

Prevalence, incidence, and outcomes across cardiovascular diseases in homeless individuals using national linked electronic health records

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Aims

The risk and burden of cardiovascular disease (CVD) are higher in homeless than in housed individuals but population-based analyses are lacking. The aim of this study was to investigate prevalence, incidence and outcomes across a range of specific CVDs among homeless individuals.

Methods and results

Using linked UK primary care electronic health records (EHRs) and validated phenotypes, we identified homeless individuals aged ≥ 16 years between 1998 and 2019, and age- and sex-matched housed controls in a 1:5 ratio. For 12 CVDs (stable angina; unstable angina; myocardial infarction; sudden cardiac death or cardiac arrest; unheralded coronary death; heart failure; transient ischaemic attack; ischaemic stroke; subarachnoid haemorrhage; intracerebral haemorrhage; peripheral arterial disease; abdominal aortic aneurysm), we estimated prevalence, incidence, and 1-year mortality post-diagnosis, comparing homeless and housed groups. We identified 8492 homeless individuals (32 134 matched housed individuals). Comorbidities and risk factors were more prevalent in homeless people, e.g. smoking: 78.1% vs. 48.3% and atrial fibrillation: 9.9% vs. 8.6%, $P < 0.001$. CVD prevalence (11.6% vs. 6.5%), incidence (14.7 vs. 8.1 per 1000 person-years), and 1-year mortality risk [adjusted hazard ratio 1.64, 95% confidence interval (CI) 1.29–2.08, $P < 0.001$] were higher, and onset was earlier (difference 4.6, 95% CI 2.8–6.3 years, $P < 0.001$), in homeless, compared with housed people. Homeless individuals had higher CVD incidence in all three arterial territories than housed people.

Conclusion

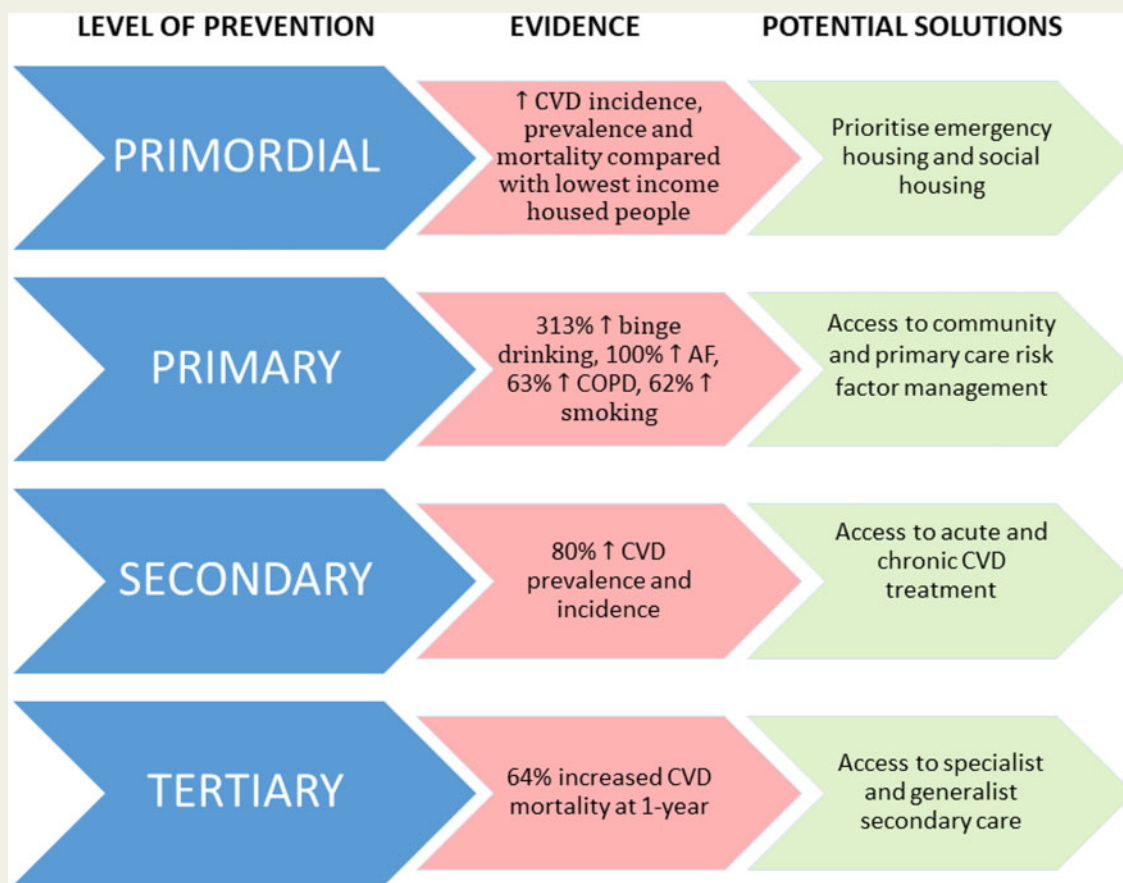
CVD in homeless individuals has high prevalence, incidence, and 1-year mortality risk post-diagnosis with earlier onset, and high burden of risk factors. Inclusion health and social care strategies should reflect this high preventable and treatable burden, which is increasingly important in the current COVID-19 context.

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Graphical Abstract



Keywords

Homeless • Cardiovascular • Electronic health records • Health inequalities • COVID-19

Introduction

Homelessness affects an estimated 100 million people worldwide.¹ Social exclusion (including homeless individuals) and low socioeconomic status are associated with increased mortality and morbidity,^{2,3} but the relationship between homelessness and specific health outcomes remains under-investigated, leading to a dearth of specific targeted healthcare interventions.

