

Geographical clustering of incident acute myocardial infarction in Denmark: A spatial analysis approach



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ABSTRACT

Objectives: To examine the geographical patterns in AMI and characterize individual and neighborhood sociodemographic factors for persons living inside versus outside AMI clusters.

Methods: The study population comprised 3,515,670 adults out of whom 74,126 persons experienced an incident AMI (2005–2011). Kernel density estimation and global and local clustering methods were used to examine the geographical patterns in AMI. Median differences and frequency distributions of sociodemographic factors were calculated for persons living inside versus outside AMI clusters.

Results: Global clustering of AMI occurred in Denmark. Throughout the country, 112 significant clusters with high risk of incident AMI were identified. The relative risk of AMI in significant clusters ranged from 1.45 to 47.43 (median=4.84). Individual and neighborhood socioeconomic position was markedly lower for persons living inside versus outside AMI clusters.

Conclusions: AMI is geographically unequally distributed throughout Denmark and determinants of these geographical patterns might include individual- and neighborhood-level sociodemographic factors.

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Abbreviations: AMDHI, Annual median disposable household income; AMI, Acute myocardial infarction; BHR, Building and Housing Register; CPR-number, Unique personal identification number; CRS, Danish Civil Registration System; GIS, Geographical Information Systems; ID, Immigrant and descendants; ISR, Income Statistics Register; NPR, Danish National Patient Register; RCD, Danish Register of Causes of Death; SEP, Socioeconomic position.

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1. Introduction

Acute myocardial infarction (AMI) is a major cause of death and disability worldwide with severe consequences for both individuals and society (Thygesen et al., 2007; Murray et al., 2015). Although the incidence of AMI in Denmark has declined during the last decades (Koch et al., 2013; Schmidt et al., 2012), AMI remains socially unequally distributed within the population (Rasmussen et al., 2006). Development of AMI is associated with a wide range of individual risk factors such as smoking, physical inactivity, and sedentary behavior (Held et al., 2012;

Yusuf et al., 2004; Manrique-Garcia et al., 2011). However, individual-level factors can only explain about 50–60% of the social inequalities in AMI (Marmot et al., 2008) and there is a need to look beyond the individual-level risk factor to understand the etiology of AMI. Epidemiologic contextual oriented theories argue that the contexts, in which people live, are of certain importance in relation to development of disease (Diez-Roux, 1998; Krieger, 2011). Incorporating the spatial dimension in epidemiological studies is one strategy to address the contextual factors influencing the etiology of AMI, since the etiology may include both individual and contextual factors (e.g., the demography and socioeconomic position (SEP) in neighborhood) not accounted for in existing research. The underlying assumption in spatial epidemiology is that information on *where* an event (e.g. disease or death) occurs may provide information on *why* it occurs (Waller and Gotway, 2004). Thus, investigating the spatial distribution of AMI and characterize individual and neighborhood sociodemographic factors in areas with high AMI disease burden may generate new hypotheses on determinants of the disease.

Studying the geographical patterns in disease requires that appropriate data sources are obtainable. Nationwide registers are valuable resources for research. The usefulness of data in registers depends on the possibility to combine different sources of data and the validity of the recorded information. In Denmark, all persons with permanent residence in the country or persons who are paying Danish taxes have a unique personal identification number (CPR-number) (Pedersen, 2011; Danish Health Data Authority, 2016). The distinctive CPR-number enables reliable individual-level linkage of information from different data sources (Thygesen and Ersboll, 2011). Regarding the quality of register data, AMI is a well-defined diagnosis with good validity in the Danish Register of Causes of Death (RCD) and the Danish National Patient Register (NPR) legitimizing the use of register-based information on AMI in health studies (Madsen et al., 2003).

Although international studies have found geographical patterns in AMI when analyzing aggregated data sources (Burnley, 1999; Chow et al., 2005; Davies et al., 2009; Francisci et al., 2008; Hammar et al., 2001; Havulinna et al., 2008; Loughnan et al., 2008; Marrugat et al., 2004; Pedigo et al., 2011; Thalib et al., 2011; Tyden et al., 2001; Viik-Kajander et al., 2003), to our knowledge neither national nor international studies have so far used individual-level data obtained from nationwide population registers to detect spatial clustering of AMI or other cardiovascular diseases. Nevertheless, studies based on simulated datasets have found that cluster analyses using individual-level data are more valid than analyses using data aggregated in polygons, as they found the cluster detection power to decrease when increasing the spatial resolution (Olson et al., 2006; Ozonoff et al., 2007). The present study examined the geographical patterns in incident AMI in Denmark (2005–2011) and identified clusters with significantly elevated risk of incident AMI by use of spatial analysis of individual-level data obtained from nationwide population registers. Furthermore to gain insights into determinants of potential geographical inequalities in AMI, we aimed to

characterize persons living inside versus outside clusters with high risk of AMI (hereafter called *AMI clusters*) by individual and neighborhood sociodemographic factors.

2. Methods

2.1. Data sources and study population

The study area equaled the surface of Denmark: approximately 43,000 km². Data used in the present study was sourced from Danish nationwide registers: The Danish Civil Registration System (CRS), the RCD, the NPR, the Building and Housing Register (BHR), and registers at Statistics Denmark (e.g. the Income Statistics Register (ISR)). These registers are described elsewhere (Pedersen, 2011; Baadsgaard and Quitzau, 2011; Christensen, 2011; Helweg-Larsen, 2011; Jensen and Rasmussen, 2011; Lyngé et al., 2011). The NPR and the RCD contain information on fatal and non-fatal AMI cases. The BHR includes information on *x*- and *y*-coordinates of all buildings in Denmark and the CRS contains information on all historical and current residential locations. Location is given by UTM EUREF89, zone 32 coordinates. The Danish Agency for Data Supply and Efficiency under the Danish Ministry of Energy, Utilities and Climate is responsible for producing and maintaining geographical data in cooperation with the Danish municipalities (GeoDanmark, 2016). Linking information from the RCD, the NPR, the BHR, and the CRS makes it possible to geocode both fatal and non-fatal AMI cases as well as the residential location for the entire population of Denmark at the individual level. The study population was constructed by merging the AMI population and the background population. The study was designed to include information on geographical location, socioeconomic and demographical factors for each person at the date of diagnosis or death for the AMI population and at the median date of the study period (i.e., January 1, 2005 to December 31, 2011) being July 1, 2008 for the background population.

2.1.1. AMI population

Between 2005 and 2011, 71,401 persons were admitted to a Danish hospital with an AMI as either primary or secondary diagnosis registered in the NPR. AMI cases were identified by the World Health Organization's 10th International Classification of Disease code I21. During the study period, AMI was recorded as the underlying or the contributory cause of death among 24,058 persons registered in the RCD, out of whom 14,331 were out-of-hospital deaths. In total, 85,732 persons experienced a fatal or non-fatal AMI in Denmark between 2005 and 2011. In order to identify the incident first-time cases of AMI, we excluded persons who had experienced an AMI before, i.e. between 1995 and 2004 ($N = 9649$). Patients with an invalid CPR-number (e.g. tourists or illegal workers) ($N = 1110$), who lived in Greenland ($N = 87$), or had an unknown address at time of AMI diagnosis or death ($N = 272$) were excluded. The final AMI population comprised 74,614 persons.

2.1.2. Background population

A total of 6,196,835 persons were registered in the CRS July 1, 2008. People living in Greenland ($N = 31,949$) and

those with an unknown address, mostly persons paying taxes in Denmark, but living abroad on July 1, 2008 ($N = 696,886$) were excluded. In addition, persons with an incident AMI between 2005 and 2011 were also deleted from the background population ($N = 58,794$). Hence, the background population consisted of 5,409,206 persons.

