed from a multidimensional perspective(44). Many of the studies mentioned use indicators of individual socioeconomic position(22,24,38). Others use the socioeconomic status of the area and evaluate its relationship with survival after a cardiovascular event(45). In fact, the deprivation of the area has been shown to be a better predictor than the individual socioeconomic situation when studying the occurrence of cardiovascular events(46). In this case, an aggregate indicator, the MEDEA index, was chosen because of its availability, multiple approaches and ability to correctly capture the social situation and be useful in the study of inequality(30).

This study was subjected to several potential limitations. Given its design, causal inferences cannot be made, individual socioeconomic variables have not been included, other variables such as marital status have not been considered, underlying diseases have not been controlled, and there are limitations inherent to studies that use registries not designed for research. Among its potential strengths, this study points out that the monitoring of the outcomes could be done exhaustively by combining two independent sources. Since the study population is elderly, the identification of the socioeconomic level with that of the area of residence may be more plausible. Also, the generalizability of the results is good enough, as accessibility to the health system, specifically to the PC doctor, is very high in our environment. In 2018, the closing date of the study, 80% of the assigned population visited their family doctor on a PCC(47).

The implications of the results discussed are clear. As has been suggested, to reduce the burden of disease derived from HTN, strategies are needed to accelerate the socioeconomic improvements of the most vulnerable population and the development of environments that promote health(48). If primary care, which provides greater accessibility to the health system, and the implementation of preventive strategies are responsible for the reduction of socioeconomic differences in mortality, enhancing access to care through investment and organizational resources is necessary. Public health policies that affect healthy behaviours should also be reinforced.

Conclusion

The deprivation index of the area in which one lives is associated with an increase in kidney or CV events in hypertensive patients diagnosed after age 65 and without previous cardiovascular history, but no association was found when mortality from all causes was studied.

The role of access to health care and preventive activities should be established, as well as future research on the lack of association between socioeconomic status and total mortality.

Declarations

Ethics approval and consent to participate

Authorization was obtained from the Ethics Committee at the Alcorcon Foundation University Teaching Hospital (18/115).

The study was carried out in accordance with the guidelines of good research practices, the principles of the Declaration of Helsinki (Fortaleza 2013), the provisions of Organic Law 3/2018 of December 5 for the Protection of Personal Data and guarantee of digital rights, and Law 14/2007 on Biomedical Research. Once all the databases were related, the data were dissociated, eliminating any potential identifiers.

The protocol approved by the Ethics Committee (see above) did not include a request for informed consent because the data handled by the researchers were dissociated and made patient identification impossible.

Consent for publication

Not applicable (see above)

Availability of data and materials

All data analysed during this study are included in this published article as a supplementary information file (Additional file 2, Raw data).

Competing interests

The authors declare no conflicts of interest.

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Authors' contributions

Conceived and designed the experiments: JMF, TAS, EPC, GRM, ABG.

Performed the experiments: JMF, TAS, EPC.

Analysed the data: JMF, TAS, PMG.

Discussed the results: JMF, TAS, PMG, EPC, GRM, ICG, ABG.

Wrote the manuscript: JMF, PMG, ICG.

Revised and approved the manuscript: JMF, TAS, PMG, EPC, GRM, ICG, ABG.

All authors read and approved the final manuscript.