Cardiovascular diseases (CVDs) are the leading cause of burden of disease in the UK and worldwide,^{4,5} but the majority of research concerning health and healthcare of homeless people has focused on infectious diseases, mental health, and acute crisis management,² even though the CVD burden among homeless people may be higher than the general population.⁶

Existing studies show higher risk of chronic diseases and death, including CVDs^{2,7,8} in homeless people, but have considered single or composite measures of CVD, neither looking across different CVDs together, nor the whole population, nor all age categories.^{9–13}

Such data are crucial, whether to inform pathways for treatment and prevention in individuals, or to understand the population burden of homelessness and CVD for planning and implementation of public health interventions and policies, and even more so in the context of COVID-19.^{14,15} If homeless people have elevated burden and risk of CVDs, they are at higher mortality risk with COVID-19.

In housed individuals, studies across different CVDs have been instructive, whether in comparative epidemiology and time trends, or quality of treatment and prioritization in clinical practice and research,^{16,17} increasingly using electronic health records (EHRs),¹⁸ but not in homeless populations, which are defined variably across studies and countries.¹⁹ Translating these definitions into EHR presents obstacles, but if overcome, an overall view of CVD in homeless people could be gained.

We conducted a retrospective cohort study using national linked EHRs to investigate prevalence, incidence, and outcomes across major CVDs in homeless individuals, compared with housed individuals.

Methods

Data source

The study population used linked data from three sources of EHRs in the UK: Clinical Practice Research Datalink (CPRD), hospital episode statistics, and the Office of National Statistics for mortality data. CPRD is a primary care database that directly collects de-identified data of individuals from general practices (GPs) in the UK and is representative of the UK population in terms of age, sex, and ethnicity.²⁰ This study was part of CALIBER (CArdiovascular disease research using LInked Bespoke studies and Electronic health Records).¹⁸

Phenotype algorithm development

The CPRD GOLD database was searched for Read codes relating to homelessness. [Supplementary material online](#), Table S1 provides a full list of the terms. We developed an EHR algorithm for homelessness, which was reviewed by a panel of clinical and academic experts in homeless health, including primary and secondary care.

Study population

Individuals aged ≥ 16 years between 1 January 1998 and 31 January 2019 were included based on the EHR homelessness phenotype and had been registered in a practice meeting research data recording standards for at least 1 year. Individuals were excluded if 'homeless' status was missing. Controls (matched by age, sex, and GP region) were selected (5:1 for each homeless person) from eligible individuals without the homeless EHR phenotype (*Figure 1*). The homeless and housed samples were 8492 (7511 for incidence analyses) and 32 134 (30 061 for incidence analyses), respectively.

Baseline characteristics

At baseline (i.e. the first record in the study period 1998–2019), variables included socio-demography [age, gender, ethnicity, rurality, and deprivation level by Index of Multiple Deprivation (IMD)]. Since IMD is a postcode measure of deprivation and the recorded postcode of a homeless individual

is unlikely to be a good measure of their level of deprivation (e.g. if a hostel is in an area with comparatively low social deprivation or the address of a relative is given), we did not apply IMD measures to homeless individuals. Clinical data included body mass index (BMI), blood pressure, total serum cholesterol, smoking, and alcohol. Comorbidities included atrial fibrillation, hypertension, diabetes, chronic obstructive pulmonary disease, chronic kidney disease (CKD), dyslipidaemia, and osteoarthritis. Medication usage included statin, antihypertensive medication, angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, and beta-blocker.

Outcomes

Primary outcomes were 12 CVD event types [using code lists and validated algorithms as per previous CALIBER studies^{18,21,22}: stable angina (SA), unstable angina (UA), myocardial infarction (MI), sudden cardiac death/cardiac arrest, unheralded coronary death, heart failure (HF), transient ischaemic attack, ischaemic stroke or stroke not further specified, subarachnoid haemorrhage, intracerebral haemorrhage, peripheral arterial disease, and abdominal aortic aneurysm]. Diseases were grouped as CVD overall (all 12 subtypes), cardiac (SA, UA, MI, sudden cardiac death/cardiac arrest, and unheralded coronary death), cerebrovascular (transient ischaemic attack, ischaemic stroke, subarachnoid haemorrhage, and intracerebral haemorrhage), and peripheral vascular (peripheral arterial disease and abdominal aortic aneurysm). Mortality from all causes after the first diagnosis of CVD was also investigated.

Statistical analysis

Prevalence was the number of individuals with disease prior to baseline, divided by total number of individuals (per 1000 persons). Incidence rate was the number of individuals (free from the 12 subtypes of CVD, as defined above, at baseline) who developed disease during follow-up, divided by the total person-years at risk (rate per 1000 person-years). Prevalence and incidence rates were estimated for homeless and housed individuals and reported by sex and age (<35, 35–44, 45–54, 55–64, 65–74, and ≥ 75 years). Overall prevalence rate ratios and incidence rate ratios (IRRs) comparing age- and sex-matched homeless and housed people were calculated. We also provide plots of age- and gender-specific prevalence and incidence for each disease category comparing the homeless and housed population. To explore the additional impact of homelessness above and beyond neighbourhood measures of social deprivation, these plots also include lines for the housed population in IMD1 (least deprived) and IMD5 (most deprived).