2.1.3. Study population

The study population was created by merging the AMI and background populations ($N = 5,483,820$). When geocoding data, it was not possible to match the residential location of 0.3% of the study population with x - and y -coordinates obtained from the BHR and these persons were therefore excluded ($N = 16,340$). Finally, persons under the age of 30 years at time of AMI or July 1, 2008 ($N = 1,985,771$), were excluded, confirming that AMI was relatively uncommon among people under this age, i.e. only 159 persons experienced an AMI before the age of 30 years. The final study population consisted of 3,515,670 persons of whom 74,126 persons had been registered with an incident AMI.

2.1.4. Neighborhood sociodemographic factors

In order to describe the sociodemography at the neighborhood-level, four measures were used: 1) Proportion of elderly people (≥ 60 years) out of the entire population (≥ 0 years) living within a radius of 0.5 km for each person in the study population calculated by use of information from the CRS; 2) Annual median disposable income per household calculated for each parish by use of information from the ISR at Statistics Denmark; 3) Proportion of adult immigrants and descendants from non-Western countries of the adult population (≥ 30 years) calculated for every parish by use of information from registers at Statistics Denmark; and 4) Proportion of unemployed in the adult population (≥ 30 years) in each parish. Unemployed was defined as people who had been unemployed for half a year or more as well as people that received social security benefits in 2008. Information on unemployment was obtained from a variable constructed by use of different sources of information on personal income at Statistics Denmark (Statistics Denmark, 2016a).

The neighborhood was defined as an ego-centered neighborhood, i.e. the neighborhood within a Euclidean radius of 0.5 km from each individual's home address, for the proportion of elderly in the neighborhood, whereas the neighborhood for the remaining three indicators was defined by parish, since these indicators were derived at Statistics Denmark where no information on x - and y -coordinates is available.

2.1.5. Individual sociodemographic factors

Age was calculated as the age at time of diagnosis or death from AMI for the AMI population and age at July 1, 2008 for the background population. Information on sex and age was obtained from the CRS. Age was categorized into three age groups; 30–64 years, 65–74 years and ≥ 75 years. In the present study, individuals' SEP was assessed by two indicators: annual disposable household income and highest obtained educational level. Another Danish study has used a comparable measure of individual

SEP (Wallach-Kildemoes et al., 2013). The annual disposable household income per person was calculated as the sum of the household income divided by 1.5 if the family consisted of a married/cohabiting couple. The factor 1.5 is used by Statistic Denmark when calculating the equivalent household income (Statistics Denmark, 2016b). For persons living alone the annual household income equaled the annual disposable personal income. The disposable household income was grouped into quintiles for men and women separately and stratified by age above and below 65 years to account for the income drop associated with retirement. The disposable income measure was obtained for the year before an AMI event for the AMI population and 2008 for the background population. The highest obtained educational level was categorized into four groups according to the formal length of the education: ≤ 9 years; 9.1 to 12 years; 12.1 to 15 years, ≥ 15.1 years. The educational measure was obtained for the year of AMI for the AMI population and 2008 for the background population. Information on disposable income was obtained from the ISR and information about education from the Populations' Education Register at Statistics Denmark.

2.2. Data analysis

The data analysis of the present study was divided into three parts: an exploratory analysis including visualization of the data and global and local clustering of incident AMI cases; a characterization of the individual and neighborhood sociodemographic factors for persons living inside versus outside AMI clusters; and a sensitivity analysis with the purpose to determine the robustness of the study results. All non-spatially statistical analyses and the global clustering analysis were completed using SAS version 9.3 (SAS Institute, Cary, NC, US) software. The kernel density estimation was performed by using the "sm" and "SpatialKernel" packages in R software and SaTScan v.9.1.1 64-bit software (Kuldorff, 2013) was applied for the local cluster analysis.

2.2.1. Exploratory analysis

The exploratory analysis was performed by use of multiple spatial analysis techniques (i.e. both visual and statistical techniques) to identify spatial patterns in the data. The three steps in the exploratory analysis were: 1) visualization of spatial patterns in the data by use of kernel density estimation; 2) a test of global clustering; and 3) local cluster analysis.

Kernel density estimation: A descriptive map of the spatial patterns of AMI in Denmark was created by calculating a smoothed estimate of the intensity function of the location of cases compared to the intensity function of all locations in the study region. The estimate was calculated for grid cells of 2.5 km \times 2.5 km. A non-parametric kernel estimator was used to estimate the intensity function of the point processes. In applying the kernel estimator the type of kernel function and the bandwidth must be specified as this controls the degree of smoothing applied and can have profound impact on the smoothing results. We used a bandwidth of 5 km to produce a detailed map of the

geographical patterns in AMI. The Gaussian kernel function is one of the most commonly applied kernel estimator functions and was used in this study, but a range of potential functions exists. The impact of the choice of kernel function on the results is often small (Waller and Gotway, 2004). When mapping the data we categorized the ratio between the smoothed estimate of the intensity function of AMI cases and the intensity function of the total population into quintiles.

Global clustering analysis: The *K*-function is a summarized measure of the spatial dependence between events as a function of distance (Ersbøll and Ersbøll, 2009). In order to examine global clustering of events, in this case incident AMI cases, the *K*-function of AMI cases (i.e. the observed geographical distribution of AMI cases) was compared to a null-hypothesis version of the *K*-function that represented a random distribution of AMI cases. In the present study 999 Monte Carlo simulations were performed and the random labeling hypothesis was used as the null-hypothesis against which the *K*-function of the observed AMI cases was compared (Ersbøll and Ersbøll, 2009). The median of the 999 simulated sample estimates was then used as the null-hypothesis version of the *K*-function. Hence, the *K*-function analysis was performed by estimating a *D*-function, i.e. the difference between the observed *K*-function of AMI cases and the simulated null-hypothesis version of the *K*-function with a similarly simulated 95% envelope. The 95% simulated envelope of the null-hypothesis version of the *K*-function lies between the 2.5 and 97.5 percentiles of the 999 sample estimates. Deviations from the null-hypothesis can be determined by plotting the *D*-function and the 95% simulated envelope against distance. Clustering of AMI cases occurs at distances where the *D*-function lies above or below the 95% simulated envelope (Ersbøll and Ersbøll, 2009). The maximum distance in the present study was set to be 25 km with intervals of 100 m.

Local cluster analysis: Spatial scan statistics in SaTScan were used to identify the location of statistically significant AMI clusters (Kulldorff, 1997; Kulldorff, 2010). A Bernoulli model for point data was applied in which the residence of all included people was divided into persons who had or had not experienced an AMI. Using the spatial scan statistics, a series of circles (or ellipses) of different radii are constructed for each location including all locations that fall inside the circle (or ellipse). The radii range from zero to the user-defined maximum not greater than 50% of the population. Alternatively, the maximum radius applied for the search window can also be defined by Euclidean distance. In the present study we chose a circular search window of 10 km, since the study aimed to identify clusters of local areas for which a maximum distance of 10 km seemed reasonable. To detect the area that is most likely to be a cluster, the test estimates the area that maximizes the likelihood function. The circle that maximizes the likelihood function is the cluster that is least likely to occur by chance. In the present study the most restrictive option was chosen in which secondary clusters were reported only if they did not overlap with the previously reported clusters. The underlying disease distribution was obtained by running 999 Monte Carlo simulations based

on the random labeling hypothesis (Waller and Gotway, 2004).