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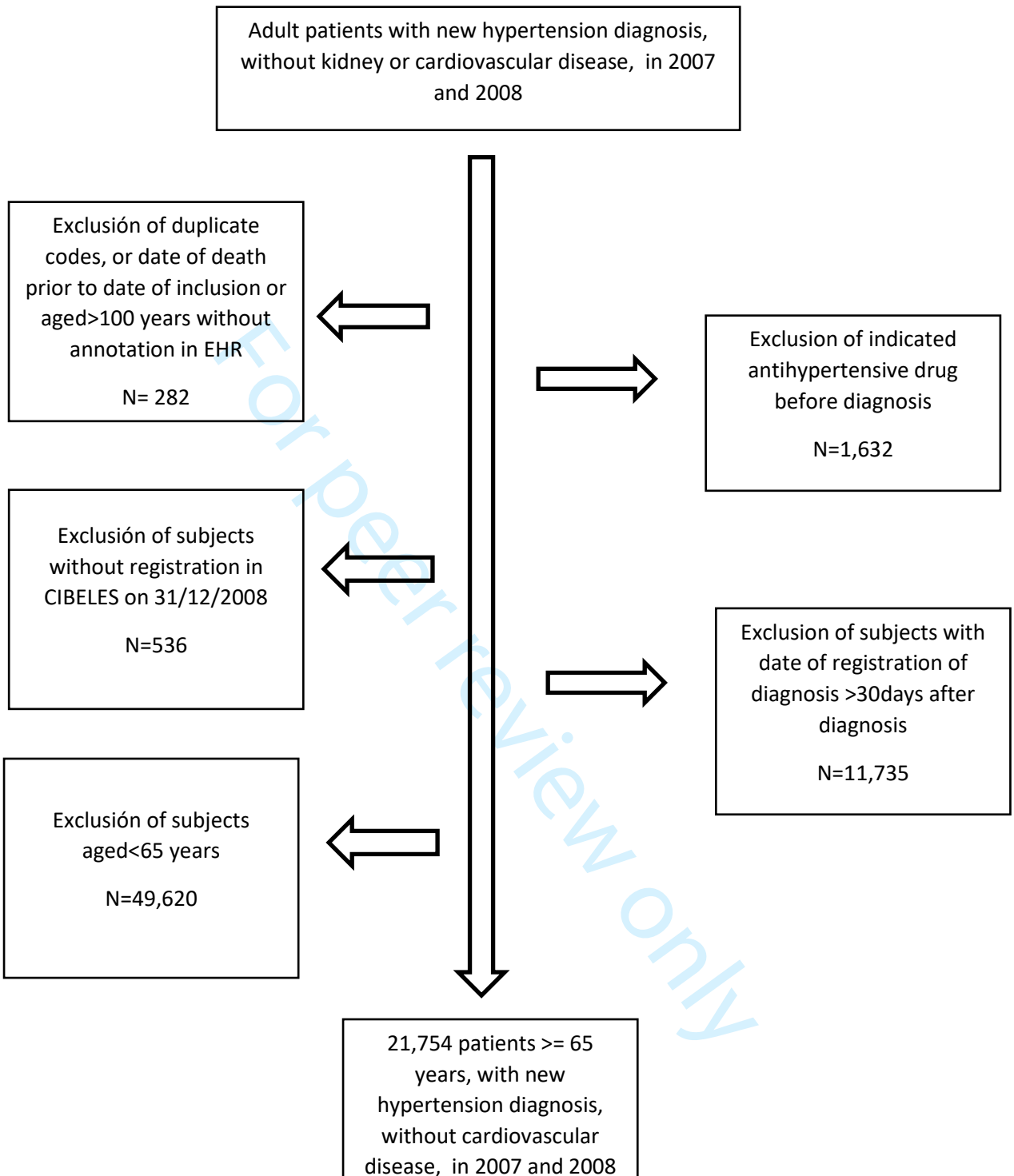
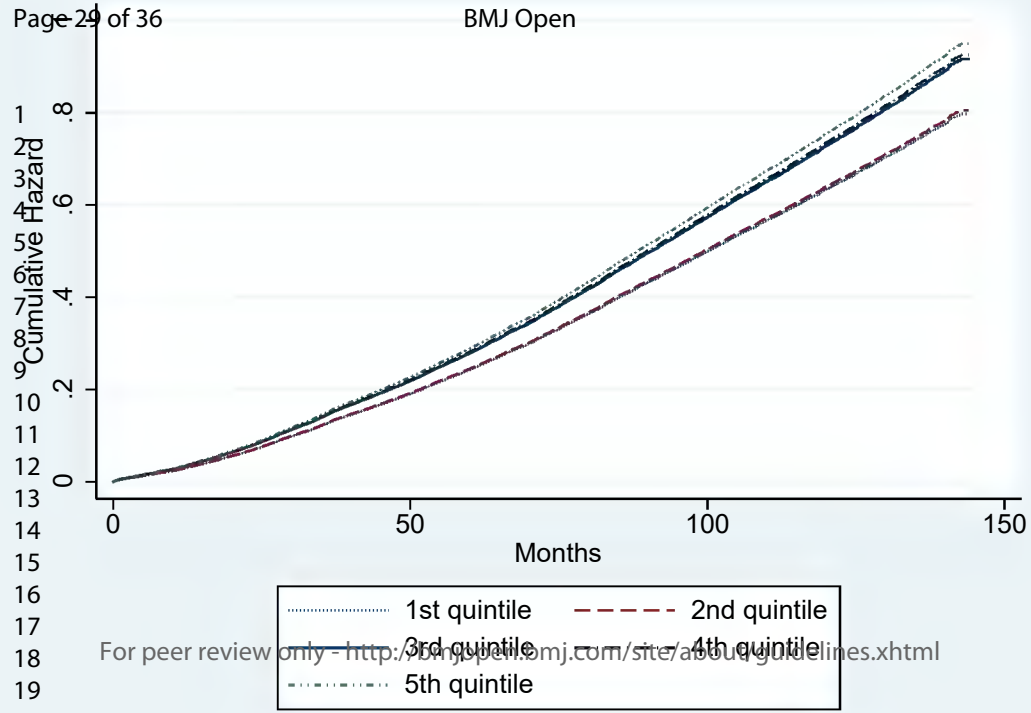
Figure 1. Cohort generation flow diagram

EHR: Electronic Health Record; CIBELES: Centre of strategic basic information for health enviroments

Figure 2. Cumulative hazard function of suffering a kidney or cardiovascular event (including death from these causes) according to MEDEA quintile, adjusted for age, sex, presence of diabetes mellitus, smoking and hypercholesterolemia (model in table 2).





Supplementary tables

Table 1. Cox model for kidney and cardiovascular events, including mortality from these causes, adjusted for the covariates shown (only men)

Variable	HR	HR CI 95%	p> z
Age			
75-84 vs. 65-74 years	1.656	1.542- 1.779	<0.001
≥ 85 vs. 65-74 years	2.639	2.262- 3.078	<0.001
Diabetes mellitus	1.335	1.234- 1.445	<0.001
Baseline smoking	1.219	1.111- 1.337	<0.001
Hypercholesterolemia	1.072	0.994- 1.157	0.065
Socioeconomic group			0.018
2nd vs. 1st quintile	1.082	0.958- 1.222	0.206
3rd vs. 1st quintile	1.141	1.007- 1.294	0.039
4th vs. 1st quintile	1.142	1.019- 1.28	0.022
5th vs. 1st quintile	1.213	1.078- 1.366	0.001
Characteristics of the model: No. of subjects = 7,942, number of clusters (centres): 392, Number of events: 3,852			

Table 2. Cox model for kidney and cardiovascular events, including mortality from these causes, adjusted for the covariates shown (only women)

Variable	HR	HR CI 95%	p> z
Age			
75-84 vs. 65-74 years	1.830	1.728- 1.937	<0.001
≥ 85 vs. 65-74 years	3.121	2.816- 3.459	<0.001
Diabetes mellitus	1.372	1.281- 1.469	<0.001
Baseline smoking	1.161	1.015- 1.327	0.029
Hypercholesterolemia	1.064	1.012- 1.119	0.018
Socioeconomic group			<0.001
2nd vs. 1st quintile	0.972	0.873- 1.082	0.601
3rd vs. 1st quintile	1.151	1.027- 1.29	0.016
4th vs. 1st quintile	1.171	1.062- 1.291	0.001
5th vs. 1st quintile	1.176	1.06- 1.304	0.002
Characteristics of the model: No. of subjects = 13,801, number of clusters (centres): 392, Number of events: 6,791.			

Table 3. Cox model for total mortality, adjusted for the covariates shown (only men)

Variable	HR	HR CI 95%	p> z
Age			
75-84 vs. 65-74 years	2.897	2.657- 3.159	<0.001
≥ 85 vs. 65-74 years	9.861	8.648- 1.125	<0.001
Diabetes mellitus	1.264	1.127- 1.419	<0.001
Baseline smoking	1.380	1.221- 1.56	<0.001
Hypercholesterolemia	0.791	0.713- 0.877	<0.001
Socioeconomic group			0.462
2nd vs. 1st quintile	0.892	0.755- 1.053	0.177
3rd vs. 1st quintile	0.919	0.783- 1.079	0.304
4th vs. 1st quintile	0.915	0.78- 1.073	0.273
5th vs. 1st quintile	0.994	0.854- 1.158	0.942
Characteristics of the model: No. of subjects = 7,942, number of clusters (centres): 392, Number of events: 2,349.			