We used Kaplan–Meier analysis to estimate 1-year mortality rates after first CVD diagnosis. Patient follow-up was started on the date on which all eligibility criteria were met after 1 January 1998 and was censored on the date of first CVD presentation, death from other causes, last data collection from CPRD (31 January 2019) or deregistration from the practice, whichever occurred first. Cox regression models were used to calculate hazard ratios for homeless compared to housed individuals, adjusted by sex and age at incidence. Survival curves are shown comparing homeless and housed groups with additional curves for housed IMD 1 and IMD 5 population. Proportional hazard assumption was assessed by plotting log–log survival functions, stratified by homelessness. The t-test was used to assess age difference at incidence. We used R 3.4.3, RStudio 1.1414, and Stata 15.1.

Ethical approval and funding

The study was approved by the Independent Scientific Advisory Committee of the Medicines and Healthcare products Regulatory Agency (protocol 18_283). The funder of the study (National Institute of Health Research, NIHR, Programme Development Grant: RP-DG-0117-10003) had no role in study design, data collection, data analysis, data interpretation,

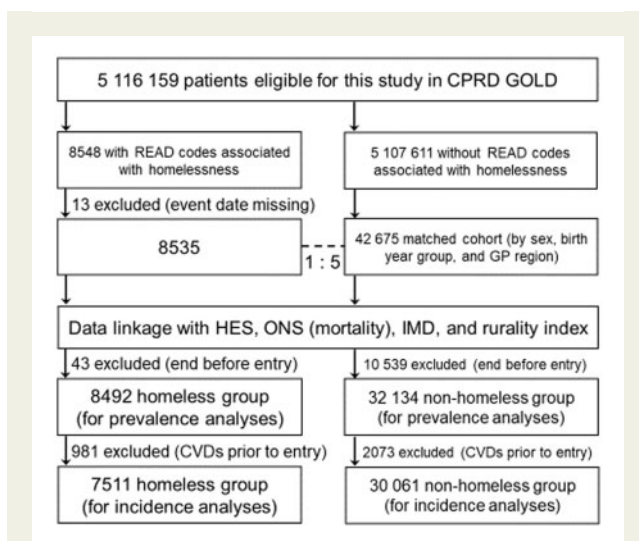


Figure 1 Inclusion criteria for study of cardiovascular disease in homeless and housed individuals. CPRD, Clinical Practice Research Datalink; CVDs, cardiovascular diseases; HES, hospital episode statistics; IMD, Index of Multiple Deprivation; ONS, Office of National Statistics.

or writing of the report. The corresponding author had full access to all the data and had final responsibility for the decision to submit for publication.

Results

Baseline characteristics

The study cohort included 40 626 individuals, 8492 of whom were homeless and 32 134 were housed (Figure 1), with matched sex

and age structures between the two groups (Table 1). Homeless individuals were more likely to be in urban areas compared to housed people (92.5% vs. 89.3%, $P < 0.001$). Homeless individuals had lower BMI, blood pressure, and total cholesterol, but higher rates of previous/current smoking and excess/binge drinking (all $P < 0.001$). Comorbidities and use of statins and beta-blockers were more common in homeless individuals (all $P < 0.001$). There was no significant difference in the use of antihypertensive medication between the two groups. Smoking and alcohol use were

Table 1 Baseline characteristics of homeless and housed individuals in the study population

	Homeless, n (%)	Housed, n (%)	P-values
Total number	8492	32 134	–
Age (years), mean [SD]	39.0 [14.6]	38.8 [14.7]	Matched
Gender, male	4975 (58.6)	18 650 (58.0)	Matched
Social deprivation (IMD)			n/a
Least deprived	n/a	6629 (20.6)	–
Most deprived	n/a	5205 (16.2)	–
Ethnicity			<0.001
White	6094 (81.2)	17 670 (81.3)	–
South Asian	163 (2.2)	742 (3.4)	–
Black	499 (6.6)	746 (3.4)	–
Others	749 (10.0)	2578 (11.9)	–
Urban area	7854 (92.5)	28 711 (89.3)	<0.001
BMI (kg/m ²), mean [SD]	25.8 [6.1]	26.4 [5.6]	<0.001
SBP (mmHg), mean [SD]	124.2 [17.3]	125.7 [17.0]	<0.001
DBP (mmHg), mean [SD]	76.5 [11.1]	77.0 [10.7]	0.002
Total serum cholesterol (mmol/L), mean [SD]	5.17 [1.20]	5.26 [1.12]	<0.001
Smoking status			<0.001
Non-smoker	1515 (21.9)	12 471 (51.7)	–
Ex- or current smoker	5412 (78.1)	11 635 (48.3)	–
Alcohol consumption			<0.001
Non-drinker	1237 (45.4)	3475 (52.4)	–
Ex- or current drinker	1217 (44.7)	2992 (45.1)	–
Excess or binge drinker	271 (9.9)	161 (2.4)	–
Comorbidities			
Atrial fibrillation	115 (1.4)	238 (0.7)	<0.001
Hypertension	837 (9.9)	2752 (8.6)	<0.001
Diabetes	468 (5.5)	1000 (3.1)	<0.001
Chronic obstructive pulmonary disease	1939 (22.8)	4501 (14.0)	<0.001
CKD	98 (1.2)	297 (0.9)	0.05
Dyslipidaemia	321 (3.8)	1103 (3.4)	0.12
Osteoarthritis	555 (6.5)	1478 (4.6)	<0.001
Medication use			
Statin	1075 (12.7)	3663 (11.4)	0.001
Antihypertensive medication	1118 (13.2)	4192 (13.0)	0.77
ACE inhibitor	762 (9.0)	3027 (9.4)	0.21
Angiotensin receptor blocker	220 (2.6)	1047 (3.3)	0.002
Beta-blocker	1170 (13.8)	3106 (9.7)	<0.001

Proportion of participants with non-missing values: social deprivation 99.9% (40580/40626), ethnicity 72% (29241), BMI 59.8% (24280), blood pressure 68.2% (27713), total cholesterol 26.6% (10789), smoking status 76.4% (31033), alcohol consumption 23% (9353). P-value was for the difference between homeless and housed individuals. ACE, angiotensin-converting enzyme; BMI, body mass index; CKD, chronic kidney disease; DBP, diastolic blood pressure; IMD, Index of Multiple Deprivation; SBP, systolic blood pressure; SD, standard deviation.

greater in men than women in both homeless and housed populations (data not shown).