To validate the results, we performed a post hoc evaluation of small clusters, as the spatial cluster analysis of point data is a sensitive method able to identify very small and specific clusters (Meliker et al., 2009). When examining the results from the local cluster analysis, a number of clusters had a small radius (i.e., 0 to a few hundred meters) and a relatively high risk of AMI and hence we examined the characteristics of these clusters further, as we hypothesized that they might reflect nursing homes for elderly people (hereafter called *nursing home clusters*), i.e. clusters appearing as a result of the way care for elderly people is organized in our society. In order to examine the characteristics of small clusters, we investigated whether a nursing home was located within AMI clusters with a median age of 75 years or older by use of information on the location of nursing homes and special housing environments for elderly people from the Danish Central Business Register (The Danish Business Authority, 2016) and two map search engines, Google maps (www.googlemaps.com) and the Danish search engine Krak (www.krak.dk), as well as Google's general search engine (www.google.com). It should be noted that 2.6% of the nursing homes in the Danish Central Business Register could not be geocoded.

2.2.2. Characterization of individual and neighborhood sociodemography inside versus outside AMI clusters

The individual and neighborhood sociodemography for persons living inside versus outside AMI clusters was described by frequency distributions and the median, minimum and maximum values. We excluded persons living in nursing home clusters in this analysis.

2.2.3. Sensitivity analyses

The effect of the choice of search window (i.e. the maximum proportion of the population to be included or the maximum radius of the cluster) in the local cluster analysis was further explored in a sensitivity analysis. Conducting multiple analyses using different search windows may reinforce findings and provide confidence that the detected AMI clusters are in fact “unlikely”. Therefore, six analyses with six different search windows (radii of 5 km, 10 km, and 25 km and 0.25%, 0.5%, and 1% of the population, respectively) were performed and the results and degree of overlap between the six local cluster analyses were determined.

2.3. Mapping

All maps were created at the country scale showing the study results across Denmark. The cartographic displays were created in ArcGIS version 10.1 and by use of R software.

2.4. Ethical considerations

Working with data at the individual level in Denmark requires permission from the Danish Data Protection Agency. The present study obtained permission on January 17, 2013 with case number 2012-41-1417. The present

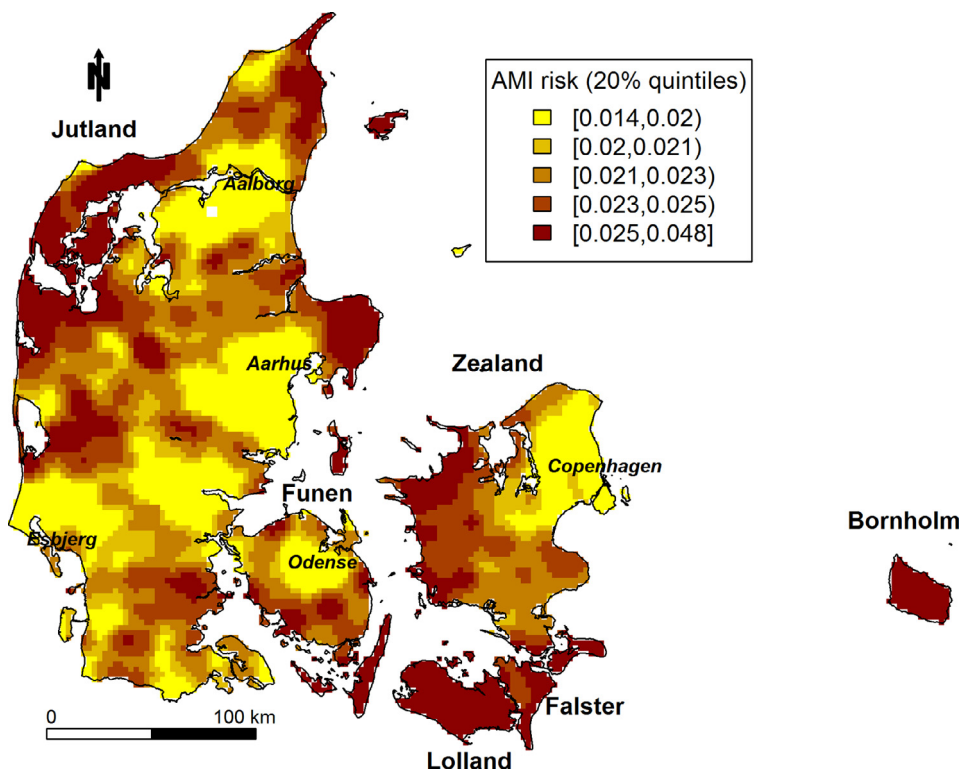


Fig. 1. Descriptive map with kernel density of incident AMI (bandwidth = 5 km). Exploratory map of the geographical patterns in incident AMI performed by use of the kernel density estimation method using $2.5 \text{ km} \times 2.5 \text{ km}$ grid cells, Gaussian kernel function and a bandwidth of 5 km. Caution should be taken when interpreting the density surface of incident AMI in smaller islands with relative few inhabitants since rates on these islands may be unstable and only a few cases may change the rates markedly. Names of the largest cities in Denmark are shown in italic and names of regions and islands are in bold.

Table 1
Frequency distribution of sex and age in the population stratified by AMI.

| Variables | Background population <i>N</i> = 3,441,544 | | AMI population <i>N</i> = 74,126 | | |
|-----------|---|-----------|-------------------------------------|--------|------|
| | <i>N</i> | % | <i>N</i> | % | |
| Sex | Females | 1,776,017 | 51.6 | 28,654 | 38.7 |
| | Males | 1,665,527 | 48.4 | 45,472 | 61.3 |
| Age | 30–64 years | 2,615,654 | 76.0 | 24,343 | 32.8 |
| | 65–74 years | 465,241 | 13.5 | 17,562 | 23.7 |
| | ≥ 75 years | 360,649 | 10.5 | 32,221 | 43.5 |
| | | | | | |

Figures are counts and percentages for the background population and the AMI population, respectively.

study was an observational study without direct contact to individuals and with no interventions of any kind. AMI was solely analyzed by use of information from registers. All results were presented in tables and maps that ensured the confidentiality of individuals.

3. Results

Table 1 shows the frequency distribution of sex and age in the population stratified by AMI. The study population consisted of 3,515,670 persons aged 30 years or older living on a geocoded address in Denmark at either date of AMI or July 1, 2008. A total of 74,126 persons, constituting the AMI population, had experienced an incident AMI between

2005 and 2011. Men accounted for a larger proportion of the AMI population than the background population and the AMI population was overall older than the background population.

3.1. Exploratory spatial analysis

3.1.1. Visualization of the spatial patterns in AMI

Fig. 1 shows a map of a smoothed surface representing the kernel density of incident AMI in Denmark. Areas with a high density of incident AMI cases were mainly located in the northwestern part of Jutland, Lolland, Falster, and Bornholm. High density areas were also seen in the central and eastern parts of Jutland as well as the northwestern part of Zealand. In general, we found low density of AMI in the urban areas of the largest cities in Denmark (i.e. Copenhagen, Aarhus, Odense, Aalborg, and Esbjerg). Note that the density surface of incident AMI in smaller islands with relative few inhabitants is unstable as only a few cases may change the incidence rate remarkably and these results should therefore be interpreted with caution.

3.1.2. Global clustering analysis

Fig. 2 shows the difference between the observed *K*-function and the simulated null-hypothesis version of the *K*-function (the *D*-function) against the distance (km).