Table 4. Cox model for total mortality, adjusted for the covariates shown (only women)

Variable	HR	HR CI 95%	p> z
Age			
75-84 vs. 65-74 years	4.056	3.723- 4.419	<0.001
≥ 85 vs. 65-74 years	15.814	14.433- 17.327	<0.001
Diabetes mellitus	1.361	1.234- 1.501	<0.001
Baseline smoking	1.378	1.133- 1.676	0.001
Hypercholesterolemia	0.786	0.726- 0.85	<0.001
Socioeconomic group			0.388
2nd vs. 1st quintile	0.982	0.838- 1.149	0.819
3rd vs. 1st quintile	0.909	0.776- 1.065	0.237
4th vs. 1st quintile	0.872	0.749- 1.016	0.079
5th vs. 1st quintile	0.917	0.799- 1.052	0.217
Characteristics of the model: No. of subjects = 13,801, number of clusters (centres): 392, Number of events: 3,429.			

We agree with the reviewer that these calculations may no longer be necessary.The RECORD statement –checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 1 Page 3-4	RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and time period within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	Page 3 Page 3 Page 3
Background rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 6-7		
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 7		
Study Design	4	Present key elements of study design early in the paper	Page 7		
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 7-8		

Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case	Page 7-8	RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	Page 8 & Figure 1 Page 8 Page 8-9 & Figure 1
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	Page 8-9	RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	Page 8-9
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page 8-9		

Bias	9	Describe any efforts to address potential sources of bias	Page 9-10		
Study size	10	Explain how the study size was arrived at	Page 10		
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	Page 9-10		
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses	Page 9-10		
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population.	Page 9

				RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	Page 9
Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	Page 8-9
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (e.g., numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram	(a) Page 10 Non applicable (c) Figure 1	RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	Figure 1
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)	(a) Page10-11, Table 1 Non applicable (c) Page 10		
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time	Page 11-14 Table 2, 3 Figure 2		

		Case-control study - Report numbers in each exposure category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or summary measures			
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Page 11-13 Table 2,3, Figure 2		
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	Non applicable		
Discussion					
Key results	18	Summarise key results with reference to study objectives	Page 14		
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page 17	RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	Page 17

Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 16-17		
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 17		
Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 19		
Accessibility of protocol, raw data, and programming code		..		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	Additional file 2

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.

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Association of socioeconomic status with prognosis in hypertensive patients over age 65: A cohort study in the community setting

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Association of socioeconomic status with prognosis in hypertensive patients over age 65: A cohort study in the community setting

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ABSTRACT:

Objective:

To examine whether socioeconomic status is associated with prognosis after the diagnosis of hypertension (HTN), in a population older than 65 years, in the community setting.

Design:

Retrospective cohort study.

Setting:

All the Primary Care Centres (PCC) of the Community of Madrid (n=392).

Participants:

All patients (> 65 years) with a new diagnosis of HTN in 2007-2008, without previous kidney or cardiovascular (K/CV) events (n=21,754).

Patient records from primary care Electronic Health Records (HER) and Spanish mortality database were analysed from January 2007 through December 2018. Sociodemographic data such as age, gender, area deprivation index the area (MEDEA -Mortalidad en áreas pequeñas Españolas y Desigualdades Socioeconómicas y Ambientales- index in quintiles), and characteristics, such as smoking, type 2 diabetes mellitus and hypercholesterolemia, were collected at the time of enrolment.

Primary and secondary outcome measures:

The occurrence of K/CV events (including mortality from these causes) and total mortality were evaluated using Cox regression.

Results:

Patients had a mean age of 73.5 (SD 6.5) years, and 63.5% were women. The median follow-up was 128.7 months (IQR: 110.6-136.7 months). There were 10,648 first K/CV events, including 1,508 deaths from these causes and 4,273 deaths from other causes. Adjusted for age, gender, smoking, diabetes and hypercholesterolemia, when comparing the third, fourth and last quintiles (less affluent) of the deprivation index with respect to the first quintile, the hazard of K/CV events increased by 14.8% (95%CI: 3.3-27.6%), 16.0% (95%CI: 6.4-26.4%) and 19.1% (95%CI: 8.9-30.2%), respectively. The MEDEA index was not associated with differences in adjusted total mortality.

Conclusion:

Living in a low socioeconomic status area is associated with an increase in kidney or cardiovascular events in hypertensive patients diagnosed after age 65 years, which will result in a significant increase in disease burden even if not related to an increase in total mortality.

Keywords: hypertension; socioeconomic factors; survival; ageing; primary care

Strengths and limitations of this study

The combination of mortality regional registries and "hard events" recorded in Electronic Health Records (EHRs) can be a powerful method for monitoring outcomes.

As elderly individuals may be more likely to have stable housing situations, the identification of socioeconomic level based on area of residence may be more plausible.

In 2018, the closing date of the study, 80% of the assigned population visited their family doctor on a PCC, which enhance study generalizability.

Some potential confounders as social support or individual socioeconomic variables have not been included.

The accuracy and completeness of registries in Electronic Health Records has been only validated for hypertension, diabetes mellitus, acute myocardial infarction and stroke diagnosis.

INTRODUCTION

Hypertension (HTN) is one of the most prevalent cardiovascular risk factors in the community environment, and the number of diagnoses has doubled in the past 30 years(1). HTN is associated with an excess of mortality, mainly mediated by cardiovascular (CV) disease(2,3). Although the control of hypertension through pharmacological and lifestyle measures has been shown to decrease mortality from these causes(4–7), it seems that hypertensive patients have an excess risk of cardiovascular events(8,9) and overall mortality(9–13). HTN is attributed to a large disease burden, making it responsible for the loss of 143 million disability-adjusted life years (DALYs) globally in 2015(3). Most of this burden of disease is due to cardiovascular and renal complications and mortality from these causes associated with the HTN diagnosis(14). However, neither the incidence of HTN nor its prognosis are homogeneous in all social groups. Almost two decades ago, potential associations between population characteristics and individual blood pressure figures began to emerge, and these figures were influenced by circumstances such as lower educational levels(15). Social deprivation in the place of residence was significantly associated with the appearance of hypertension, even after adjusting for demographic variables and lifestyles(16). Some studies showed that the probability of suffering HTN increased by up to 30% when comparing those who had spent their childhood among the most disadvantaged social classes with people who lived in advantaged areas(17). The association between socioeconomic status and HTN seems clear, and some authors proposed that it is strongly mediated by education level(18) and that the risk of HTN increases with age(19). Subsequently, it has been shown that a lower socioeconomic situation across the lifecourse was associated with a higher incidence of HTN and that both the accumulation of socioeconomic risks and the models of social mobility with more adverse socioeconomic trajectories increased the incidence rate of HTN(20,21).

