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PhD Thesis

Do neighborhoods affect mortality and cancer incidence?

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Summary

Through the 1990s there has been increasing scientific interest in how contexts, especially neighborhoods, influence individual health. Research suggests that peoples' health is shaped not only by individual-level factors such as biology, demography and socioeconomic status (SES), but also by the neighborhoods in which they live. Individual health behavior is affected through interaction with fellow inhabitants and by the physical characteristics of the neighborhood. Both the social and the physical determinants are influenced by the ethnic and socioeconomic composition of inhabitants. This thesis consists of four papers analyzing the association between neighborhoods and health. The aims were to

- to conduct a systematic review of multilevel studies controlling for individual SES to evaluate if neighborhoods affect mortality and cancer-specific incidence and to conduct a meta-analysis investigating the association between area-level socioeconomic status (ALSES) and all-cause mortality.

- investigate how best to measure ALSES with a single indicator and to conduct multilevel modeling investigating how ALSES and population density affect individual all-cause mortality.

- conduct multilevel modeling evaluating the effects of population density and ALSES on breast, lung and prostate cancer incidence.

- construct an empirically based Danish deprivation index capable of explaining variation in health on a small-scale geographic level.

A systematic review was conducted to investigate if neighborhoods affect mortality and cancer-specific incidence (paper 1). By searching five databases a total of 40 studies were found eligible for the systematic review while 18 studies qualified for the meta-analysis. No clear associations were found for income inequality or social cohesion. Studies including more than one area level suggested that all levels contribute to variation in mortality. It was also found that studies including lag time between neighborhood influences and health outcomes found greater effects. In the meta-analysis all-cause mortality was found to be significantly higher among inhabitants living in areas with low SES (OR=1.05, 95% CI=1.04-1.06) compared to those living in affluent areas. Associations were stronger for men, younger age groups and in studies analyzing geographical units with fewer inhabitants. No

effects were found for the type of welfare state regime in which the studies were conducted or for the number of covariates controlled for.

Two multilevel analyses were conducted to investigate area effects on all-cause mortality (paper 2) and cancer-specific incidence (paper 3) in Denmark. All individuals with residence in Denmark in 2004 between 30-81 years (all-cause mortality), 30-83 years (breast cancer incidence) and 50-83 years (prostate and lung cancer incidence) were followed through 2006 (all cause) and 2008 (breast, prostate and lung cancer incidence). Frailty modeling was conducted and age, sex, marital status, education, disposable income and occupational SES were adjusted for on the individual level. On the area-level the effect of population density and ALSES was examined.

Results in paper 2 showed that living in areas with the lowest population density was associated with reduced mortality among individuals between 30 and 49 years, HR:0.85 (95% CI=0.76-0.95), compared to those living in areas with the highest population density. The effects were HR:0.81 (95% CI=0.76-0.86) and HR:0.86 (95% CI=0.83-0.89) for individuals aged 50-64 years and 65-81 years respectively. In addition, living in the most deprived areas was associated with excess mortality in the two older age groups, HR:1.05 (95% CI=1.01-1.09) and HR:1.05 (95% CI=1.02-1.07) respectively. No association was found between all-cause mortality and ALSES for individuals aged 30-49 years.

In paper 3 a reduced risk of breast cancer in areas with lower population density was found HR:0.93 (0.86-0.99) compared to areas with higher population density. There was no effect of ALSES. For prostate cancer higher risk was found among inhabitants in affluent areas HR:1.14 (95% CI=1.08-1.21) compared to those living in deprived areas. No effect was found for population density. Lung cancer risk was lower in the least densely populated areas HR:0.80 (95% CI=0.74-0.85) and in affluent areas HR:0.88 (95% CI=0.84-0.92) while being controlled for each other and for individual-level characteristics.

In paper 4 an area-based deprivation index was constructed for Denmark. Individual-level data of all Danes (N=5,391,995) were aggregated to 11 indicators describing parishes (N=2,113) by characteristics in income, employment, education, health, housing, demography and crime. A principal component analysis was conducted to determine the relative weights of the variables and to reduce them to a set of components. The index was validated using standardized mortality ratios (SMRs) in all parishes in 2005. To compare the strength of the index with the Townsend index and to evaluate to what extent the index could be used as a proxy for individual-level SES factors, index scores were applied to 2.7 million individuals in Denmark in a shared frailty model evaluating the risk of death between 2004 and 2006 and compared to a similar model containing individual education, income and occupation-based SES. The index measures material deprivation on one dimension and socioeconomic

deprivation on another dimension. There were clear gradients in SMRs in both dimensions: SMR for men in materially deprived parishes were 1.06 (1.05-1.07) and 0.79 (0.76-0.82) in affluent areas. In parishes deprived on the socioeconomic dimension SMR for men was 1.14 (1.12-1.16) and 0.88 (0.87-0.89) in the more affluent areas. The same pattern existed among women although the effects were smaller. The index was better at explaining variation in all-cause mortality compared to the Townsend index (76% vs. 69.6% of frailty variation) and was able to account for as much variation as individual SES factors could (76% of frailty variation). The index can be used to identify Danish parishes by their material and socioeconomic status and as a predictor of mortality on the area-level. The index provides policy makers with a tool to allocate health related resources and can assist in planning area-specific health interventions. It can also be used in epidemiological studies investigating or adjusting for area-effects on individual health outcomes.

