

BMJ Open Geographical inequalities in acute myocardial infarction beyond neighbourhood-level and individual-level sociodemographic characteristics: a Danish 10-year nationwide population-based cohort study

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ABSTRACT

Objective This study examined whether geographical patterns in incident acute myocardial infarction (AMI) were explained by neighbourhood-level and individual-level sociodemographic characteristics.

Design An open cohort study design of AMI-free adults (age ≥30 years) with a residential location in Denmark in 2005–2014 was used based on nationwide administrative population and health register data linked by the unique personal identification number. Poisson regression of AMI incidence rates (IRs) with a geographical random effect component was performed using a Bayesian approach. The analysis included neighbourhood-level variables on income, ethnic composition, population density and population turnover and accounted for individual-level age, sex, calendar year, cohabitation status, income and education.

Setting Residents in Denmark (2005–2014).

Participants The study population included 4 128 079 persons (33 907 796 person-years at risk) out of whom 98 265 experienced an incident AMI.

Outcome measure Incident AMI registered in the National Patient Register or the Register of Causes of Death.

Results Including individual and neighbourhood sociodemographic characteristics in the model decreased the variation in IRs of AMI. However, living in certain areas was associated with up to 40% increased IRs of AMI in the adjusted model and accounting for sociodemographic characteristics only moderately changed the geographical disease patterns.

Conclusions Differences in sociodemographic characteristics of the neighbourhood and individuals explained part, but not all of the geographical inequalities in incident AMI. Prevention strategies should address the confirmed social inequalities in incident AMI, but also target the areas with a heavy disease burden to enable efficient allocation of prevention resources.

INTRODUCTION

Geographical variation in ischaemic heart disease, including acute myocardial infarction

Strengths and limitations of this study

- The main strength of the study was the individual-level linkable data from registers on residential location, hospital admissions, sociodemographic characteristics and death for the entire adult Danish population.
- Data in the administrative nationwide registers used had high internal validity, long follow-up and were geocoded at the parish level providing data with the location of residence for a nationwide 10-year cohort including incident acute myocardial infarction cases.
- A merit of the study was the nuanced definition of sociodemographic indicators including both neighbourhood-level and individual-level sociodemographic characteristics of the population.
- Incorporating parish level into the hierarchical structure of the model was not feasible due to non-nested administrative area boundaries and it was not possible to run a three-level hierarchical model.

(AMI), exists globally and within countries.^{1–3} Identifying and understanding geographical patterns in disease provide important information on potential drivers of disease inequalities and disease aetiology as well as where to implement prevention strategies that target the most vulnerable populations and areas.^{4,5}

The underlying determinants of geographical patterns in incident AMI remain unknown. Contextual oriented epidemiological theories suggest characteristics of the environment in which people live to be important disease determinants.^{6–8} According to the model developed by Chaix, neighbourhood sociodemographic, social interactional,

service and physical environments are four environments that influence the development of coronary heart disease. The present study focused on the neighbourhood sociodemographic environment, as empirical findings supported that areas with increased risk of AMI were associated with low neighbourhood socioeconomic position.¹ The neighbourhood sociodemographic environment consists of four dimensions: neighbourhood socioeconomic position, ethnic composition, population density and population turnover.⁶ The neighbourhood sociodemographic environment in which people live is closely linked to individual-level sociodemographic characteristics either because an individual's socioeconomic position is influenced by the surrounding area or because people select where to live based on their sociodemographic profile (ie, selective migration).⁶ Both mechanisms might exist simultaneously; however, the latter might be the most likely scenario. Hence, as individual-level sociodemographic characteristics are also associated with the risk of AMI, it is important to adjust for individual-level socioeconomic and demographic factors when studying whether neighbourhood sociodemographic characteristics explain the geographical variation in AMI. To our knowledge, no previous studies have examined whether the sociodemographic environment explains the geographical inequalities in incident AMI when accounting for potential confounding by individual-level sociodemographic characteristics. Denmark constitutes an appropriate setting for studying the interplay between social and geographical inequalities as geographically linkable data on the sociodemographic environment and incident AMI are obtainable for the entire population for a long period of time. Geographical inequalities were considered as non-randomly distributed differences in the incidence of AMI across the country. Social inequalities reflect differences in disease risk observed between individuals with different social characteristics or between neighbourhoods with distinct sociodemographic environments.

The aim of this study was to investigate whether and to what extent sociodemographic characteristics of the neighbourhood explained the geographical patterns in incident AMI after accounting for individual-level sociodemographic characteristics of the population.