The mechanisms that explain this association are not entirely clear. It seems that unhealthy lifestyles and other risk factors (e.g., smoking and obesity), which are more frequently found in

subjects from lower socioeconomic classes, could partly explain these relationships(17). In studies carried out in our environment, it has been observed that the differences in the prevalence of hypertension according to socioeconomic factors in an older population are small, and it is suggested that, in women, the direct effect of socioeconomic status and level of education on hypertension are negligible. However, in men education and socioeconomic status are related to hypertension without being mediated by the usual risk factors(22).

More recent studies show that a higher number of social vulnerabilities are associated with a progressively greater risk of developing HTN(23). The association of a lower socioeconomic situation and the incidence of cardiovascular disease is well described(17,24). Additionally, it is associated with higher mortality from these causes(25) and with total mortality. Inverse association between educational level and cardiovascular mortality has been found in our country and it was particularly strong among women(26). Some studies relate this inequity to worse health care received by people with low socioeconomic status(27). However, it is not clear whether patients with HTN in a setting with universal access to healthcare suffer from these potential differences in their prognosis associated with socioeconomic situation.

The study of socioeconomic status can be approached from an individual or contextual perspective. There are multiple characteristics that can define the socioeconomic situation, which can be considered from a multidimensional perspective(28). Many of the studies mentioned use indicators of individual socioeconomic status(23,25,29). Others use the socioeconomic status of the area and evaluate its relationship with survival after a cardiovascular event(30). In fact, the deprivation of the area has been shown to be a better predictor than the individual socioeconomic situation when studying the occurrence of cardiovascular events(31). In our setting, the MEDEA project ("Mortalidad en áreas pequeñas Españolas y Desigualdades Socioeconómicas y Ambientales") generated an area deprivation index capable of detecting areas of low socioeconomic level, which has been shown to explain differences in mortality(32). Addressing socioeconomic differences from a contextual

perspective has been successful in investigating differences in cardiovascular mortality due to certain diseases(30).

In this framework, the evidence of the association between socioeconomic status and risk factors for cardiovascular events was stronger in older subjects(19,25). Therefore, we aimed to evaluate the potential association between the area-level socioeconomic status and the risk of kidney and cardiovascular events and mortality after the diagnosis of HTN, in a population aged 65 and older in the community setting.

Methods

This is a retrospective observational study

We studied a cohort of all patients aged 65 years or older diagnosed with HTN without evidence of kidney or cardiovascular disease at inclusion in their Electronic Health Record (EHR) in the Primary Care Centres (PCC) of the Community of Madrid from January 1, 2007 to January 31, 2008. We used the code ICP-2 K86, which has been previously validated for the HTN diagnosis(33). (Figure 1).

The exclusion criteria were being under 65 years of age, having suffered from kidney or cardiovascular disease, having been diagnosed with hypertension or taking antihypertensive medication, before the start of the observation period.

The follow-up lasted until December 31, 2018, or until the moment in which the patient died or was discharged from the health records of the Autonomous Community.

Variables

Exposure variable: area socioeconomic status. The deprivation index assigned to each census area in the MEDEA project is calculated from indicators related to work (unemployment, manual

and casual workers) and education (total insufficient education among young people)(32). The index was categorized into quintiles, with the first being the most favoured and the fifth the least favoured.

Covariates

Demographic and clinical variables were collected. Age at inclusion and gender were collected from clinical records. The following clinical conditions were also collected as covariates: 1) Diabetes mellitus type 2 (DM, ICPC-2 T89 and T90); 2) Smoking history (any review that the patient smokes or diagnosis of active smoking- ICPC-2P17-at the time or in the year prior to inclusion); 3) Hypercholesterolemia (ICPC-2 T93)

Age, gender and these three clinical conditions were recorded at the time of inclusion.

Outcome variables

In the follow-up, the following study outcomes were collected: 1) Kidney events: urinary microalbuminuria (yes/no), defined as a urine albumin/creatinine ratio greater than 30, existence of proteinuria (yes/no) defined as the presence of 300 mg/dl of protein in urine in at least two consecutive samples in the absence of concomitant disease, or the presence of chronic kidney disease (ICPC-2 U99.1); 2) CV events: ischaemic heart disease (acute myocardial infarction- ICPC-2 K75, angina- ICPC-2K74-, cardiac ischaemia, chronic - ICPC-2 K76, cerebrovascular disease- ICPC-2 K90, peripheral arterial disease- ICPC-2 K92; 3) Death from any cause and kidney or CV death. deaths due to chronic kidney disease (ICD10: N18), cerebrovascular accident (ICD10: G46; I60-I69), ischaemic heart disease (ICD10: I20-I25), heart failure (ICD10: I50) and peripheral arterial disease (ICD10: I70, I71, I72, I74), were classified as kidney/cardiovascular mortality.

For the definition of different diagnoses, the records of the Primary Care (PC) clinical history were used and coded according to the International Classification of Primary Care (ICPC-2)(34).

The International Classification of Diseases 10th edition (ICD-10) was used to study the causes of mortality (35).

The data sources linked using a matching algorithm were the EHR of PC and the registry of mortality by specific cause of the National Institute of Statistics. This study followed the guidelines for cohort studies, described in the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline and the RECORD statement (Additional file 1).

Analysis

The database construction involved several steps to enhance data quality (Figure 1).

The distribution of the independent variables of the subject, the mean area of residence and the follow-up times were described.