Dansk resumé

Siden 1990'erne har der været en stigende interesse for, hvordan folkesundheden påvirkes af de kontekster, som mennesker dagligt færdes i. Lokalområders indflydelse har fået særlig stor opmærksomhed. Forskningen har vist, at biologi, demografi og socioøkonomisk status ikke alene kan forklare, hvorfor nogle mennesker bliver hyppigere syge, lever mere usundt og dør tidligere. Det betyder også noget, hvor man bor. Årsagen er, at de fysiske forhold i lokalområdet og de sociale påvirkninger fra andre beboere sætter nogle rammer for, i hvor høj grad en sund levevis kan efterstræbes.

Dette ph.d.-projekt består af fire artikler, der hver især undersøger sammenhængen mellem lokalområder, dødelighed og kræftforekomst. Formålet har været at:

- foretage et systematisk litteraturstudie af, om lokalområder har indflydelse på individuel dødelighed og kræftforekomst samt at foretage en meta-analyse, der kvantificerer sammenhængen mellem lokalområders socioøkonomiske status og individuel dødelighed.

- undersøge, hvilke socioøkonomiske mål på områdeniveau der bedst kan forklare geografisk variation i dødelighed, når der er taget højde for individuelle faktorer, samt at foretage et multilevelstudie af associationen mellem områders befolkningstæthed, deres gennemsnitlige socioøkonomiske status og individuel dødelighed.

- foretage et multilevelstudie af associationen mellem områders befolkningstæthed, deres gennemsnitlige socioøkonomiske status og bryst-, prostata- eller lungekræft incidens.

- konstruere et dansk relativt deprivationsindeks, der er i stand til at beskrive danske sognes velstandsniveau og forklare geografisk variation i generel dødelighed.

Det systematiske litteraturstudie (artikel 1) afsøgte fem databaser og fandt 40 studier, der belyste problemstillingen. Der blev ikke fundet nogen sammenhæng mellem dødelighed og graden af indkomstulighed eller social kapital. Gennemgangen viste, at lav social sammenhængskraft (social cohesion) i lokalområder var associeret med høj dødelighed. Ud af de 40 studier blev 18 udvalgt til en videre meta-analyse, der viste, at der er signifikant højere dødelighed (OR=1,05, 95% CI=1,04-1,06) blandt beboere i områder med lav gennemsnitlig socioøkonomisk status sammenlignet med beboere i mere velstillede områder. Effekten var højere for mænd, yngre aldersgrupper og i studier, hvor

områderne var små. Effekten afhang ikke af, i hvilken velfærdsstatstype studierne var gennemført eller hvor mange faktorer, der var justeret for.

I to multilevelstudier blev det undersøgt, hvorvidt lokalområder havde indflydelse på generel dødelighed (artikel 2) og kræftforekomst (artikel 3). Undersøgelserne blev foretaget blandt alle danskere, der boede i landet i 2004, og som var mellem 30 og 81 år (generel dødelighed), 30 og 83 år (brystkræftincidens) og 50 og 83 år (prostata og lungekræft incidens). Populationerne blev fulgt fra 1. januar 2004 til udgangen af 2006 (generel dødelighed) og til udgangen af 2008 (bryst-, prostata- og lungekræft incidens). Der blev foretaget frailtymodellering, der på individniveau kontrollerede for alder, køn, civilstatus, uddannelse, disponibel indkomst og erhvervs-relateret socioøkonomisk klasse. På områdeniveau (2.121 sogne) blev effekten af befolkningstæthed og gennemsnitlig socioøkonomisk status undersøgt.

For personer under 50 år viste den gennemsnitlige disponible indkomst i et område at være den faktor, der forklarede mest variation i dødelighed ud over individuelle faktorer, mens det for ældre aldersgrupper var mere fordelagtigt at anvende andelen af arbejdsløse.

Beboere i områder med lav befolkningstæthed havde lavere dødelighed (HR=0,85, 95% CI=0,76-0,95), sammenlignet med områder med højeste befolkningstæthed. Derudover havde personer over 50 år forøget risiko for at dø, hvis de boede i områder med lav socioøkonomisk status (HR=1,05, 95% CI=1,02-1,07). Denne sammenhæng blev ikke fundet for personer under 50 år.