METHODS

Data, study population and study area

The study was based on prospectively collected data obtained from Danish nationwide population registers and linked by the unique personal identification number assigned to each resident of Denmark at birth or immigration.⁹

The study was designed as an open cohort with a study population including adults (≥ 30 years) without previous AMI and living in Denmark 1 January 2005, at their 30-year birthday, or at immigration, whichever came first. A run-in period of 1 year was applied for persons immigrating to Denmark due to incomplete information in

the administrative registers the first year after immigration. The follow-up period ended at the first occurrence of the following events: emigration, death, incident AMI or 31 December 2014.

The study area of Denmark covers approximately 43 000 km² and consists of one main peninsula, Jutland, the two largest islands, Funen and Zealand, and a number of smaller islands.

Outcome

Incident AMI cases occurring between 1 January 2005 and 31 December 2014 were identified as a primary or secondary diagnosis in the Danish National Patient Register (NPR)¹⁰ or an underlying or contributory cause of death in the Danish Register of Causes of Death (RCD)¹¹ by the International Classification of Disease 10th version (ICD-10) code I21 (excluding persons experiencing non-fatal AMI between 1977–1993 (ICD-8 code 410) and 1994–2004 (ICD-10 code I21)). The validity of the AMI diagnosis has previously been found to be high in NPR and RCD.^{12 13}

Sociodemographic characteristics

All neighbourhood-level and individual-level variables included (except sex) were time-varying and assigned for each person and each neighbourhood annually. The use of time-varying variables ensured that the continuously updated and available information from population registers was incorporated in the models accounting for changes in both individual-level and neighbourhood-level sociodemographic factors over the 10-year study period. The population density was assigned to each address and categorised into urban (cities with $\geq 100\,000$ inhabitants), suburban (cities with 500–99 999 inhabitants) and rural (villages < 500 inhabitants). Parish is the smallest available administrative unit in Denmark and therefore assumed to be the best operationalisation of the neighbourhood when measuring neighbourhood socioeconomic position (ie, median equivalised disposable household income) and ethnic composition (ie, the percentage of immigrants and descendants from non-Western countries in the parish). In 2014, the median parish population was 1038 persons (min–max: 25–43 052 persons) and the median parish area was 16.2 km² (min–max: 0.1–114.8 km²). Since no consistent definition of parish boundaries was obtainable throughout the study period, population turnover was calculated at the municipality level as the sum of persons moving in and out of the municipality compared with the municipality population each year. Each of the variables: neighbourhood socioeconomic position, ethnic composition and population turnover were categorised into three groups defined as lowest quintile (ie, lowest 20% of the population), medium (ie, medium 60% of the population) and highest quintile (ie, highest 20% of the population).

Individual-level characteristics included age (30–64 years, 65–74 years, ≥ 75 years), sex, equivalised disposable household income (lowest quintile, medium, highest

quintile), cohabitation status (married/cohabiting versus living alone) and educational level (elementary: ≤ 9 years, short: 10–12 years, medium/long: more than 12 years). Persons with missing educational level (4.0%) were included in the group with low educational level as they matched this group with regard to income level.

Information on age, sex, cohabitation status, population density for each residential location, parish and municipality of residence and country of origin of the individual and parents used to calculate the ethnic composition was obtained from population registers at Statistics Denmark. Information on median equivalised disposable household income (individual and aggregated to neighbourhood level) was obtained from income registers at Statistics Denmark and highest achieved educational level from the register on the populations' education at Statistics Denmark.

Statistical analysis

A Poisson regression with the number of incident AMI as an outcome and logarithmic transformation of follow-up time as offset was applied. This approach is also known as a piecewise exponential model.¹⁴ Annual updates of information on neighbourhood-level and individual-level sociodemographic characteristics were included in the analysis as time-varying variables by sorting the contingency table on which the analysis was performed by all possible combinations of the variables. This approach allows for more than one timescale to be included in the analysis. In the present study, age and calendar year were included as timescales. Risk of incident AMI is geographically clustered¹ and including geographical information on residential location into epidemiological modelling (eg, as a spatially structured random effect) enabled accounting for potential spatial autocorrelation, that is, the fact that neighbouring observations tend to correlate.¹⁵ The models used therefore consist of a fixed effect component including the sociodemographic characteristics and a geographically structured random effect component. As a Poisson regression of incidence rates (IRs) was used in the present study, the relative risk was estimated by IR ratios (IRRs).

Two models including different fixed effects were estimated with follow-up time split by the calendar year groups (2005–2007, 2008–2010 and 2011–2014) resulting in approximately constant IR of AMI in each group (IRs across the calendar years are shown in online supplementary table S1). Model 1 included the fixed effect of a calendar year and a random effect at the municipality level. Model 2 additionally included fixed effects of neighbourhood-level (ie, population density, neighbourhood socioeconomic position, ethnical composition and population turnover) and individual-level (ie, age, sex, income, cohabitation status and educational level) sociodemographic characteristics. No strong correlations between neighbourhood-level or individual-level variables were found when tested by Spearman correlation

coefficient (all correlation coefficients were within the range of -0.55 to 0.26).