Results from the global clustering test provided evidence against the null-hypothesis of randomly distributed

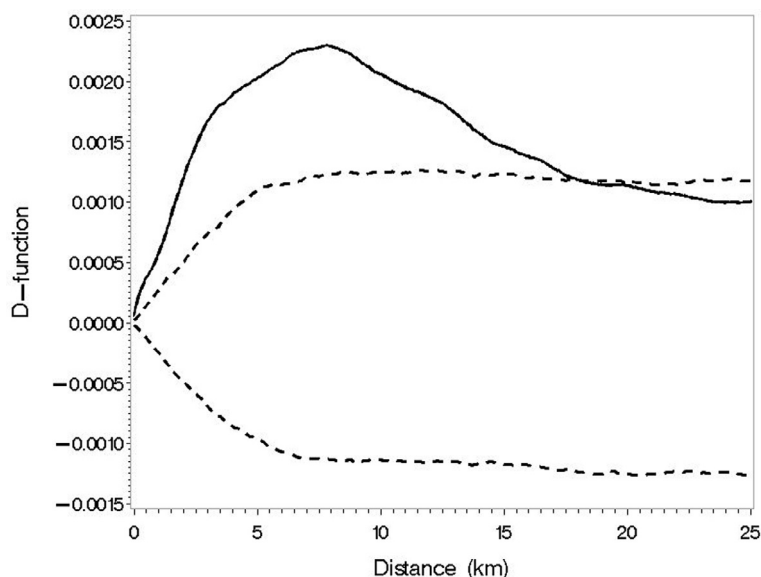


Fig. 2. Global clustering: D -function as a function of the distance. The dashed lines illustrate the 95% simulated envelope of the simulated K -function and the continuous line represents the D -function. Global clustering occurs in distances where the D -function exceeds the 95% simulated envelope of the simulated null-hypothesis version of the K -function.

Table 2

Clusters with high risk of incident AMI grouped by radii.

| Cluster radii (m) | Total number of AMI clusters | Number of persons living inside AMI clusters |
|-------------------|------------------------------|--|
| 0 | 7 | 172 |
| 1–99 | 28 | 2729 |
| 100–249 | 32 | 7310 |
| 250–499 | 10 | 6522 |
| 500–999 | 12 | 42,248 |
| 1000–2499 | 9 | 62,025 |
| 2500–4999 | 2 | 5669 |
| 5000–9999 | 12 | 120,851 |
| Total | 112 | 247,526 |

The number of AMI clusters and the number of persons living inside AMI clusters are grouped according to the radii of clusters measured in meters.

AMI cases, i.e. global clustering of incident AMI cases occurred. According to the results depicted in the graph, the incident AMI cases showed a tendency to cluster at distances of 0 to approximately 17 km (the distance at which the D -function enters the 95% simulated envelope of the expected K -function) with maximum clustering occurring at a distance of approximately 7 km (the peak of the D -function).

3.1.3. Local cluster analysis

Table 2 and Fig. 3 show the results from the local cluster analysis using a 10 km search window.

While examining the characteristics of the identified 112 AMI clusters, seven clusters had a radius of 0 meters, i.e. clustering of AMI occurred in seven single residential locations. A majority of AMI clusters had a radius of less than 500 meters ($N = 77$) and 12 AMI clusters had a radius larger than 5000 meters. The relative risk of AMI in significant clusters ranged from 1.45 to 47.43 with a median

value of 4.84 (see detailed information on the clusters in Appendix A). Fig. 3 shows the geographical location of the AMI clusters.

In accordance with the density surface illustrating the proportion of incident AMI cases throughout the country (c.f. Fig. 1), large statistically significant local AMI clusters were found in the northwestern part of Jutland, southern part of Funen, western part of Zealand as well as the islands Bornholm, and Lolland. Smaller AMI clusters were located more evenly throughout the country and some of the smaller AMI clusters were located in proximity of or within larger cities. Note that in Fig. 3 small AMI clusters were depicted larger than they were to make their location visible at a country scale.

The exploratory post hoc analyses showed that a total of 77 AMI clusters had a radius of less than 500 m. Evaluation of these clusters, 60 AMI clusters with a median age of 75 years or older and a radius ranging from 0 to 311 m were identified. Furthermore, it was seen that nursing homes or special housing environments for elderly people were located within these clusters. These nursing home clusters were excluded from the analyses characterizing persons living inside versus outside AMI clusters (see Section 3.1.4).

3.1.4. Characterization of individual and neighborhood sociodemography inside and outside AMI clusters

Table 3a shows that a higher proportion of persons living inside versus outside AMI clusters was older, living alone, has low annual disposable household income and low educational level. A greater proportion of persons inside versus outside clusters was living in suburban and urban areas, whereas only slight differences were seen with regard to gender and ethnicity. The median disposable household income in the neighborhood was markedly

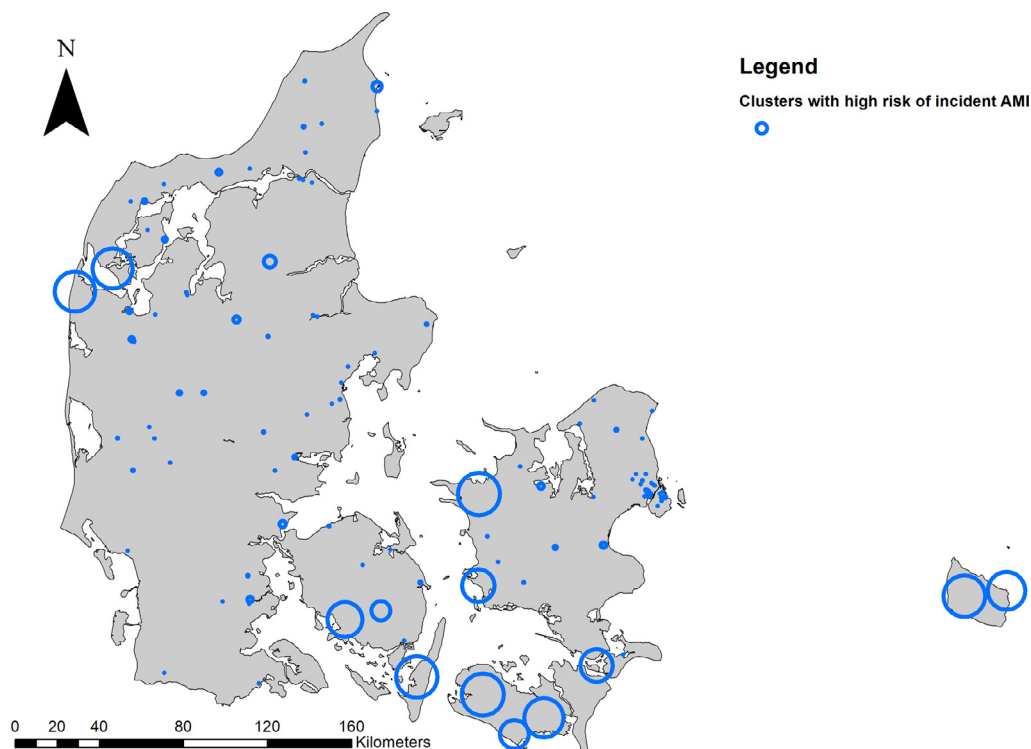


Fig. 3. Geographical location of clusters with high risk of incident AMI. AMI clusters identified by use of a 10 km search window are mapped by blue circles. Note that small AMI clusters are depicted larger than they were in order to make their location visible at a country scale.

lower among persons living inside AMI clusters compared to outside (Table 3b). The proportions of elderly people and unemployed people in the neighborhood were higher inside AMI cluster versus outside, whereas the neighborhood proportion of immigrants and descendants from non-western countries was approximately equal.

3.2. Sensitivity analysis

Six local cluster analyses were performed using different search windows (Table 4). Between 87 and 115 significant AMI clusters were identified. In general, the number of AMI clusters increased with decreasing search window both when defined by distance in kilometers and by proportion of the population included. Results show that 74 AMI clusters were identified across all six analyses. For the main analysis of this study using a 10 km search window, only 10 clusters (9%) were not identified in one or more of the five remaining analyses. Similarly, the number of unique AMI clusters was eleven for the 5 km analysis, eight for the 25 km analysis, twelve for the 0.25% analysis, eight for the 0.5% analysis, and seven for the 1% analysis. Hence, the majority of AMI clusters were identified in all six local cluster analyses while only a small proportion varied by search window.