Cox proportional hazards models were adjusted to study the risks associated with the context in which the subjects lived(36). The proportional hazards assumption in a Cox proportional hazards model was not met when using conventional tests, but hazard ratios over time were assessed and were found to be stable enough to proceed with the analysis. Additionally, other concerns such as influential outliers, missing data, or significant model misspecification were considered. The 95% confidence intervals for the Cox regression coefficients were estimated using bootstrap resampling. This approach has been suggested in large sample sizes or complex clinical scenarios(37).

The models were constructed including the MEDEA index as an independent variable and were adjusted for patient demographic and clinical variables. Two types of models were constructed. The first used the occurrence of kidney or cardiovascular events as the outcome, including mortality from these causes. In this model, follow-up was considered to end when the first of these events occurred, or when the subject was lost, or on 31 December 2018, whichever came first. The second type of models considered all-cause mortality as the event to be studied. The

final models were also built separately for men and women. Gender differences play an influential role in multiple health-related outcomes. The importance of studying gender in investigating the role of the cultural and social environment in the prognosis of HTN has been highlighted(38).

Thee estimated size for the cohort of 20,000 subjects would allow finding differences in event occurrences of 2% at 10 years in each of the deprivation index quintiles (between 12% and 20%) even in the presence of very high variance inflation factors(39).

Stata 14.2 ® software was used for data analysis.

Patient and public involvement

None

Results

We included 21,754 patients over age 65 with new diagnoses of uncomplicated HTN in 392 centres and clinics: 12,335 in 2007 and 9,419 in 2008 (Figure 1).

Table 1 shows the characteristics of the studied cohort, in which women predominate (63.5%), with a mean age at inclusion of 73.5 years (SD 6.5 years, range 65-101 years; median 72 years, interquartile range 68-78 years).

The median follow-up of the cohort was 128.7 months (IQR 110.6-136.7 months).

Table 1. Characteristics of the studied cohort (n = 21,754)

Medea Index	1st Q	2nd Q	3rd Q	4th Q	5th Q	Total*
Age						
65 to 74 years	2,562 (57.2%)	2,571 (59.2%)	2,655 (62.6%)	2,828 (64.7%)	2,797 (64.9%)	13,413 (61.7%)
75 to 84 years	1,503 (33.5%)	1,433 (33.0%)	1,301 (30.7%)	1,302 (29.8%)	1,304 (30.3%)	6,843 (31.5%)
≥ 85	417 (9.3%)	340 (7.8%)	283 (6.7%)	240 (5.5%)	207 (4.8%)	1,487 (6.8%)
Median (IQR)	73 (69-79)	73 (68-78)	72 (68-77)	72 (68-77)	72 (68-77)	72 (68-78)
Woman	3,000 (63.9%)	2,811 (64.7%)	2,666 (62.9%)	2,726 (62.4%)	2,598 (60.3%)	13,801 (63.5%)
Smokers	296 (6.6%)	272 (6.3%)	254 (6.0%)	268 (6.1%)	295 (6.9%)	1,385 (6.4%)
Diabetes mellitus	518 (11.6%)	569 (13.1%)	585 (13.8%)	685 (15.8%)	673 (15.6%)	3,030 (13.9%)
Hypercholesterolemia	1,221 (27.2%)	1,150 (26.51%)	1,168 (27.6%)	1,264 (28.9%)	1,240 (28.8%)	6,043 (27.8%)

*It was not possible to assign the MEDEA index to 11 subjects.

Q: quintile

IQR: Interquartile range

Occurrence of kidney or CV events included death from these causes

During follow-up, 10,648 first kidney/CV events occurred (including 1,508 deaths due to these causes without a previous event). A total of 1,937,655 person-months were observed, and the incidence rate of these events was 54/10,000 person-months. The median time of occurrence of the event was 62.6 months (IQR 33.6-92.3 months).

Table 2 shows the results of the best model explaining the association between the deprivation index and the occurrence of kidney/CV events (including death from these causes).

Table 2. Cox model for kidney or cardiovascular events, including mortality from these causes, adjusted for the covariates shown.

Variable	HR	HR 95%CI	*p*> z
Age			
75-84 vs. 65-74 years	1.767	1.686- 1.851	<0.001
≥ 85 vs. 65-74 years	2.980	2.731- 3.25	<0.001
Female vs. male	0.966	0.927- 1.006	0.097
Diabetes mellitus	1.357	1.283- 1.435	<0.001
Baseline smoking	1.208	1.122- 1.301	<0.001
Hypercholesterolemia	1.066	1.023- 1.111	0.002
Socioeconomic group			
2nd vs. 1st quintile	1.009	0.916- 1.112	0.849
3rd vs. 1st quintile	1.148	1.033- 1.276	0.010
4th vs. 1st quintile	1.160	1.064- 1.264	0.001
5th vs. 1st quintile	1.191	1.089- 1.302	<0.001
Included subjects = 21,743			
Number of clusters (centres): 392			
Number of events: 10,648			

HR = Hazard ratio; CI = Confidence interval

Adjusted for age, gender, smoking, diabetes mellitus and hypercholesterolemia, an association is observed between greater deprivation and the greater occurrence of kidney or CV events, starting from the third quintile of the MEDEA Index. This association increases slightly in intensity as the deprivation index worsens; the more unfavourable this index is, the stronger the association.

Figure 2 shows the cumulative hazard function by quintiles adjusted for the variables (at means) shown in the model in Table 2. The second quintile is not clearly different from the first, but there is an evident increase in cumulative hazard in the third, fourth and fifth quintiles, with respect to the first, after adjusting for the aforementioned variables.

The best model was run separately for men and women but no significant differences were found with the overall model (see Additional file 2, Supplementary Tables).

Occurrence of mortality from any cause

During follow-up, 5,781 deaths occurred from any cause, 1,508 deaths from kidney/CV causes and 4,273 from other causes. A total of 2,513,273 person-months was observed, and the incidence rate of these events was 23/10,000 person-months. The median time to death in those who died during the study period was 85.4 months (IQR 55.4–109.5 months).

The best model to study the association between the deprivation index and all-cause mortality shows no association (Table 3). Regarding the adjustment variables, the association of age with mortality was very strong; female sex and hypercholesterolemia were associated with lower mortality, smoking and DM were associated with higher mortality.

Again, the best model for total mortality was run separately for men and women and no relevant differences were found with the overall model (see Additional file 2, Supplementary Tables).

Table 3. Cox model to explain all-cause mortality, adjusted for the covariates shown.