In modelling a geographically structured random effect component, the geographical unit used in the analyses was defined by municipality boundaries as defined before January 2003 ($n=275$ municipalities, median area= 142.9 km² (min–max: 8.7 – 563.6 km²)). These municipality boundaries were used as they represent a finer spatial resolution than current municipalities ($n=98$). The random effect was modelled using a conditional autoregressive (CAR) model.¹⁶ A binary 275×275 adjacency matrix was used to incorporate the spatial correlation between neighbouring municipalities. Five municipalities being islands were in the matrix connected to municipalities to which they were connected by ferry or bridge.

To examine potential geographical clustering of incident AMI after accounting for fixed effects of sociodemographic characteristics, results from the CAR model were compared with results from a model including a non-structured random effect (independent, identically structured (IID) model).¹⁷ The model with the smallest Bayesian deviance information criterion (DIC) was considered providing the best fit to the observed data.¹⁸ In addition, Moran's I statistic was used to examine whether geographical clustering of IID random effects exists after adjusting for sociodemographic characteristics. Finally, the random effect estimates from the CAR model were mapped.

Bayesian inference was made using integrated nested Laplace approximation (INLA).¹⁹ Fixed effects (regression parameters) were assigned default Gaussian ($0, 0.001^{-1}$) prior distributions, whereas the hyperparameter of the CAR model was assigned a log-gamma distribution with default parameters ($1, 0.005$). In addition, the effect of the log-gamma distribution on the parameter estimates was evaluated by changing the parameter values to $(1, 0.001)$. The mean of the posterior distribution was extracted as a point estimate and 2.5 and 97.5 percentiles were used to define the 95% credible interval (95% CI).

Data management and descriptive analyses were performed using SAS V.9.4 statistical software and forest plot, maps and spatial analyses were performed in R x64 V.3.4.0,²⁰ the latter using the INLA package (www.r-inla.org).

Patient and public involvement

This study was based solely on register data and patients were not involved.

RESULTS

Study population

The study population was found linking the background population at risk of AMI with information on persons registered with incident AMI between 2005 and 2014. The Civil Registration System contained 4 260 152 persons aged 30 years or older registered 1 January in at least one of the years between 2005 and 2015 (figure 1).