Fig. 4 maps the results from the six local cluster analyses. It should be noticed that the smallest AMI clusters were depicted larger than they were to make their location visible on a country-scale map. Although unique AMI

clusters were found across the six cluster analyses, these AMI clusters were located in the same areas which means that approximately the same geographical patterns in AMI were found in all six analyses despite the changing search windows.

4. Discussion

Results from the present study showed that clustering of incident AMI cases in Denmark occurred. The locations of 112 AMI clusters were identified. Geographically large AMI clusters were found in areas far from the largest cities of Denmark, whereas smaller AMI clusters were more evenly distributed throughout the country. In total, 60 clusters were nursing homes or special living environments for elderly people. The remaining 52 AMI clusters were characterized as having low individual-level and neighborhood-level SEP and a higher proportion of elderly people compared to areas outside clusters. Given the cross-sectional design of the present study a causal interpretation of the relationship between sociodemographic factors and areas with high AMI risk cannot be made. The spatial patterns in AMI may emerge from multiple related processes on different levels and involve feedback-loops, selection processes, and a dynamic interplay between individuals and their neighborhood, which challenges the assessment of a causal effect of sociodemographic factors at the individual or neighborhood level on the development of AMI.

Table 3a

Characterization of persons living inside versus outside AMI clusters when excluding persons living in nursing home clusters (categorical variables).

| Variables | | AMI clusters | | | | Total (N = 3,507,783) | |
|------------------------------------|----------------------------|----------------------|------|-------------------------|------|-----------------------|------|
| | | Inside (N = 239,239) | | Outside (N = 3,268,144) | | N | % |
| | | N | % | N | % | | |
| Gender | Men | 112,805 | 47.2 | 1,595,365 | 48.8 | 1,708,170 | 48.7 |
| Age groups | 30–64 years | 160,925 | 67.3 | 2,477,574 | 75.8 | 2,638,499 | 75.2 |
| | 65–74 years | 37,289 | 15.6 | 444,380 | 13.6 | 481,669 | 13.7 |
| | ≥75 years | 41,025 | 17.2 | 346,190 | 10.6 | 387,215 | 11.0 |
| Cohabitation | Married/cohabiting | 143,599 | 60.0 | 2,250,796 | 68.9 | 2,394,395 | 68.3 |
| | Living alone | 94,974 | 39.7 | 1,006,498 | 30.8 | 1,101,472 | 31.4 |
| | Missing | 666 | 0.3 | 10,850 | 0.3 | 11,516 | 0.3 |
| Ethnicity | Native Danes | 224,240 | 93.7 | 3,007,289 | 92.0 | 3,231,529 | 92.1 |
| | IDs from Western countries | 5040 | 2.1 | 96,810 | 3.0 | 101,850 | 2.9 |
| | IDs from other countries | 9014 | 3.8 | 151,569 | 4.6 | 160,583 | 4.6 |
| | Missing | 945 | 0.4 | 12,476 | 0.4 | 13,421 | 0.4 |
| Annual disposable household Income | High | 25,760 | 10.8 | 671,081 | 20.5 | 696,841 | 19.9 |
| | 2 | 38,200 | 16.0 | 657,970 | 20.1 | 696,170 | 19.9 |
| | 3 | 49,787 | 20.8 | 645,398 | 19.8 | 695,185 | 19.8 |
| | 4 | 59,723 | 25.0 | 635,379 | 19.4 | 695,102 | 19.8 |
| | 5 Low | 64,108 | 26.8 | 630,537 | 19.3 | 694,645 | 19.8 |
| | Missing | 1661 | 0.7 | 27,779 | 0.9 | 29,440 | 0.8 |
| Education | ≤ 9 years | 69,359 | 29.0 | 682,339 | 20.9 | 751,698 | 21.4 |
| | 9–11.9 years | 37,382 | 15.6 | 515,923 | 15.8 | 553,305 | 15.8 |
| | 12–14.9 years | 93,761 | 39.2 | 1,386,689 | 42.4 | 1,480,450 | 42.2 |
| | > 15 years | 24,939 | 10.4 | 540,215 | 16.5 | 565,154 | 16.1 |
| | Missing | 13,798 | 5.8 | 142,978 | 4.4 | 156,776 | 4.5 |
| Urbanization | Rural | 44,838 | 18.7 | 680,138 | 20.8 | 724,976 | 20.7 |
| | Suburban | 81,722 | 34.2 | 1,312,701 | 40.2 | 1,394,423 | 39.8 |
| | Urban | 95,380 | 39.9 | 851,030 | 26.0 | 946,410 | 27.0 |
| | Metropolitan | 17,299 | 7.2 | 424,275 | 13.0 | 441,574 | 12.6 |

IDs = Immigrants and descendants. Figures are counts and frequency distributions for persons living inside versus outside AMI clusters.

Table 3b

Characterization of persons living inside versus outside AMI clusters when excluding persons living in nursing home clusters (continuous variables).

| Variables | AMI cluster | | | Outside clusters | | |
|-------------------------------------|-------------|-------------|----------------|------------------|-------------|----------------|
| | Median | Min–max | Missing, N (%) | Median | Min–max | Missing, N (%) |
| AMDHI (1000 DKK) | 208.4 | 159.6–306.2 | 1105 (0.5) | 236.3 | 139.8–458.3 | 14,261 (0.4) |
| Proportion of people ≥ 60 years (%) | 28.9 | 0.0–100.0 | 37 (<0.1) | 22.9 | 0.0–100.0 | 573 (< 0.1) |
| Proportion of IDs (%) | 3.8 | 0.0–36.3 | 1105 (0.5) | 3.6 | 0.0–67.3 | 14,261 (0.4) |
| Proportion of unemployed (%) | 3.8 | 0.0–15.0 | 1105 (0.5) | 2.2 | 0.0–23.1 | 14,261 (0.4) |

SEP = Socioeconomic position, AMDHI = Annual median disposable household income, IDs = Immigrants and descendants. Figures are medians, minimums and maximums for persons living inside compared to outside AMI clusters.

Table 4

The degree of overlapping clusters with high risk of incident AMI across the six local cluster analyses.

| Number of analyses in which a cluster is identified | Search window | | | | | |
|---|-----------------------|-------|-------|------------------------------|------|----|
| | Distance in kilometer | | | Proportion of the population | | |
| | 5 km | 10 km | 25 km | 0.25% | 0.5% | 1% |
| 1 (unique) | 11 | 10 | 8 | 12 | 8 | 7 |
| 2 | 6 | 2 | 1 | 4 | 0 | 1 |
| 3 | 7 | 8 | 1 | 6 | 3 | 2 |
| 4 | 5 | 6 | 1 | 5 | 6 | 1 |
| 5 | 12 | 12 | 2 | 11 | 12 | 11 |
| 6 (full overlap) | 74 | 74 | 74 | 74 | 74 | 74 |
| Total | 115 | 112 | 87 | 112 | 103 | 96 |

The number of AMI clusters in each analysis in groups according to degree of overlap with the remaining local cluster analyses. AMI clusters that only appeared in one of the six analyses are unique and those identified in all six analyses represent AMI clusters with full overlap.