Variable	HR	HR CI 95%	*p*> z
Age			
75-84 vs. 65-74 years	3.446	3.255- 3.649	<0.001
≥ 85 vs. 65-74 years	13.115	12.214- 14.083	<0.001
Female vs. male	0.695	0.656- 0.736	<0.001
Diabetes mellitus	1.319	1.223- 1.422	<0.001
Baseline smoking	1.418	1.269- 1.583	<0.001
Hypercholesterolemia	0.782	0.731- 0.837	<0.001
Socioeconomic group			0.391
2nd vs. 1st quintile	0.942	0.82- 1.081	0.395
3rd vs. 1st quintile	0.913	0.798- 1.044	0.183
4th vs. 1st quintile	0.866	0.781- 1.006	0.062
5th vs. 1st quintile	0.952	0.846- 1.072	0.420
Included subjects = 21,743			
Number of clusters (centres): 392			
Number of events: 5,781			

HR = Hazard ratio; CI = Confidence interval

Discussion

The deprivation index of the area in which one lives is associated with an increase in kidney/CV events in hypertensive patients diagnosed after age 65 and without previous cardiovascular history, in follow-up in the community environment for more than 10 years. This association remained after adjusting for other potential demographic and metabolic risk factors, such as diabetes or hypercholesterolemia, or lifestyles indicators, such as smoking. This association was not found when mortality from all causes was studied. It should also be noted that no gender differences were found when studying the aforementioned relationships between socioeconomic status and prognosis in older patients with hypertension.

In this study, an increased hazard of almost 20% of kidney/CV events (including death due to these causes) was found in patients residing in areas in the least affluent quintile compared to those who inhabited the most favoured areas. The association between the incidence of HTN and social group is already known(16,17), also in the elderly(22). In addition, an association between a lower socioeconomic status and an increased risk of cardiovascular and total mortality was found, and it seems that the factors that mediated this association had to do mainly with habits and inflammatory markers rather than with psychosocial risk(25). Other authors support that the role of conventional risk factors might be minor in explaining relationship between social and pshychological factors and cardiovascular disease(40). The study of the association between socioeconomic status and mortality in hypertensive patients has been recently reported at the individual level, but it was not evident when the socioeconomic status of the area was studied (23). Suggested mechanisms to explain the association between socioeconomic disadvantaged environments and cardiovascular disease relate to dietary habits, physical activity resources and other cardiovascular risk factors(28). In this paper we evaluated the association between area-level socioeconomic status and kidney and cardiovascular events in hypertensive patients, adjusting for the effect of other risk factors such as diabetes, smoking and hypercholesterolemia.

We found no apparent relationship between the socioeconomic status of the area and total mortality in newly diagnosed hypertensive patients over age 65 years. When the relationship between socioeconomic status and total mortality in older patients is studied, the differences in the Spanish population are lower than in the rest of Europe(41). These differences with respect to patterns of other countries have been explained by lifestyles and the existence of stronger social networks, regardless of social class. It has been mentioned how social support can be a protective factor against cardiovascular mortality in older people(42). In our country, individuals over age 65 who lived in provinces with the most adverse socioeconomic context had the highest mortality from cardiovascular diseases and the lowest mortality from cancer and external

causes(43). This may mean that the association between socioeconomic status and total mortality is not as strong as expected. In general, the trend of the past two decades is that inequalities in total mortality reduced in all European countries and, especially, in Spain. This change is attributed more to improvements in lifestyle and access to preventive activities than to policies aimed at reducing health inequalities (44). A previous study conducted in the same region as ours, reported a differential use of more intensive PC services in those subjects with lower economic situations(45). This could indicate that there are no major problems with accessibility to health care and preventive activities and would partly explain why no association was found between the socioeconomic status of the area and total mortality in this group of patients.

This study was subjected to several potential limitations. Given its design, causal inferences cannot be made, individual socioeconomic variables have not been included, other variables such as marital status have not been considered, underlying diseases have not been controlled, and there are limitations inherent to studies that use registries not designed for research. Among its potential strengths, this study points out that the monitoring of the outcomes could be done exhaustively by combining two independent sources. We included all patients newly diagnosed of HTN in two years in a region of Spain (Madrid) where more than 6 million people live which resulted in a very large sample size and less concerns for selection bias as compared to usual cohort studies or surveys. Since the study population is elderly, the identification of the socioeconomic status with that of the area of residence may be more plausible. Also, the generalizability of the results is good enough, as accessibility to the health system, specifically to the PC doctor, is very high in our environment. In 2018, the closing date of the study, 80% of the assigned population visited their family doctor on a PCC(46).

The implications of the results discussed relate to practice, health policies and research. Firstly, older patients diagnosed with hypertension in socioeconomic disadvantaged settings should be monitored particularly closely. Secondly, as has been suggested, to reduce the burden of disease

derived from HTN, strategies are needed to accelerate the socioeconomic improvements of the most vulnerable population and the development of environments that promote health (47). Public health policies should focus on reducing social inequalities as a mechanism for improving individual health, with special attention to elderly patients. Finally, these results encourage further study of the role of social support, the cultural context of care and the health care system in the prognosis of these diseases.

Conclusion

Living in a low socioeconomic status area is associated with an increase in kidney or CV events in hypertensive patients diagnosed after the age of 65 years and with no previous cardiovascular history, which will result in a significant increase in disease burden even if not related to an increase in total mortality.

The role of access to health care and preventive activities should be established, as well as future research on the lack of association between socioeconomic status and total mortality.

Declarations

Ethics approval and consent to participate

Authorization was obtained from the Ethics Committee at the Alcorcon Foundation University Teaching Hospital (18/115).

The study was carried out in accordance with the guidelines of good research practices, the principles of the Declaration of Helsinki (Fortaleza 2013), the provisions of Organic Law 3/2018 of December 5 for the Protection of Personal Data and guarantee of digital rights, and Law 14/2007 on Biomedical Research. Once all the databases were related, the data were dissociated, eliminating any potential identifiers.

The protocol approved by the Ethics Committee (see above) did not include a request for informed consent because the data handled by the researchers were dissociated and made patient identification impossible.

Consent for publication

Not applicable (see above)

Availability of data and materials

All data analysed in this study are available upon reasonable request to the research team.

Competing interests

The authors declare no conflicts of interest.