Prevalence

Baseline CVD prevalence was higher in homeless people than in housed people across subtypes: 8.7% and 5.0% (SA); 1.2% and 0.4% (UA); 1.4% and 0.7% (MI); 0.3% and 0.1% (sudden cardiac death/cardiac arrest); 0.9% and 0.6% (HF); 0.6% and 0.3% (transient ischaemic attack); 1.1% and 0.5% (ischaemic stroke); 0.2% and 0.1% (subarachnoid haemorrhage); 0.2% and 0.1% (intracerebral haemorrhage); 1.0% and 0.4% (peripheral arterial disease); and 0.1% and 0.1% (abdominal aortic aneurysm), respectively. Homeless people had higher prevalence of all CVDs than housed people (11.6% and 6.5%), in men and women, and in most age groups (Table 2 and Figures 2 and 3). A gradation from housed IMD 1, housed IMD 5, to homeless people in increasing order was seen in most sub-groups (Supplementary material online, Tables S2 and S3).

Incidence

As with prevalent CVD, homeless people had higher incidence rate for all CVDs combined, compared to their housed counterparts, in most sex and age categories. Homeless men had more than double the incidence of cardiac diseases combined than that in housed men [IRR 2.76, 95% confidence interval (CI) 2.04–3.55 in the 45–54-year group and 3.35, 1.87–6.03 in the <35-year group] (Table 2). Homeless women also had higher incidence of cardiac diseases compared to housed women (2.20, 1.26–3.85 in the 55–64-year group and 2.04, 1.38–3.00 in the <35-year group). Homeless individuals had earlier age of incidence of all CVDs [difference: 4.6 (95% CI 2.8–6.3) years], cardiac [4.9 (2.8–6.9) years], cerebrovascular [3.7 (-0.2 to 7.7) years], and peripheral vascular diseases [7.9 (2.9–12.9)] (Supplementary material online, Table S4). Other than cerebrovascular and peripheral vascular diseases in women (where numbers of events were small), incidence of CVD in all arterial territories was higher in homeless people than in housed people in most age groups (Figure 3). An additional increase between housed IMD 5 and homeless groups was observed as prevalence. Other than UA, MI, sudden cardiac death/cardiac arrest, unheralded coronary death, ischaemic stroke, intracerebral haemorrhage and peripheral arterial disease in women and transient ischaemic attack, subarachnoid haemorrhage, and abdominal aortic aneurysm in both sexes (where numbers of events were low), incidence for all CVD subtypes was higher in homeless individuals than in housed individuals (Supplementary material online, Table S3).

Mortality

Crude 1-year mortality rates after the first diagnosis of any CVDs were 15.3% and 11.6% in homeless and housed people, respectively. Homeless individuals had higher age- and sex-adjusted mortality than housed individuals for all CVDs, cardiac and cerebrovascular, but not peripheral vascular diseases (Figure 4). Being homeless was associated with higher risk of mortality for all CVDs combined (adjusted hazard ratio 1.64; 95% CI 1.29–2.08, $P < 0.001$) and cardiac diseases (1.57; 1.15–2.16, $P = 0.005$), but not for cerebrovascular (1.49; 0.90–2.45, $P = 0.12$) and peripheral vascular diseases (0.90; 0.37–2.21, $P = 0.82$) (Table 2).

Table 2 Comparisons of prevalence, incidence, and 1-year mortality (adjusted for age and sex) in homeless people vs. age- and sex-matched controls

Disease	Prevalence (%)		PRR (95% CI, P)	Incidence (per 1000 person-years)		IRR (95% CI, P)	Crude 1-year mortality (%)		aHR (95% CI, P)
	Homeless	Housed		Homeless	Housed		Homeless	Housed	
All CVDs	11.6	6.5	1.79 (1.67–1.92, <0.001)	14.7	8.1	1.80 (1.62–2.01, <0.001)	15.3	11.6	1.64 (1.29–2.08, <0.001)
Cardiac	9.3	5.4	1.73 (1.60–1.88, <0.001)	10.3	5.8	1.76 (1.55–2.01, <0.001)	11.8	10.1	1.57 (1.15–2.16, 0.005)
Cerebrovascular	1.9	0.8	2.25 (1.85–2.74, <0.001)	2.4	1.4	1.80 (1.39–2.35, <0.001)	17.8	16.1	1.49 (0.9–2.45, 0.12)
Peripheral vascular	1.1	0.5	2.33 (1.80–3.03, <0.001)	1.4	0.8	1.67 (1.19–2.36, 0.003)	9.5	15.1	0.90 (0.37–2.21, 0.82)

aHR, adjusted hazard ratio (adjusted for age and sex); CI, confidence interval; CVDs, cardiovascular diseases; IRR, incidence rate ratio; PRR, prevalence rate ratio.