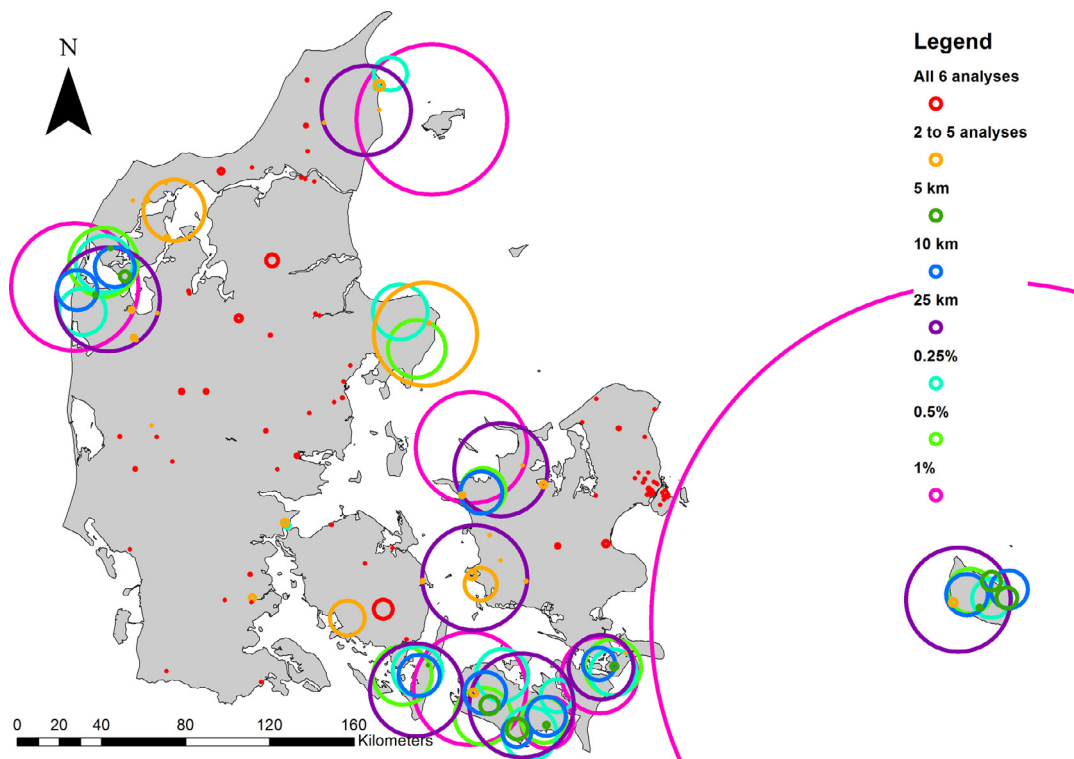


Fig. 4. Overlap between clusters with high risk of incident AMI identified by use of six different search windows. The map illustrates the degree of overlap of the results from six cluster analyses by use of different search windows, i.e. 5 km (dark green), 10 km (dark blue), 25 km (purple), 0.25% (light blue), 0.5% (light green), and 1% (pink), respectively. AMI clusters identified across all six analyses are mapped by red circles and AMI clusters identified in 2–5 analyses are mapped by orange circles.

4.1. Consistency with previous studies

Our findings of clustering of AMI are consistent with results from two studies using spatial cluster analyses on AMI data from the United States of America and Australia, respectively, despite the difference in study design, spatial scale, geography, and methods applied (Loughnan et al., 2008; Pedigo et al., 2011). While we used individual-level data sources, the studies by Loughnan et al. (2008) and Pedigo et al. (2011) relied on data aggregated into units defined by administrative boundaries (Loughnan et al., 2008; Pedigo et al., 2011). Prior studies found that spatial analyses of point data are more sensitive than analyses performed using data aggregated into polygons (Olson et al., 2006; Ozonoff et al., 2007; Meliker et al., 2009). Meliker et al. (2009) found that analyses based on individual-level data detected clusters of early stage breast cancer not identified using data aggregated into census block groups, census tracts or legislative districts. Olson et al. (2006) performed a simulation study and found that 73% of the significant clusters were detected when using exact coordinates for location of addresses compared to 45% when using zip code centroids. Ozonoff et al. (2007) found in a simulation study that cluster detection power was close to 100% when using exact locations, but decreased to approximately 40% when using the coarsest level of aggregation. Hence, studies examining clustering of AMI using aggre-

gated data sources may overlook important spatial patterns in AMI.

The association between areas with high AMI incidence and sociodemographic factors has been addressed previously (Pedigo et al., 2011; Rose et al., 2009; Stjarne et al., 2006). In the study by Rose et al. (2009), neighborhood SEP was measured as the median household income divided into tertiles (Rose et al., 2009) and Pedigo et al. (2011) examined several neighborhood SEP indicators (Pedigo et al., 2011). Stjärne et al. (2006) calculated the median equivalent disposable household income and examined the neighborhood SEP when taking individual SEP into account (Stjärne et al., 2006). Our findings of low neighborhood SEP in areas with high AMI risk were consistent with findings from these studies (Pedigo et al., 2011; Rose et al., 2009; Stjarne et al., 2006).

4.2. Strengths and limitations

Study merits include the accurate and valid ascertainment of AMI cases (Madsen et al., 2003), the use of almost the entire Danish population aged 30 years or older, the close to complete geocoding of all residential locations in Denmark, and the unique linkage between registers. In contrast to other studies (Loughnan et al., 2008; Pedigo et al., 2011), the data sources used in the present study are unique in the opportunity to geocode not only AMI cases,

but also the background population with adequate accuracy and completeness (99.7%). Bias introduced as a consequence of inadequate geocoding of data is therefore minimized and the geographical data available made it possible to analyze spatial patterns in AMI by use of point data.

Limitations involve: 1) the uncertainty in relation to selection of the optimal user defined search window for the spatial scan statistics; and 2) that it was not possible to include information on past residential location and mobility patterns of the study population.

4.2.1. Pre-selection of the search window

When performing the local cluster analysis both the shape and the maximal distance of the search window are user-defined parameters. In the present study we chose a circular window of maximum 10 km. However, an elliptic search window might have been preferable as it would have increased the possibility of identifying non-circular AMI clusters. Nonetheless, we used a circular search window due to computational limitations when working with a huge data set of approximately 3.5 million people. The Bernoulli models with circular windows to examine local AMI clusters took between 65 h and 272 h on an Intel(R) Xeon(R) computer with 2.67 GHz CPU, 24.0GB RAM and a 64-bit Operating System. Regarding the size of the search window, results from the sensitivity analysis using six different search windows showed that the spatial scan statistics method is both sensitive and robust as the identified AMI clusters were approximately the same across the six analyses. Thus, the size of the search window did not seem to affect the study results substantially.

4.2.2. Latency of disease

Using the residential location at time of AMI may be problematic because the residential location at this point in time does not always reflect the place where the person was actually exposed. This is especially important when considering diseases with a long latency (Werneck, 2008). Mapping the residential location at time of AMI diagnosis or death may consequently reflect exposures that trigger AMI rather than exposures that contribute to the development of disease. To address this issue, it would be interesting to account for the mobility patterns over the life course in the analysis; however, this would not be feasible due to how computer intensive these methods are. Nevertheless, in the present study, persons who experienced an AMI had lived on average 21 years at the location where they lived at time of diagnosis or death (the median value was 13 years). Thus, the residential location at time of diagnosis may be an adequate proxy of the address location where the people lived during disease development.

4.2.3. Measuring neighborhood socioeconomic position

Measuring neighborhood SEP in relation to health outcomes in a population is challenging. The idea of measuring indicators of neighborhood SEP is that they provide proxies of specific features in the neighborhood relevant for health outcomes that are not directly measurable (Diez Roux, 2003). In the present study four different indicators were assessed in order to operationalize a more nuanced measure of the neighborhood SEP than using just a

single SEP indicator; however, there may still be important features of neighborhood SEP not measured adequately.