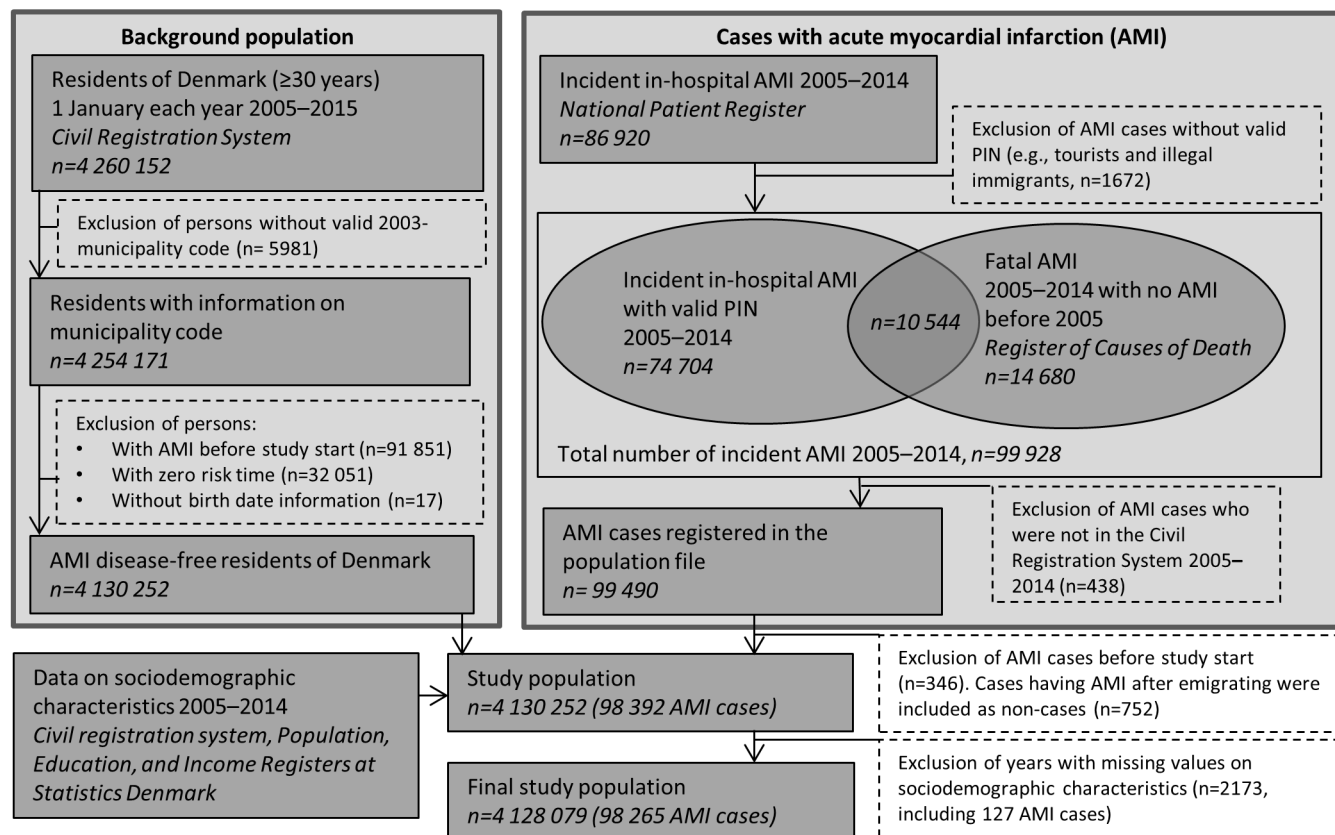


Figure 1 Construction of the study population based on linked data from the nationwide population registers. The background population at risk of AMI registered in the Civil Registration System was combined with information on incident AMI cases identified in the Danish National Patient Register and the Register of Causes of Death. PIN, personal identification number.

Persons without a valid municipality code according to the before 2003 municipality boundaries, with previous AMI, with zero risk time or no data on date of birth were excluded leaving 4 130 252 persons at risk of AMI. From 2005 to 2014, 86 920 incident AMI cases were registered in NPR out of which 1672 were excluded due to the invalid personal identification number (eg, tourists). In the same period, 25 224 fatal AMI cases without previous AMI before 2005 were registered in RCD. The overlap between the two registers consisted of 10 544 persons, hence, 99 928 had incident AMI between 2005 and 2014. Cases who were not in the population file or had AMI before study start were excluded, and persons having AMI after study exit were included as non-cases. The joined population consisted of 4 130 152 persons out of whom 98 392 developed an incident AMI during the study period. Observation years with one or more missing values were deleted and the final data set contained 4 128 079 unique persons contributing with 33 907 796 person-years at risk and out of whom 98 265 experienced an incident AMI between 2005 and 2014 corresponding to a crude IR of 289.8 AMI events/100 000 person-years for individuals aged 30 years or older.

Geographical patterns in incident AMI

Geographical patterns in incident AMI were found as the comparison between CAR and IID models showed

that CAR models performing better (DIC of 313 441 in model 2) than IID models (DIC of 313 499 in model 2) indicating spatial autocorrelation. Moreover, results from Moran's I also showed geographical clustering of the non-structured random effect estimates from the IID model after adjusting for sociodemographic characteristics ($p < 0.001$). Fixed effect estimates were overall similar across the two modelling approaches (online supplementary table S2). Consequently, only results from CAR models were reported below.

The geographical distribution of the random effect estimates showed where IRs of AMI were higher or lower compared with the country average after accounting for fixed effects. When accounting for a calendar year, results in model 1 showed overall low residual IRs of AMI surrounding the largest cities in Denmark (mapped in yellow), whereas areas with high residual IRs of AMI were located far from the largest cities (mapped in dark blue) (figure 2A). Geographical patterns in incident AMI were to some extent changing when additionally accounting for differences in neighbourhood-level and individual-level sociodemographic characteristics in model 2 (figure 2B). The number of municipalities in some areas with low residual IRs of AMI (eg, in the surroundings of Copenhagen and Aarhus) and high residual IRs of AMI (eg, in Northwestern part of Jutland and Lolland)