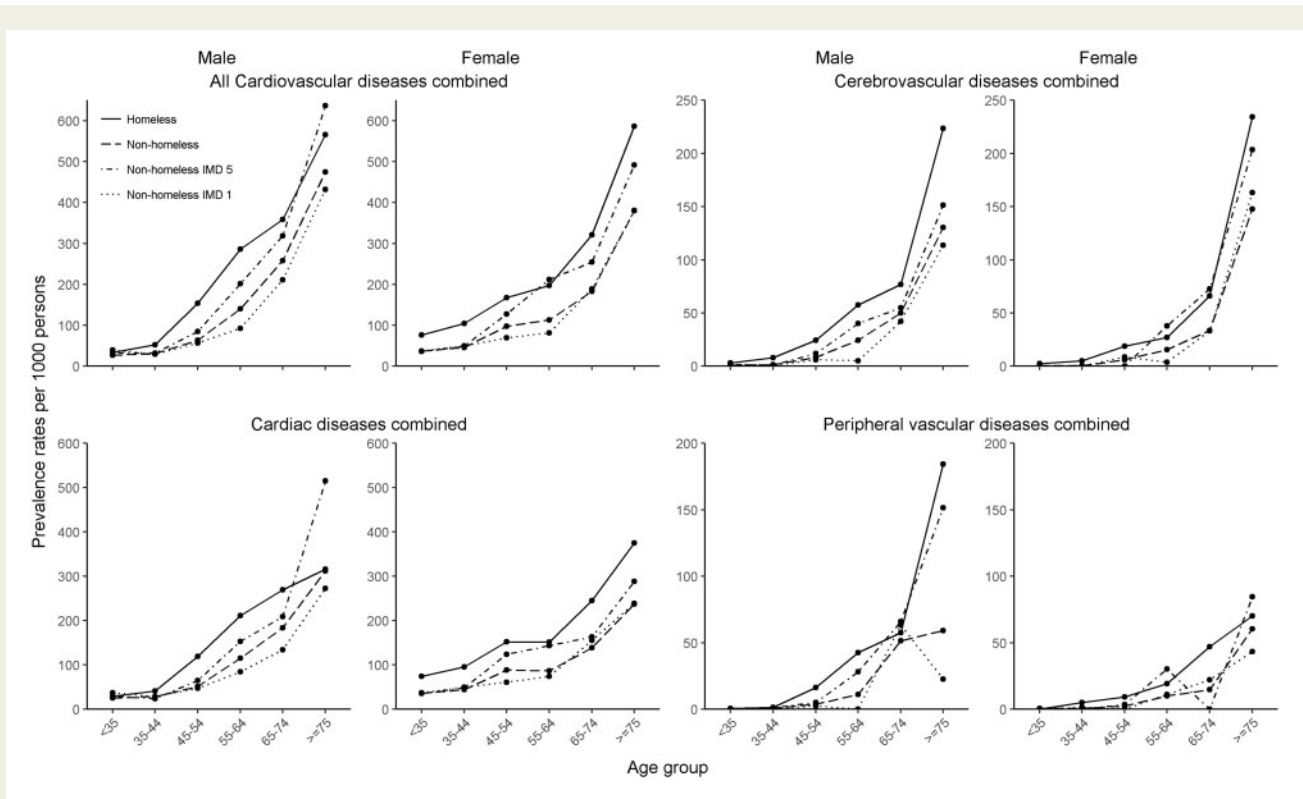


Figure 2 Prevalence of all cardiovascular, cardiac, cerebrovascular diseases and peripheral vascular diseases.