Important issues that have to be considered when conducting studies including neighborhood-level variables are the selection of a contextual unit and the operationalization of the chosen unit. The operationalization of “neighborhood” in the present study may not correspond perfectly with how each and every person defines their neighborhood (Diez-Roux, 1998). Furthermore, the size and the shape of “neighborhood” may vary across the country depending on e.g. degree of urbanization. In the present study “neighborhood” was whenever possible defined as an ego-centered neighborhood with a radius of 0.5 km that exist independently of administrative boundaries. However, information on geographical coordinates for individuals’ residential location is not available at Statistics Denmark, and we therefore chose the smallest administrative area available, i.e. parish, as a proxy of the neighborhood for variables derived at Statistics Denmark.

4.3. Implications

In the field of public health, spatial analysis and geographical information systems (GIS) are relevant tools in minimizing health inequalities and in disease prevention in general, because taking the spatial distribution of disease into account can help ensure that resources and efforts are targeted to the population most in need (Miranda et al., 2013). The present study is exploratory and identifies geographical patterns of AMI and it is beyond the scope of the study to explain these geographical health inequalities. However, when excluding nursing home clusters, we found that AMI clusters were characterized by a higher proportion of elderly people, but also low individual and neighborhood SEP. Our results indicate that sociodemographic factors might contribute to the observed geographical patterning in AMI; however, further research is needed to fully understand what drives spatial inequities (Diez Roux, 2009) and should look into determining the overlap between social and geographical inequities of AMI.

5. Conclusions

AMI is geographically unequally distributed throughout Denmark and 112 clusters with statistically significant increased risk of AMI were identified out of which 60 clusters were found to be nursing homes or special housing environments for elderly people. When excluding nursing home clusters, we found that AMI clusters were characterized by a higher proportion of elderly people as well as low individual and neighborhood SEP.

Authors’ contributions

TMK participated in the design of the study, performed the non-spatial and spatial statistical analyses, and drafted the manuscript. JS contributed to conceptualize the ideas of the manuscript and help with the statistical analyses especially those involving GIS. GG participated in designing the study design and provided expert advice on heart disease and analyses of data from nationwide registers. AKE participated in the design and coordination of the study,

the linkage of data sources, and helped performing the statistical analyses. JS, GG, AKE have critically revised the article and all authors have approved the final manuscript.

Conflicts of interest

None.

Appendix A

Table A.1 shows the detailed results for every significant AMI cluster. Each cluster was identified by a num-

ber (i.e. the number shown in the first left column). Additional information consisted of the cluster radius, number of persons within each cluster, number of observed and expected AMI cases inside the cluster, the log likelihood ratio test (LLR), p-value and the relative risk (RR). The P-value was the significance level based on 999 Monte Carlo replications. The relative risk was calculated as the observed number of cases divided by the expected number of cases within the circle as the numerator and the observed cases divided by the expected cases outside the circle as the denominator.

Table A.1
Results from the local cluster analysis (10 km search window).

| Cluster | Radius (m) | Number of persons in cluster | $N_{\text{Observed AMI cases}}$ | $N_{\text{Expected AMI cases}}$ | LLR | P-value | RR |
|---------|------------|------------------------------|---------------------------------|---------------------------------|-------|---------|-------|
| 1 | 55 | 112 | 30 | 2.36 | 52.44 | <0.001 | 12.70 |
| 2 | 9920 | 18,330 | 600 | 386.48 | 51.98 | <0.001 | 1.55 |
| 3 | 9995 | 16,168 | 529 | 340.89 | 45.71 | <0.001 | 1.55 |
| 4 | 122 | 355 | 44 | 7.48 | 43.42 | <0.001 | 5.88 |
| 5 | 185 | 828 | 67 | 17.46 | 42.13 | <0.001 | 3.84 |
| 6 | 893 | 5311 | 215 | 111.98 | 38.33 | <0.001 | 1.92 |
| 7 | 2288 | 13,655 | 446 | 287.91 | 38.22 | <0.001 | 1.55 |
| 8 | 0 | 14 | 11 | 0.30 | 35.24 | <0.001 | 37.27 |
| 9 | 94 | 548 | 49 | 11.55 | 34.70 | <0.001 | 4.24 |
| 10 | 105 | 121 | 24 | 2.55 | 34.42 | <0.001 | 9.41 |
| 11 | 108 | 118 | 23 | 2.49 | 32.58 | <0.001 | 9.24 |
| 12 | 1039 | 4194 | 173 | 88.43 | 32.46 | <0.001 | 1.96 |
| 13 | 9626 | 4542 | 183 | 95.77 | 32.19 | <0.001 | 1.91 |
| 14 | 9242 | 8633 | 297 | 182.02 | 31.31 | <0.001 | 1.63 |
| 15 | 9583 | 6684 | 243 | 140.93 | 31.19 | <0.001 | 1.72 |
| 16 | 877 | 4329 | 175 | 91.27 | 31.07 | <0.001 | 1.92 |
| 17 | 7668 | 15,868 | 486 | 334.57 | 30.92 | <0.001 | 1.45 |
| 18 | 130 | 560 | 47 | 11.81 | 30.90 | <0.001 | 3.98 |
| 19 | 761 | 5440 | 207 | 114.70 | 30.78 | <0.001 | 1.80 |
| 20 | 1463 | 6794 | 245 | 143.25 | 30.59 | <0.001 | 1.71 |
| 21 | 42 | 134 | 23 | 2.83 | 29.69 | <0.001 | 8.14 |
| 22 | 202 | 798 | 56 | 16.83 | 29.17 | <0.001 | 3.33 |
| 23 | 318 | 752 | 54 | 15.86 | 29.05 | <0.001 | 3.41 |
| 24 | 167 | 167 | 25 | 3.52 | 29.00 | <0.001 | 7.10 |
| 25 | 70 | 142 | 23 | 2.99 | 28.41 | <0.001 | 7.68 |
| 26 | 155 | 149 | 23 | 3.14 | 27.35 | <0.001 | 7.32 |
| 27 | 80 | 73 | 17 | 1.54 | 27.18 | <0.001 | 11.04 |
| 28 | 591 | 1720 | 88 | 36.27 | 27.10 | <0.001 | 2.43 |
| 29 | 0 | 7 | 7 | 0.15 | 27.01 | <0.001 | 47.43 |
| 30 | 143 | 273 | 30 | 5.76 | 26.42 | <0.001 | 5.21 |
| 31 | 8928 | 5300 | 195 | 111.75 | 26.03 | <0.001 | 1.75 |
| 32 | 66 | 67 | 16 | 1.41 | 26.01 | <0.001 | 11.33 |
| 33 | 105 | 103 | 19 | 2.17 | 25.87 | <0.001 | 8.75 |
| 34 | 104 | 68 | 16 | 1.43 | 25.76 | <0.001 | 11.16 |
| 35 | 143 | 421 | 37 | 8.88 | 25.68 | <0.001 | 4.17 |
| 36 | 67 | 193 | 25 | 4.07 | 25.66 | <0.001 | 6.14 |
| 37 | 117 | 92 | 18 | 1.94 | 25.57 | <0.001 | 9.28 |
| 38 | 146 | 211 | 26 | 4.45 | 25.52 | <0.001 | 5.84 |
| 39 | 122 | 26 | 11 | 0.55 | 25.06 | <0.001 | 20.07 |
| 40 | 7715 | 5546 | 200 | 116.93 | 24.96 | <0.001 | 1.71 |
| 41 | 1461 | 9946 | 318 | 209.71 | 24.79 | <0.001 | 1.52 |
| 42 | 555 | 523 | 41 | 11.03 | 24.77 | <0.001 | 3.72 |
| 43 | 311 | 435 | 37 | 9.17 | 24.71 | <0.001 | 4.03 |
| 44 | 628 | 2150 | 99 | 45.33 | 24.37 | <0.001 | 2.18 |
| 45 | 92 | 64 | 15 | 1.35 | 24.09 | <0.001 | 11.12 |
| 46 | 523 | 5217 | 189 | 110.00 | 23.96 | <0.001 | 1.72 |
| 47 | 86 | 101 | 18 | 2.13 | 23.90 | <0.001 | 8.45 |
| 48 | 194 | 383 | 34 | 8.08 | 23.87 | <0.001 | 4.21 |
| 49 | 117 | 115 | 19 | 2.42 | 23.83 | <0.001 | 7.84 |