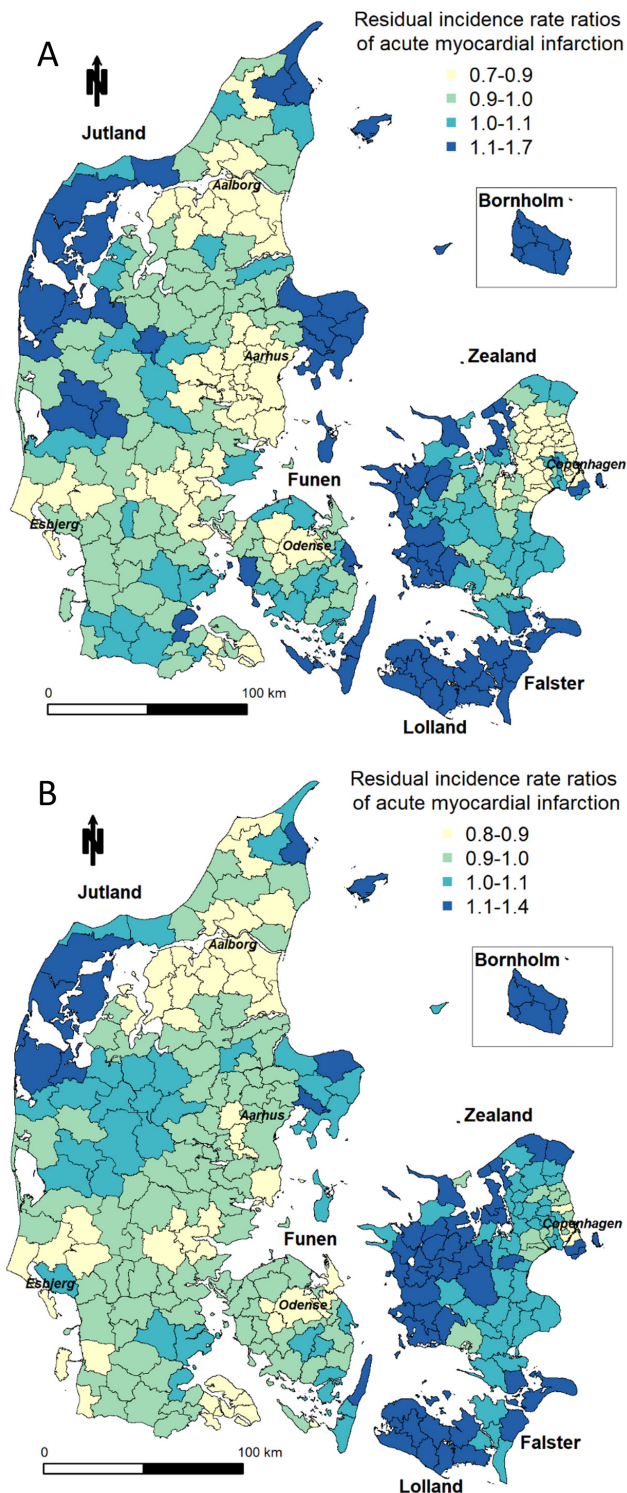


Figure 2 Geographical distribution of the residual incidence rate ratios (IRRs) of acute myocardial infarction (AMI) for each municipality compared with the country mean when accounting for the fixed effect of calendar years (A) and additionally accounting for differences in neighbourhood-level and individual-level sociodemographic characteristics (B). The residual IRRs were ranging from the lowest IRRs of AMI mapped in yellow to the highest residual IRRs of AMI mapped in blue. Names of the largest cities of Denmark are in italic and names of the main peninsula and islands are in bold.

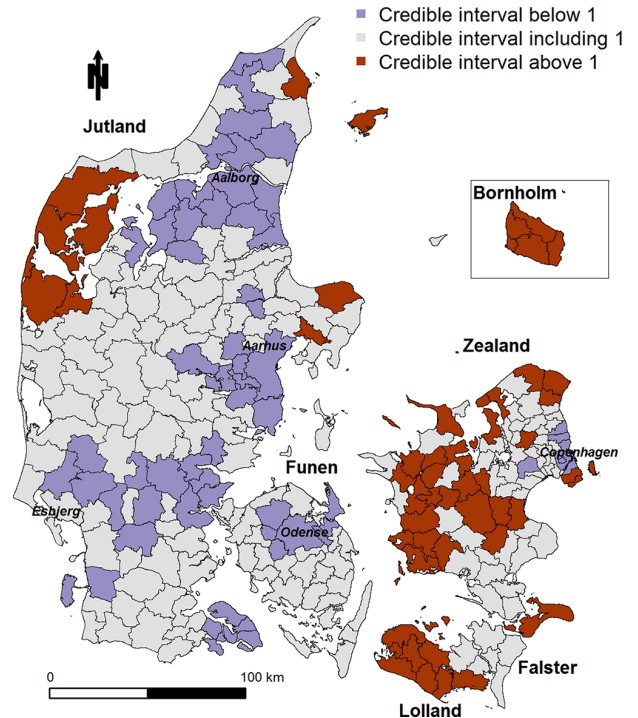


Figure 3 Geographical distribution of incidence rate ratios (IRRs) was mapped according to whether the 95% credible interval (95% CI) overlapped 1 (corresponding to the country mean). Municipalities with an increased IRR of acute myocardial infarction (AMI) and corresponding 95% CI above 1 were mapped in orange. Municipalities with low residual IRR of AMI and corresponding 95% CI below 1 were mapped in purple. Names of the largest cities of Denmark are in italic and names of the main peninsula and islands are in bold.

decreased when including sociodemographic characteristic in the model. In contrast, results also showed that some areas with high or low residual IRs of AMI remained or even expanded after adjusting for sociodemographic characteristics (eg, the stable areas with low residual IRs of AMI surrounding the city of Aalborg and the area of stable high residual IR of AMI at Bornholm). Results showed increasing precision of the spatially structured random effect, that is, the residual variation in incident AMI decreased, with an increasing number of variables in the model from 26.61 (SD: 3.18) in model 1 to 54.02 (SD: 7.72) in model 2. Residual IRRs ranged from 0.7 to 1.7 in model 1 narrowing to 0.8–1.4 in model 2.