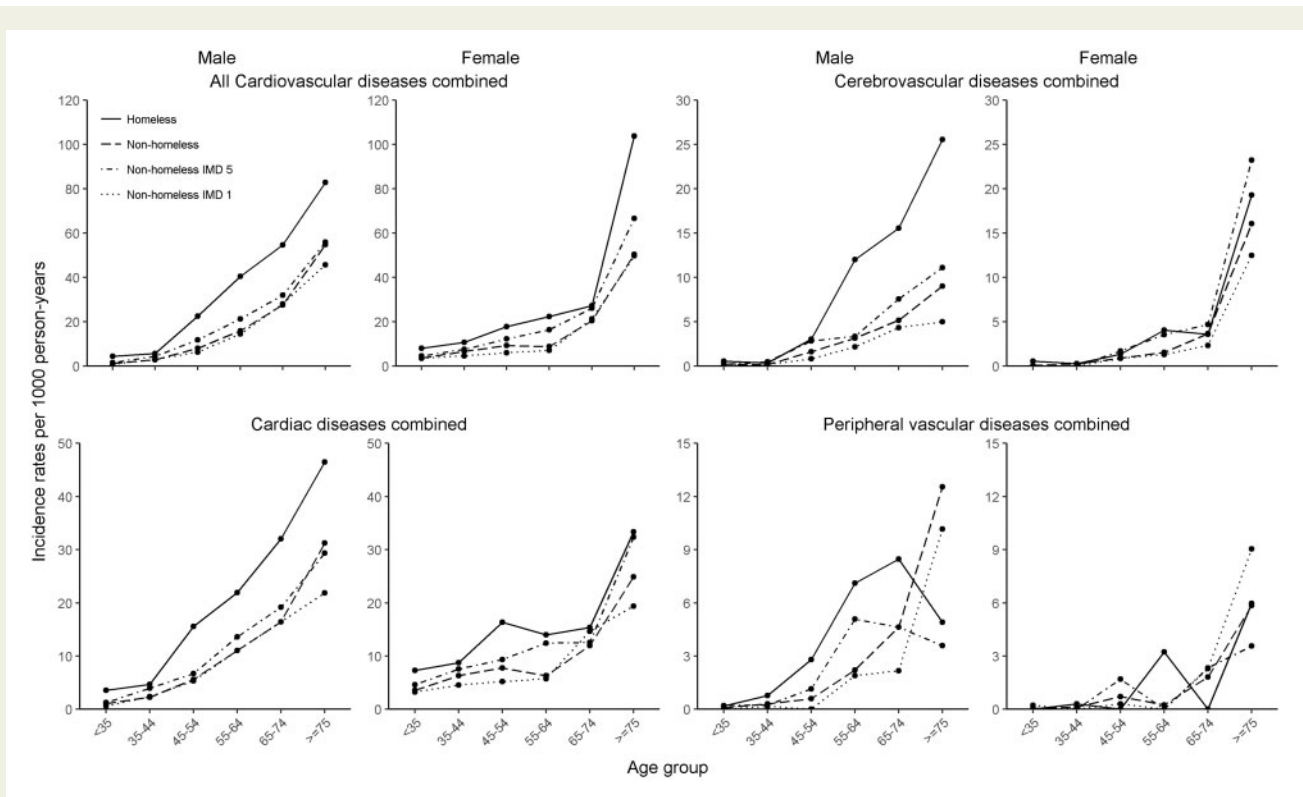
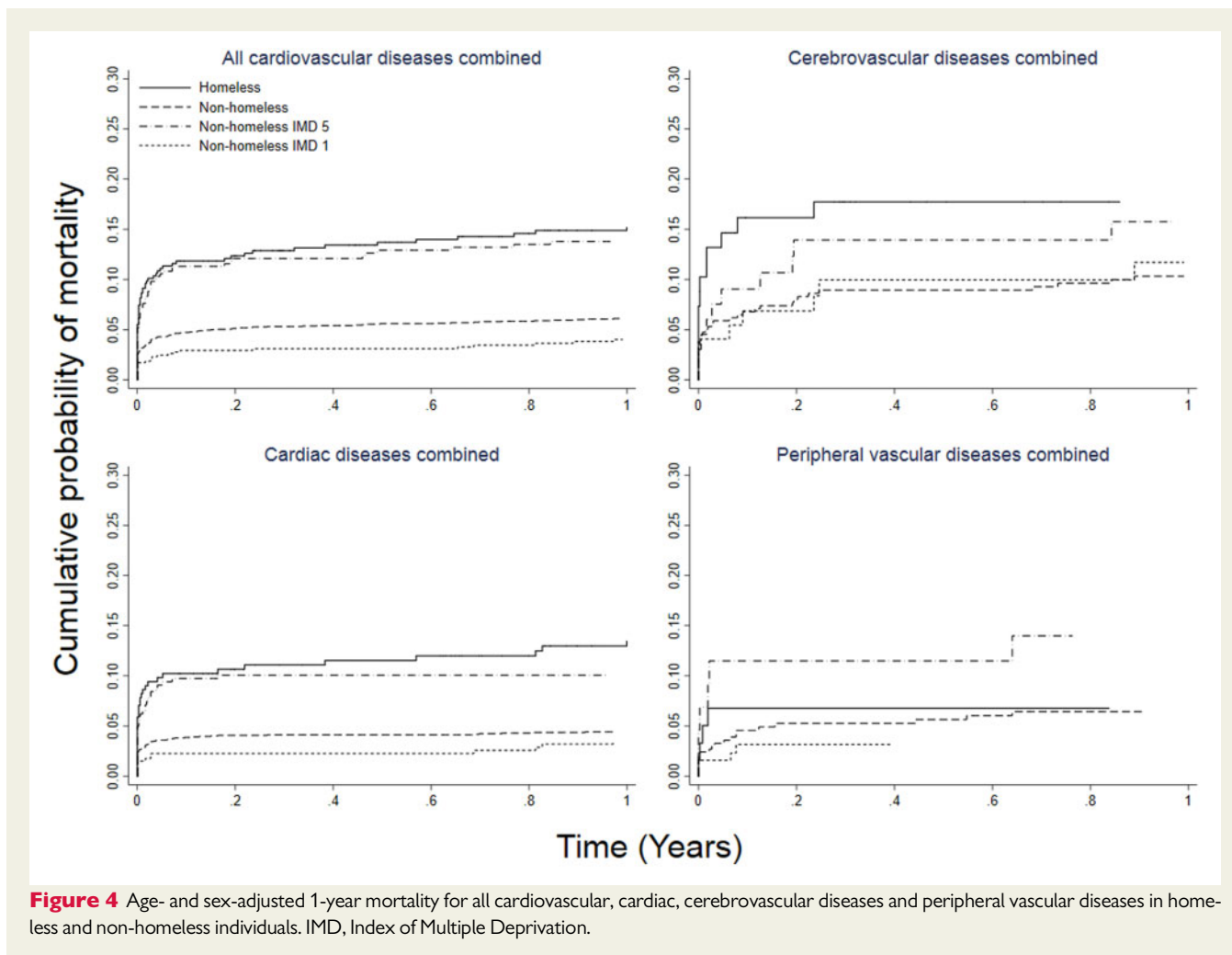


Figure 3 Incidence of all cardiovascular, cardiac, cerebrovascular diseases and peripheral vascular diseases.