(continued on next page)

Table A.1 (continued)

| Cluster | Radius (m) | Number of persons in cluster | $N_{\text{Observed AMI cases}}$ | $N_{\text{Expected AMI cases}}$ | LLR | P-value | RR |
|---------|------------|------------------------------|---------------------------------|---------------------------------|-------|---------|-------|
| 50 | 988 | 2829 | 119 | 59.65 | 23.50 | <0.001 | 2.00 |
| 51 | 84 | 56 | 14 | 1.18 | 23.43 | <0.001 | 11.86 |
| 52 | 6780 | 5233 | 188 | 110.33 | 23.16 | <0.001 | 1.70 |
| 53 | 0 | 6 | 6 | 0.13 | 23.16 | <0.001 | 47.43 |
| 54 | 9941 | 7410 | 247 | 156.24 | 22.99 | <0.001 | 1.58 |
| 55 | 1010 | 4622 | 170 | 97.45 | 22.67 | <0.001 | 1.74 |
| 56 | 0 | 9 | 7 | 0.19 | 22.29 | 0.001 | 36.89 |
| 57 | 9944 | 16,397 | 475 | 345.72 | 22.26 | 0.001 | 1.37 |
| 58 | 64 | 141 | 20 | 2.97 | 22.20 | 0.001 | 6.73 |
| 59 | 337 | 344 | 31 | 7.25 | 22.14 | 0.001 | 4.27 |
| 60 | 859 | 3035 | 123 | 63.99 | 21.98 | 0.001 | 1.92 |
| 61 | 58 | 62 | 14 | 1.31 | 21.94 | 0.001 | 10.71 |
| 62 | 109 | 86 | 16 | 1.81 | 21.92 | 0.001 | 8.82 |
| 63 | 482 | 1461 | 73 | 30.80 | 21.43 | 0.001 | 2.37 |
| 64 | 210 | 182 | 22 | 3.84 | 21.22 | 0.002 | 5.73 |
| 65 | 1349 | 6700 | 224 | 141.27 | 21.10 | 0.002 | 1.59 |
| 66 | 125 | 78 | 15 | 1.64 | 21.05 | 0.002 | 9.12 |
| 67 | 706 | 6968 | 231 | 146.92 | 21.03 | 0.002 | 1.57 |
| 68 | 382 | 473 | 36 | 9.97 | 20.93 | 0.002 | 3.61 |
| 69 | 4553 | 4702 | 169 | 99.14 | 20.85 | 0.002 | 1.70 |
| 70 | 95 | 223 | 24 | 4.70 | 20.71 | 0.003 | 5.10 |
| 71 | 24 | 47 | 12 | 0.99 | 20.36 | 0.003 | 12.11 |
| 72 | 8280 | 10,740 | 327 | 226.45 | 20.16 | 0.004 | 1.44 |
| 73 | 0 | 48 | 12 | 1.01 | 20.09 | 0.004 | 11.86 |
| 74 | 460 | 792 | 48 | 16.70 | 20.03 | 0.005 | 2.87 |
| 75 | 287 | 332 | 29 | 7.00 | 19.99 | 0.005 | 4.14 |
| 76 | 237 | 30 | 10 | 0.63 | 19.92 | 0.005 | 15.81 |
| 77 | 70 | 39 | 11 | 0.82 | 19.85 | 0.005 | 13.38 |
| 78 | 107 | 60 | 13 | 1.27 | 19.81 | 0.005 | 10.28 |
| 79 | 55 | 86 | 15 | 1.81 | 19.60 | 0.007 | 8.27 |
| 80 | 2823 | 967 | 54 | 20.39 | 19.60 | 0.007 | 2.65 |
| 81 | 1191 | 729 | 45 | 15.37 | 19.34 | 0.008 | 2.93 |
| 82 | 0 | 5 | 5 | 0.11 | 19.30 | 0.015 | 47.43 |
| 83 | 69 | 89 | 15 | 1.88 | 19.10 | 0.016 | 7.99 |
| 84 | 96 | 52 | 12 | 1.10 | 19.07 | 0.016 | 10.94 |
| 85 | 100 | 64 | 13 | 1.35 | 18.96 | 0.018 | 9.63 |
| 86 | 426 | 686 | 43 | 14.46 | 18.93 | 0.018 | 2.97 |
| 87 | 119 | 284 | 26 | 5.99 | 18.91 | 0.018 | 4.34 |
| 88 | 66 | 33 | 10 | 0.70 | 18.84 | 0.019 | 14.37 |
| 89 | 388 | 851 | 49 | 17.94 | 18.76 | 0.019 | 2.73 |
| 90 | 686 | 2524 | 103 | 53.22 | 18.76 | 0.019 | 1.94 |
| 91 | 43 | 25 | 9 | 0.53 | 18.74 | 0.019 | 17.07 |
| 92 | 100 | 44 | 11 | 0.93 | 18.41 | 0.024 | 11.86 |
| 93 | 112 | 498 | 35 | 10.50 | 18.27 | 0.027 | 3.33 |
| 94 | 56 | 56 | 12 | 1.18 | 18.15 | 0.027 | 10.16 |
| 95 | 47 | 46 | 11 | 0.97 | 17.89 | 0.030 | 11.34 |
| 96 | 576 | 2202 | 92 | 46.43 | 17.85 | 0.031 | 1.98 |
| 97 | 0 | 83 | 14 | 1.75 | 17.84 | 0.031 | 8.00 |
| 98 | 98 | 58 | 12 | 1.22 | 17.72 | 0.033 | 9.81 |
| 99 | 101 | 47 | 11 | 0.99 | 17.65 | 0.035 | 11.10 |
| 100 | 75 | 37 | 10 | 0.78 | 17.58 | 0.035 | 12.82 |
| 101 | 144 | 325 | 27 | 6.85 | 17.53 | 0.035 | 3.94 |
| 102 | 115 | 148 | 18 | 3.12 | 17.46 | 0.039 | 5.77 |
| 103 | 308 | 396 | 30 | 8.35 | 17.34 | 0.040 | 3.59 |
| 104 | 120 | 60 | 12 | 1.27 | 17.31 | 0.043 | 9.49 |
| 105 | 54 | 38 | 10 | 0.80 | 17.29 | 0.044 | 12.48 |
| 106 | 1375 | 8301 | 257 | 175.02 | 17.21 | 0.044 | 1.47 |
| 107 | 94 | 102 | 15 | 2.15 | 17.15 | 0.047 | 6.97 |
| 108 | 146 | 246 | 23 | 5.19 | 17.12 | 0.047 | 4.43 |
| 109 | 107 | 226 | 22 | 4.77 | 17.11 | 0.048 | 4.62 |
| 110 | 84 | 61 | 12 | 1.29 | 17.11 | 0.049 | 9.33 |
| 111 | 114 | 188 | 20 | 3.96 | 17.06 | 0.049 | 5.05 |
| 112 | 1393 | 7084 | 225 | 149.36 | 17.00 | 0.050 | 1.51 |

LLR = Log likelihood ratio test. RR = relative risk.

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