Results mapped in [figure 3](#) confirmed the observed geographical patterns in incident AMI as the 95% CIs of several municipalities were not overlapping the value of 1 (ie, corresponding to the country mean). Municipalities with 95% CIs above 1 indicating high IRs of AMI were mapped in orange and municipalities with 95% CIs below 1 indicating areas with low IRs of AMI were mapped in purple.

Sociodemographic characteristics and incidence of AMI

Results of the fixed effects in the fully adjusted model 2 showed that low neighbourhood socioeconomic position was associated with increased IR of AMI (IRR 1.08,

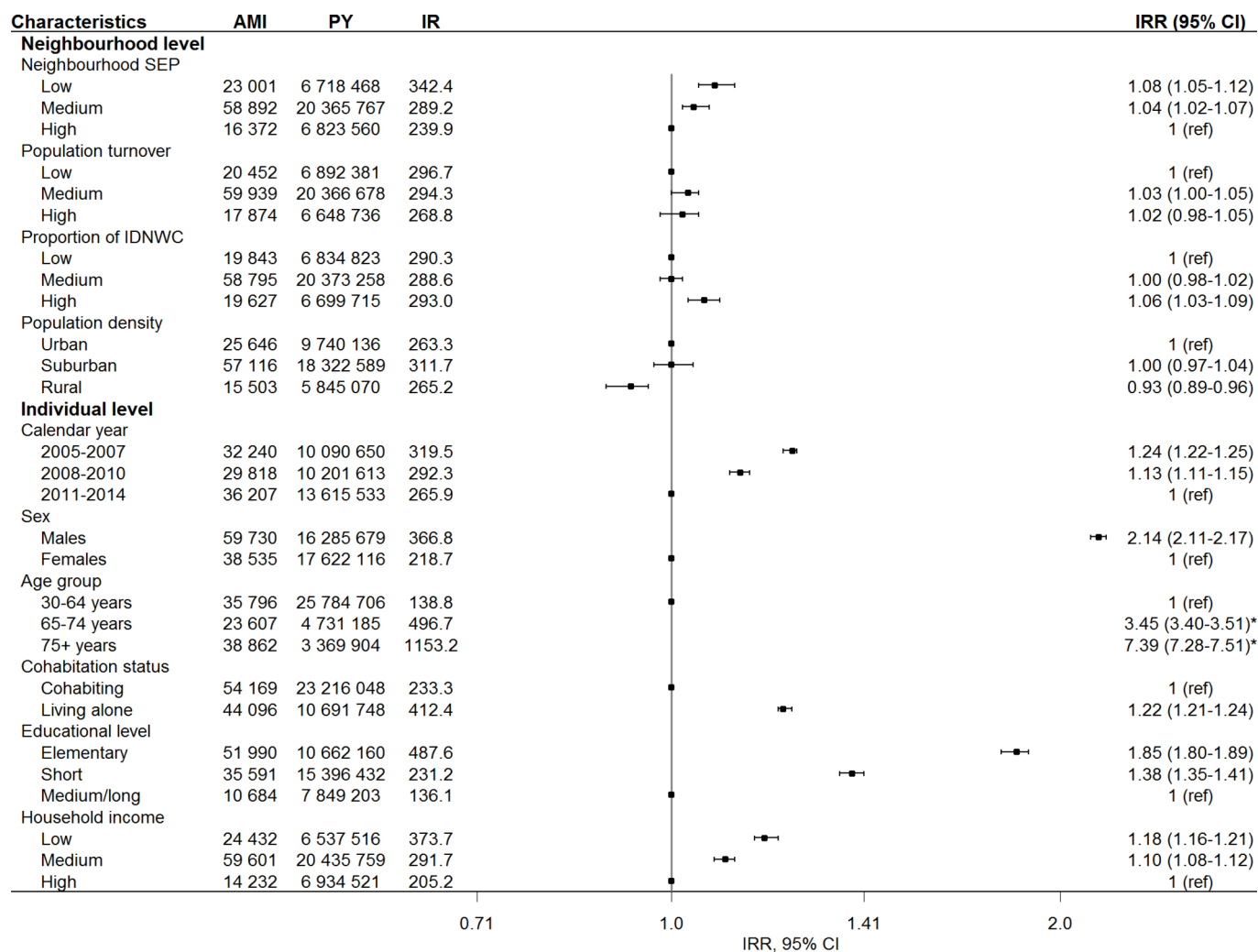


Figure 4 Descriptive figures are the number of persons with incident acute myocardial infarction (AMI), person-years at risk (PY) and crude incidence rates (IR) of AMI. Mutually adjusted IR ratios (IRR) of AMI with corresponding 95% credible intervals (95% CI) across levels of sociodemographic characteristics were estimated using a Poisson regression model with the random effect modelled using a conditional autoregressive model. A log scale was used for the x-axis. *The effect of age on AMI was not illustrated in the forest plot as it was markedly larger than the other estimates and expanded the scale. IDNWC, immigrants and descendant from non-Western countries; Ref, reference category; SEP, socioeconomic position.

95% CI 1.05 to 1.12) when accounting for differences in individual-level sociodemographic characteristics (figure 4). Moreover, persons living in neighbourhoods with a high proportion of immigrants and descendants from non-Western countries had an increased IR of AMI compared with persons living in neighbourhoods with a low proportion (IRR 1.06, 95% CI 1.03 to 1.09). Persons living in rural areas had a slightly decreased IR of AMI compared with persons living in urban areas (IRR 0.93, 95% CI 0.89 to 0.96). Population turnover in the municipality was not associated with incident AMI. Changing the parameter values of the log-gamma distribution did not affect parameter estimates.

DISCUSSION

This nationwide study examined if differences in incident AMI existed across the country when accounting for sociodemographic characteristics of the population

and neighbourhood in which people lived. The main results of this study were that accounting for differences in neighbourhood-level and individual-level sociodemographic characteristics decreased the geographical variation in incident AMI. However, after accounting for sociodemographic differences at both the neighbourhood and individual level, the residual variation in AMI was geographically unequally distributed across the country meaning that some areas remained associated with higher IRs of AMI compared with the country average. Hence, a complex disease pattern revealed when studying the dynamic interplay between geographical and social determinants of incident AMI and inequalities in incident AMI across the population cannot be seen exclusively as a difference between social groups.