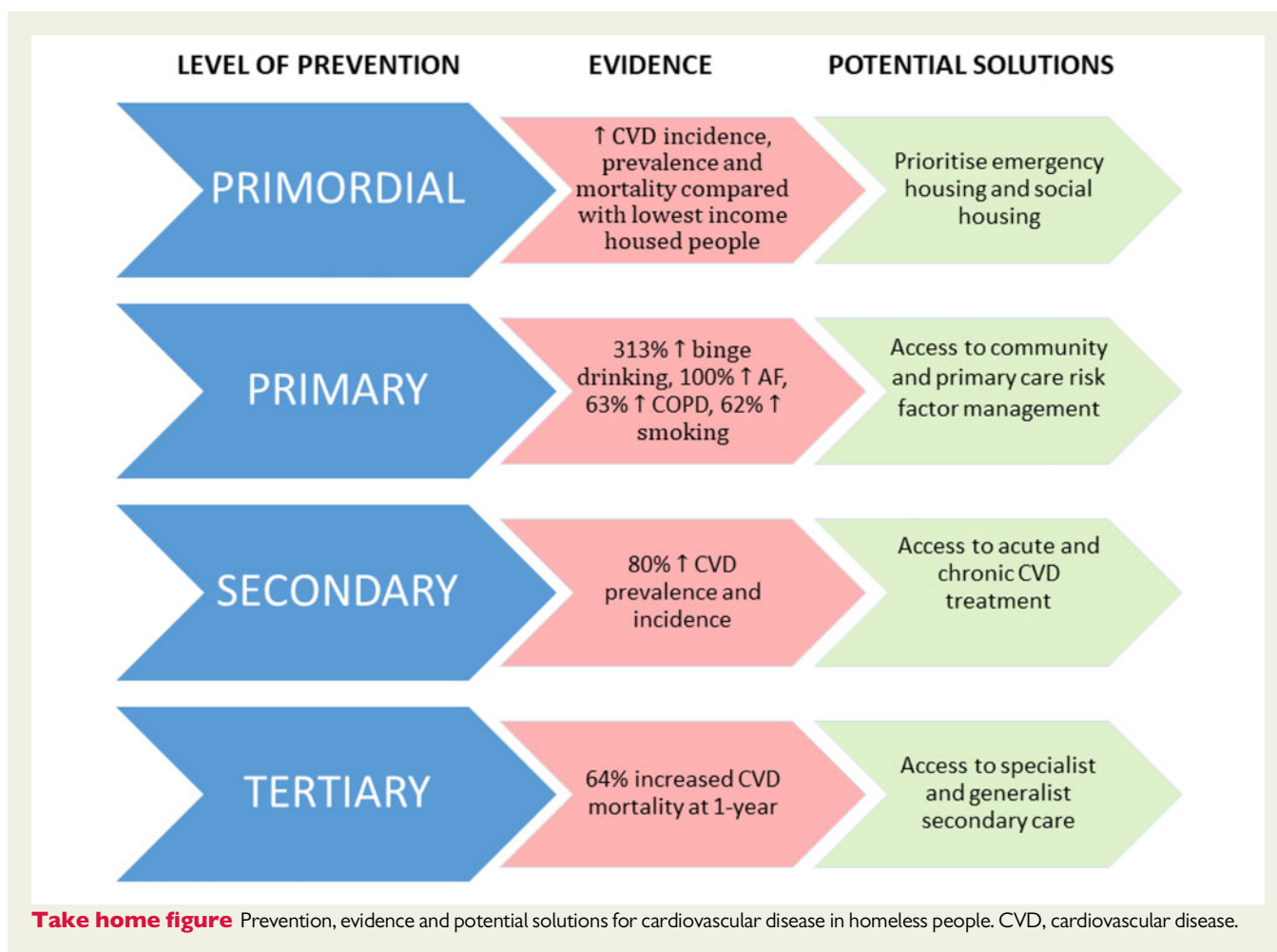
Discussion

This first large-scale population-based study of CVDs in the homeless population has four major findings. First, homeless people have increased burden of comorbidities, particularly smoking, alcohol, diabetes, and hypertension, compared with housed individuals. Second, they are around 1.8 times more likely to have CVDs at baseline, compared with their housed counterparts. Third, homeless people are around 1.8 times more likely to develop new CVD, with important differences by age, sex, and arterial territory. Fourth, homeless individuals are around 1.6 times more likely to die within 1 year of diagnosis, compared with housed individuals.

High rates of smoking and comorbidities indicate an unmet need for primary prevention and integrated care of homeless CVD ([Take home figure](#)).²³ Prior studies corroborate the high burden of hypertension and CVD risk factors,^{24,25} but there are no specific interventions for homeless or inclusion health populations and limited research regarding CVD to-date.²⁶ The relatively high burden of chronic obstructive pulmonary disease, atrial fibrillation, and other chronic conditions highlight that services to prevent and treat CVD

cannot be 'stand-alone' and must account for the multimorbidity and complex social, psychological, and physical factors encountered by this heterogeneous population. Homeless people have been identified as particularly vulnerable in the current COVID-19 pandemic.²⁷ The UK government has emphasized particular high-risk conditions (including CVD, chronic obstructive pulmonary disease and diabetes), which are associated with high excess COVID-19-related risk of mortality and indicate a greater need for social isolation.²⁸ We now show that homeless individuals have higher prevalence of these same factors, making them high risk for poor outcomes associated with COVID-19 infection.

The high prevalence of CVD compared with housed individuals shows that the current paradigm for managing homeless and inclusion health, which largely neglects CVD and non-communicable diseases (NCDs), needs a total shift in thinking. As homelessness increases in the UK and globally,²⁹ CVD, which is already known to be a cause of homeless morbidity and mortality,⁶ is likely to also increase. Part of the neglect is likely to be due to under-diagnosis and under-treatment of risk factors, which require improvements in system approaches to individuals and populations. However, beyond



gaps in evidence and implementation, there are clearly gaps in awareness and advocacy. There are parallels with the global neglect of CVD and NCDs in low- and middle-income countries three decades ago.³⁰ A combination of robust epidemiologic data and mobilization of stakeholders was needed to begin to address the global burden of NCDs, and it is likely that the same strategies will be required to improve CVD management in homeless individuals.