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Authors' contributions

Conceived and designed the experiments: JMF, TAS, EPC, GRM, ABG.

Performed the experiments: JMF, TAS, EPC.

Analysed the data: JMF, TAS, PMG.

Discussed the results: JMF, TAS, PMG, EPC, GRM, ICG, ABG.

Wrote the manuscript: JMF, PMG, ICG.

Revised and approved the manuscript: JMF, TAS, PMG, EPC, GRM, ICG, ABG.

JMF and TAS assume the role of guarantors of the paper.

All authors read and approved the final manuscript.

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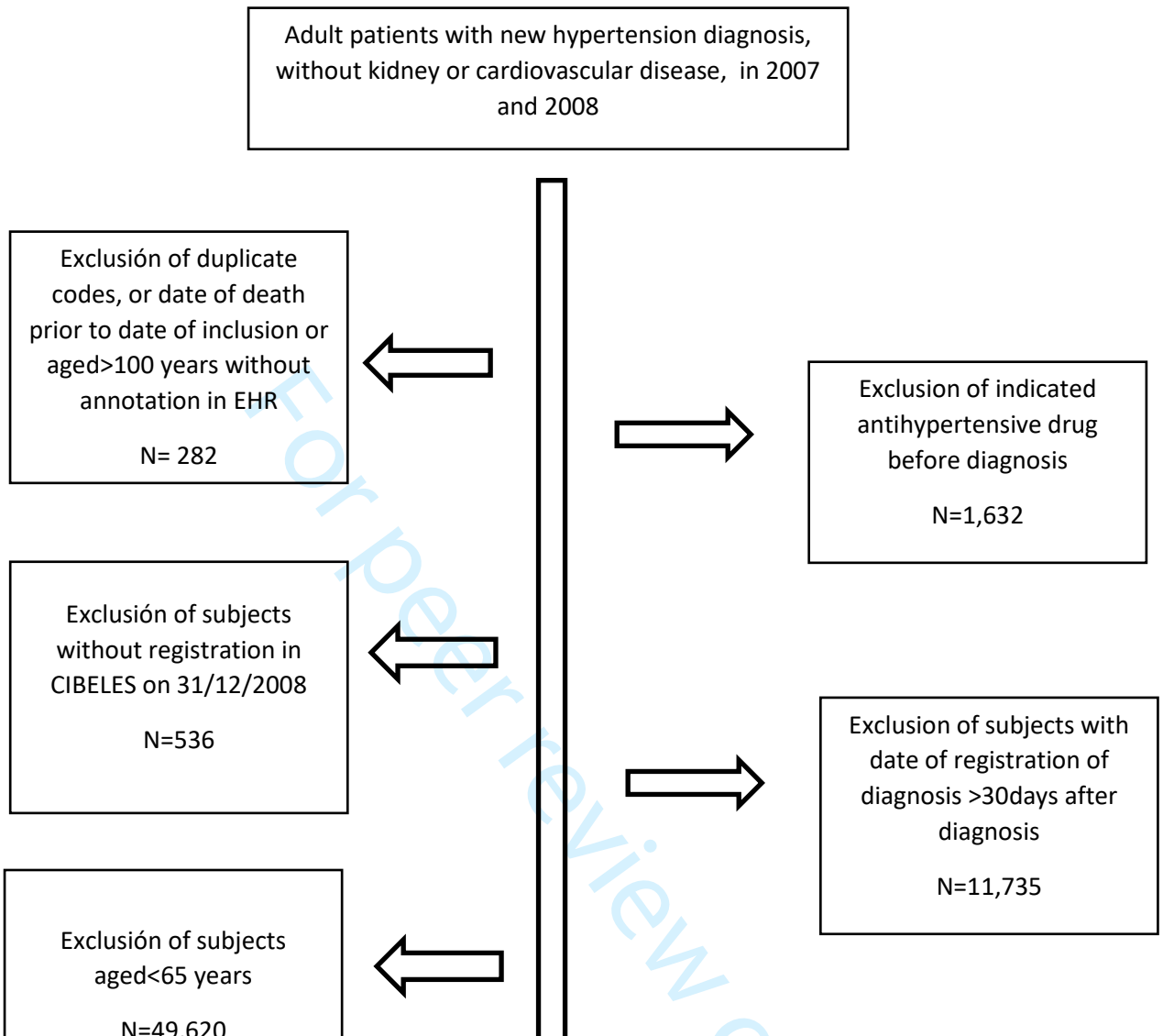
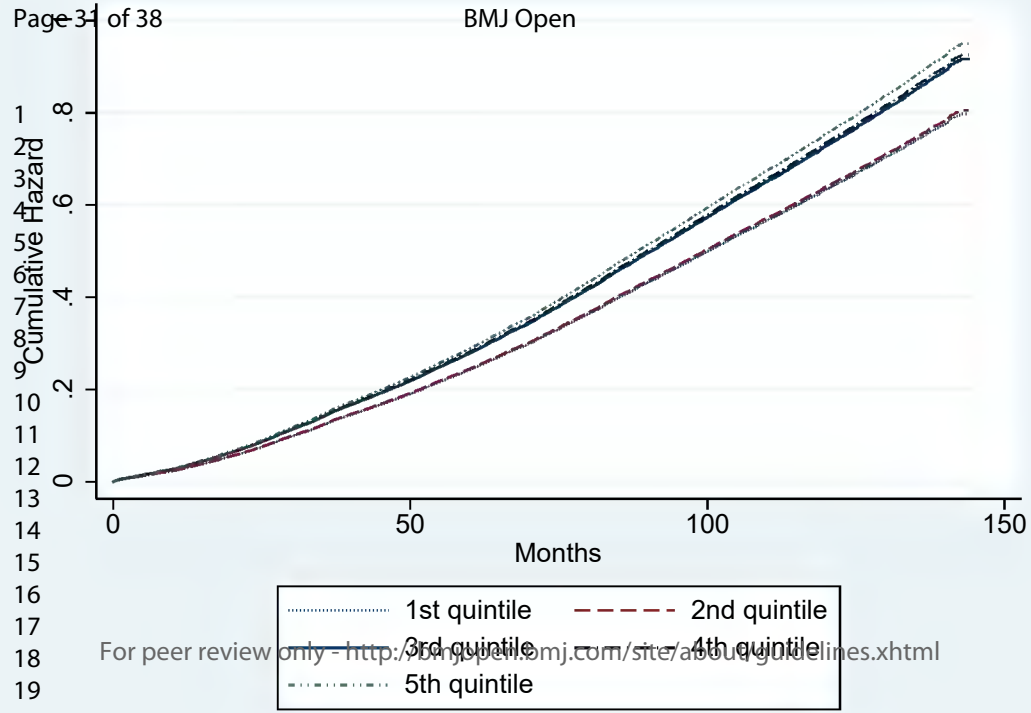
Figure 1. Cohort generation flow diagram

EHR: Electronic Health Record; CIBELES: Centre of strategic basic information for health enviroments

Figure 2. Cumulative hazard function of suffering a kidney or cardiovascular event (including death from these causes) according to MEDEA quintile, adjusted for age, gender, presence of diabetes mellitus, smoking and hypercholesterolemia (model in table 2).