Comparison with other studies

The present study observed geographical patterns in incident AMI after adjusting for neighbourhood-level

and individual-level sociodemographic characteristics. Geographical patterns in incident AMI were also observed in an ecological spatial analysis study from middle Tennessee, USA.²¹ After adjusting for area-level sociodemographic characteristics, residual relative risk estimates ranged from 0.44 to 1.95, that is, a slightly wider range of the residual relative risk estimates compared with results from our study. However, comparisons should be made with caution as the ecological estimates by Odoi and Busingye were not adjusted for individual-level socio-demographic characteristics.

Low neighbourhood sociodemographic position was in the present study found to be associated with increased IRs of AMI when accounting for differences in individual-level sociodemographic characteristics. Similar findings have been reported in multilevel studies. In contrast to spatial analysis, areas in multilevel analysis are assumed to be independent units and these models do not account for the correlation between observations in space.^{15 22 23} A simulation study found that fixed effect estimates from multilevel and spatial analysis models are similar, but measures of random effect variance are less comparable across the two methods.¹⁵ The effect size of low neighbourhood income on ischaemic heart disease was found to be slightly lower in a Swedish quasi-experimental sibling study than in the present study (OR 1.02, 95% CI 1.02 to 1.04).²⁴ Compared with our results, a study based on a national sample from Sweden reported larger fixed effects sizes of low neighbourhood educational and income level on incident coronary heart disease after adjusting for individual risk factors (HR 1.23, 95% CI 1.00 to 1.52 and HR 1.25, 95% CI 1.02 to 1.54, respectively).²⁵ The larger effects sizes found by Sundquist *et al* might be due to differences in the association between neighbourhood factors and coronary heart disease across Sweden and Denmark or occur because of design differences. Sundquist *et al* included a population sample and not the entire population, they did not account for spatial autocorrelation between observation, and they did not account for population density and cohabitation status as was done in the present study.

Interpretation of findings

The effect size of the residual IRRs of incident AMI across municipalities was not as large as the fixed effects of, for example, age and sex. However, the residual relative risk estimates varied considerably across municipalities ranging from 20% lower to 40% higher IRs of AMI compared with the country mean.