Compared with housed populations, increased incidence of cardiac and cerebrovascular disease appears to be greater public health concerns than peripheral vascular disease in homeless people. The observed lower rates of peripheral vascular disease may reflect under-diagnosis rather than true lower rates, which warrants further investigation. Our incidence analyses demonstrate the extreme impact of homelessness beyond the impact of social deprivation. As in previous population-based studies of arterial disease across territories,¹⁶ incidence of CVD in women seems to lag behind men by approximately 10 years but catches up in later life. For example, the highest IRR for all CVD among female individuals was seen in the 55–64 age group, while among male individuals, IRR decreased as age increased, with a second peak in 45–54 years. The sex difference in older age can potentially be attributed to the increased risk of cardiac diseases associated with

menopause in women.³¹ It appears that homelessness further increases this risk for older women. There has been no study focusing on the cardiac risk management of women after menopause, which seems worthy of further investigation.

We showed that homeless people had a 1.6-fold higher mortality risk at 1 year, compared to their housed counterparts, if they developed any CVD, even after adjustment for age and sex. This may simply be because homeless people are at higher mortality risk than the housed population,² but it can also be argued that the elevated mortality risk after CVD onset can be attributed to delayed diagnosis or challenges in disease management, including potentially worse adherence to medications.²³ Interestingly, our baseline data do not suggest a difference between homeless and housed individuals with respect to the prescription of antihypertensive medications. However, adherence is likely to be low, which we are not able to analyse with these data. Furthermore, given that incidence rates of CVD are higher in homeless individuals, a greater need for anti-hypertensives may be expected. We also found very poor 1-year survival from CVD beyond the poor rates observed in the most deprived (IMD 5), housed individuals, the reasons for which warrant further investigation, but could include later diagnosis in relation to stage of disease or poor access to interventions.

The feasibility of developing EHR phenotypes for homelessness is an added value of our study. Although Read codes have been replaced by SNOMED-CT in UK clinical practice, the code lists (Supplementary material online, Table S1) can be easily adapted for research and practice. To accelerate health research in this particularly vulnerable population, a more accessible and less costly methodology is needed, which an EHR phenotype (which should be validated) can address.

The age- and disease-specific prevalence in homeless individuals were similar to that seen in a recent cross-sectional (Supplementary material online, Figure S1 and Supplementary material online, Table S5),⁷ validating the algorithm we have developed. Age-specific incidence rates of territory-specific CVD in housed individuals in this study were similar to rates observed in the Oxford Vascular Study (Supplementary material online, Figure S4).

Limitations

There are several limitations of the current study. Although this is large population-based study, it is observational by design and CPRD is restricted to those registered by GPs. GP registration rates for homeless individuals are likely to be poor, particularly for younger individuals, which might have affected the observed relationship between homelessness and burden of CVDs, which are strongly associated with age.¹⁶ In addition, housing status is not measured in the Quality and Outcomes Framework, the presence of which has enhanced the data quality of CPRD.²⁰ As such, GPs may not be incentivized to record this information in a Read code. If this is the case, some potentially homeless people may have been classified as housed. However, we have assumed low rates of misclassification, due to the relative size of the housed population compared to the homeless population. Unmeasured confounders may have impact on the increased risk and worse outcomes for homeless people observed in this study. Potential confounders include smoking, alcohol, hypertension, and other comorbidities, social factors, and more importantly, drug use. We did not adjust for behavioural risk factors because they are likely to be on the causal pathway and we were interested in burden rather than causation. Existing studies suggest a relationship between prevalent drug abuse and CVD risks⁹; however, this was not measured in the current study, partly due to a lack of established phenotyping for recreational drug use.

Conclusions

Despite limitations, we provide a comprehensive and multi-dimensional picture of the burden and risk across a wide range of CVDs and across the whole age spectrum within the homeless population (Take home figure), compared to a housed matched cohort. In terms of risk factors, sex- and age-specific prevalence and incidence rates, and disease-specific mortality rates, we have quantified the elevated CVD risks among homeless people. Health professionals, policymakers, and the public need to recognize homeless populations as a high-risk group for CVDs and plan appropriate interventions and policies.

Perspectives

Competency in medical knowledge: CVD has higher prevalence, incidence, and mortality in homeless individuals than their housed counterparts.

Competency in patient care: in homeless individuals, screening, and diagnosis of CVD across arterial territories, as well as prevention through optimal management of risk factors, should be prioritized.

Translational outlook 1: although this is a retrospective EHR study, the observations of early onset and high incidence of CVD, and the high-risk factor burden, will inform future studies of how homelessness increases CVD risk, which in turn will guide integrated interventions.

Translational outlook 2: health and social care strategies in inclusion health should reflect this high burden of treatable risk factors and disease, which is increasingly important in the current context of COVID-19.

Data availability

Data for these analyses are not available and require application to and approval by Clinical Practice Research Datalink (CPRD).

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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A.N. acquired, analysed, and interpreted the data. A.B. was the principal investigator and had the original research idea. K.D. contributed to the data acquisition and prepared the data. H.E. contributed to the study design. A.B., A.N., H.E., and A.H. contributed to the analysis plan. A.B. and A.N. wrote the initial manuscript and all authors provided critical analysis for the final manuscript.

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