We agree with the reviewer that these calculations may no longer be necessary.The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found		RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	Page 1,3 Page 3 Page 3
Background rationale	2	Explain the scientific background and rationale for the investigation being reported			Page 6-7
Objectives	3	State specific objectives, including any prespecified hypotheses			Page 8
Study Design	4	Present key elements of study design early in the paper			Page 7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection			Page 7-8

Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case		RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	Page 8 & Figure 1 Page 9 Page 9-10 & Figure 1
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.		RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	Page 8-9
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group			

Bias	9	Describe any efforts to address potential sources of bias			Page 8,9,10
Study size	10	Explain how the study size was arrived at			Page 11
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why			Page 10, 11
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses			Page 10, 11
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population.	Page 10; Declarations

				RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	Page 10
Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	Page 8, 9, 10
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (e.g., numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram	(c)	RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.*, study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	Figure 1
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)			(a) Page 11, Table 1 (c) Page 11
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure			Page 12-14 Table 2, 3 Figure 2

		category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or summary measures			
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period			Page 12-14 Table 2,3, Figure 2
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses			Non applicable
Discussion					
Key results	18	Summarise key results with reference to study objectives			Page 15
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias		RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	Page 17
Interpretation	20	Give a cautious overall interpretation of results considering objectives,			Page 16-18

		limitations, multiplicity of analyses, results from similar studies, and other relevant evidence			
Generalisability	21	Discuss the generalisability (external validity) of the study results			Page 17
Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based			Page 20
Accessibility of protocol, raw data, and programming code		..		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	Additional file 2

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.

Supplementary tables

Table 1. Cox model for kidney and cardiovascular events, including mortality from these causes, adjusted for the covariates shown (only men)

Variable	HR	HR CI 95%	p> z
Age			
75-84 vs. 65-74 years	1.656	1.542- 1.779	<0.001
≥ 85 vs. 65-74 years	2.639	2.262- 3.078	<0.001
Diabetes mellitus	1.335	1.234- 1.445	<0.001
Baseline smoking	1.219	1.111- 1.337	<0.001
Hypercholesterolemia	1.072	0.994- 1.157	0.065
Socioeconomic group			0.018
2nd vs. 1st quintile	1.082	0.958- 1.222	0.206
3rd vs. 1st quintile	1.141	1.007- 1.294	0.039
4th vs. 1st quintile	1.142	1.019- 1.28	0.022
5th vs. 1st quintile	1.213	1.078- 1.366	0.001
Characteristics of the model: No. of subjects = 7,942, number of clusters (centres): 392, Number of events: 3,852			

Table 2. Cox model for kidney and cardiovascular events, including mortality from these causes, adjusted for the covariates shown (only women)

Variable	HR	HR CI 95%	p> z
Age			
75-84 vs. 65-74 years	1.830	1.728- 1.937	<0.001
≥ 85 vs. 65-74 years	3.121	2.816- 3.459	<0.001
Diabetes mellitus	1.372	1.281- 1.469	<0.001
Baseline smoking	1.161	1.015- 1.327	0.029
Hypercholesterolemia	1.064	1.012- 1.119	0.018
Socioeconomic group			<0.001
2nd vs. 1st quintile	0.972	0.873- 1.082	0.601
3rd vs. 1st quintile	1.151	1.027- 1.29	0.016
4th vs. 1st quintile	1.171	1.062- 1.291	0.001
5th vs. 1st quintile	1.176	1.06- 1.304	0.002
Characteristics of the model: No. of subjects = 13,801, number of clusters (centres): 392, Number of events: 6,791.			

Table 3. Cox model for total mortality, adjusted for the covariates shown (only men)

Variable	HR	HR CI 95%	p> z
Age			
75-84 vs. 65-74 years	2.897	2.657- 3.159	<0.001
≥ 85 vs. 65-74 years	9.861	8.648- 1.125	<0.001
Diabetes mellitus	1.264	1.127- 1.419	<0.001
Baseline smoking	1.380	1.221- 1.56	<0.001
Hypercholesterolemia	0.791	0.713- 0.877	<0.001
Socioeconomic group			0.462
2nd vs. 1st quintile	0.892	0.755- 1.053	0.177
3rd vs. 1st quintile	0.919	0.783- 1.079	0.304
4th vs. 1st quintile	0.915	0.78- 1.073	0.273
5th vs. 1st quintile	0.994	0.854- 1.158	0.942
Characteristics of the model: No. of subjects = 7,942, number of clusters (centres): 392, Number of events: 2,349.			

Table 4. Cox model for total mortality, adjusted for the covariates shown (only women)

Variable	HR	HR CI 95%	p> z
Age			
75-84 vs. 65-74 years	4.056	3.723- 4.419	<0.001
≥ 85 vs. 65-74 years	15.814	14.433- 17.327	<0.001
Diabetes mellitus	1.361	1.234- 1.501	<0.001
Baseline smoking	1.378	1.133- 1.676	0.001
Hypercholesterolemia	0.786	0.726- 0.85	<0.001
Socioeconomic group			0.388
2nd vs. 1st quintile	0.982	0.838- 1.149	0.819
3rd vs. 1st quintile	0.909	0.776- 1.065	0.237
4th vs. 1st quintile	0.872	0.749- 1.016	0.079
5th vs. 1st quintile	0.917	0.799- 1.052	0.217
Characteristics of the model: No. of subjects = 13,801, number of clusters (centres): 392, Number of events: 3,429.			