The geographical variation in incident AMI decreased when adjusting for sociodemographic characteristics. However, the identification of areas with high and low residual IRRs of AMI in [figure 2B](#) and [figure 3](#) supported that IRs of AMI remained geographically unequally distributed across the country after accounting for differences in sociodemographic characteristics across neighbourhoods and individuals. The CAR models performing better than IID models likewise supported that clustering of incident

AMI occurred across neighbouring municipalities. Finally, geographical clustering of the random effect estimates from the IID model also confirmed the geographical unequal distribution of incident AMI after accounting for differences in sociodemographic characteristics. The reasons for the unexplained residual variation in incident AMI after adjusting for the neighbourhood-level and individual-level socioeconomic structure remain unknown. As suggested in the theoretical model by Chaix, other environments to study further might be the physical environment (eg, outdoor and indoor public places and street network), service environment (eg, transportation, healthcare services, food environment) or social interactional environment (eg, knowledge, norms and culture).⁶ In Denmark, geographical variation in location and use of general practitioners has been reported²⁶ and studies focusing on these differences might complement this study's results in explaining the geographical variation in incident AMI. Beside unequal distribution of healthcare services across the country, factors as infrastructure and health behaviour may also differ considerably geographically. Moreover, factors from more than one environment may affect the development of disease simultaneously and certain factors may be more important in explaining an increased IR of AMI in some areas compared with others.

Strengths and limitations

In Denmark, individual-level socioeconomic data are only available when working at servers at Statistics Denmark. However, it is not allowed to assess individual-level address information with x and y coordinates when working at Statistics Denmark and this study was therefore not possible to perform at the address level. An address-level explorative spatial cluster analysis of incident AMI in Denmark found, however, that areas with high AMI risk generally covered larger spaces than determined by municipality boundaries and therefore supported municipalities being relevant geographical units when studying geographical variation in incident AMI.¹

Parishes are not geographically nested into municipalities in Denmark and parish boundaries were moreover changing continuously throughout the study period. Consequently, incorporating parish level into the hierarchical structure of the model was not doable. Moreover, models were computationally intensive to run and it will, therefore, most likely be unfeasible to run a three-level hierarchical model with the available computational resources.

Neighbourhood socioeconomic position was in the present study measured by median disposable household income. Other measures could have been used to measure neighbourhood socioeconomic position such as the unemployment rate. However, unemployment influence income markedly and median equalised disposable household income was found to be a more comprehensive measure of neighbourhood socioeconomic position as it is likely to incorporate the effect of unemployment and at the same time include information on available resources in the household when accounting for family size.

Due to the complexity of measuring neighbourhood and individual sociodemographic characteristics, there might be aspects of the sociodemographic structure that were not captured with the variables included in the model leading to potential residual confounding. However, the present study limited the risk of bias by incorporating several sociodemographic variables accounting for different facets of the sociodemographic structure.

This study focused on the neighbourhood sociodemographic characteristics in explaining the geographical patterns in AMI when accounting for individual-level sociodemographic factors. Nevertheless, other residential and non-residential environments were also proposed in the conceptual model proposed by Chaix.⁶ It was beyond the scope of this study to address all environments of important and this limits a complete understanding of the complex interplay between residential and non-residential environments and the effect of these environments in the development of AMI. In addition, it was beyond the scope of this paper to address the role of health behaviour factors (eg, as smoking and diet) as mediators of the association between sociodemographic factors and AMI. However, as health behaviours are assumed to be mediators, adjusting for sociodemographic characteristics both at the individual and neighbourhood level accounts for at least some of the effect of health behaviours on the development of AMI.

The study findings on geographical inequalities in incident AMI beyond individual-level and neighbourhood-level sociodemographic characteristics are based on nationwide data and may be generalisable to other similar countries. However, the magnitude of the geographical inequalities might depend on the healthcare system, general socioeconomic inequalities and resource allocation in the particular setting.

Implications

Results from the present study confirm the well-known association between incident AMI and age, sex and socioeconomic background, but findings from this study additionally emphasise that neighbourhood sociodemographic environments and where in the country you live also influence the risk of developing AMI. In contrast to non-spatial analyses, results from the present study provide information on where the increased risk of disease is observed. This information can be of relevance when planning public health interventions and supports an evidence-based approach to disease prevention that targets populations and areas most in need. This study's findings moreover demonstrate the complexity of determining the variation in incident AMI across the population. Hence, exclusively focusing on social inequality may not give the complete picture as inequalities in disease can be seen from other perspectives too, for example, geographical inequalities.

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Contributors TMK, KB, IA, GHG, MLL and AKE contributed to the planning, conception and design of the study. TMK performed the data management and data analysis and drafted the manuscript. KB and AKE supervised the statistical analyses. TMK, KB, IA, GHG, MLL and AKE contributed to the interpretation and discussion of the results. KB, IA, GHG, MLL and AKE critically revised the manuscript and final approval of the manuscript was done by TMK, KB, IA, GHG, MLL and AKE.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval According to Danish law, register-based studies can be carried out without approval from an ethic committee or consent from the data subjects. Danish Data Protection Agency approved the study (approval number: 2015-57-008, no.16/4085).

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

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