Der blev fundet reduceret risiko for at få en brystkræftdiagnose blandt kvinder i områder med den laveste befolkningstæthed (HR=0,93, 95% CI=0,86-0,99), mens effekten af områdets socioøkonomiske status ikke var signifikant. Blandt mænd var der højere risiko for at få prostatakræft, hvis de boede i områder med høj socioøkonomisk status (HR=1,14, 95% CI=1,08-1,21). Der blev ikke fundet nogen effekt af befolkningstæthed. Risikoen for at få lungekræft var lavest for beboere i områder med lav befolkningstæthed (HR=0,80, 95% CI=0,74-0,85) og med høj socioøkonomisk status (HR=0,88, 95% CI=0,84-0,92).

I artikel 4 blev der konstrueret et todimensionelt relativt deprivationsindeks på sogneniveau, som kan anvendes til at karakterisere områders velstand. Yderligere kan det anvendes til at allokere ressourcer mellem danske sogne og til at måle områders velstandsniveau i epidemiologiske undersøgelser. Indekset blev konstrueret ved at aggregere 11 socioøkonomiske indikatorer på individniveau (5.391.995 personer) til områdeniveau (2.113 sogne). Indikatorerne beskrev sognene i forhold til deres indkomst, uddannelse, beskæftigelse, ejendomme og deres beboelse, kriminalitet, folkesundhed og demografi. Der blev foretaget en principal komponent analyse for at reducere antallet af indikatorer, for at gruppere dem i dimensioner og for at give dem vægte. Den ene dimension i indekset måler materiel levestandard og er korreleret med Townsend-indekset (r=0.88), mens den anden dimension måler socioøkonomisk status, som ikke er korreleret med Townsend (r=0.01). Begge dimensioner viste sig at kunne forklare forskelle i den standardiserede mortalitetsratio (SMR) mellem danske sogne. Mænds SMR i områder der er materielt fattige var 1,06 (1,05-1,07) og 0,79 (0,76-0,82) i materielt velstillede områder. I områder der havde lav socioøkonomisk status var SMR 1,14 (1,12-1,16) for mænd mens den var 0,88 (0,87-0,89) i områder med høj gennemsnitlig socioøkonomisk status. Samme mønster gjorde sig gældende for kvinder omend forskellene var mindre. I en multilevelanalyse var indekset signifikant bedre end Townsend-indekset til at forklare geografisk variation i dødelighed (76% vs. 69,6% forklaret variation). Indekset forklarede tillige den samme variation i dødeligheden som individuel uddannelse, disponibel indkomst og erhvervsrelateret socioøkonomisk status (76% forklaret variation). Foruden at kunne identificere områder mht. deres materielle og socioøkonomiske velstand kan indekset anvendes til at allokere sundhedsrelaterede ressourcer mellem geografiske områder og til at planlægge interventioner i lokalområder. Desuden vil det kunne bruges i epidemiologiske studier til at undersøge og justere for områders indflydelse på bl.a. folkesundheden.

Konklusion

Det er blevet vist, at lokalområder har indflydelse på individuel dødelighed og kræftforekomst – også når der tages højde for individuelle socioøkonomiske forhold. I Danmark er lokalområder med høj befolkningstæthed og med lav socioøkonomisk status selvstændige risikofaktorer. Mens der kan være fordele i at rette forebyggelsesinitiativer mod disse områder, og der kan være ting, der taler for, at man fra politisk side bør stimulere depriverede områder, anbefales det, at de medierende årsager til disse sammenhænge findes først.

List of papers

1. Meijer, M.; Röhl, J.; Bloomfield, K.; Grittner, U. Do neighborhoods have an effect on mortality? A systematic review and meta-analysis of multilevel studies. Social Science & Medicine (accepted*).

2. Meijer, M; Kejs, AM.; Stock, C.; Bloomfield, K.; Ejstrud, B.; Schlattmann, P. Population density, socioeconomic environment and all-cause mortality: A multilevel survival analysis of 2.7 million individuals in Denmark. Health & Place (accepted*).

3. Meijer, M.; Bloomfield, K.; Engholm, G. Neighborhoods matter too: The association between neighborhood socioeconomic position, population density and breast, prostate and lung cancer incidence in Denmark between 2004 and 2008. Journal of Epidemiology & Community Health (under review).

4. Meijer, M.; Engholm, G.; Grittner, U.; Bloomfield, K.; An empirically based index of material and socioeconomic deprivation for Denmark. Scandinavian Journal of Public Health (under review*).

***** in a slightly revised version than it appears in the appendix

Abbreviations and definitions

ALSES	Area-level socioeconomic status
CI	Confidence interval
HR	Hazard ratio
IMSD	Index of material and social deprivation
Incidence	New cases in a given period in a given population
Mortality	Deaths in a given period in a given population
OR	Odds ratio
RR	Relative risk
SES	Socio economic status

Introduction

Why neighborhoods have become a public health concern

It is well-established that health, morbidity and mortality is associated with individual socioeconomic status (SES) (Marmot, 2010; Marmot, 2006). After age and sex, SES has often shown to be the most influential determinant of health (Berkman and Kawachi, 2000). The primary used explanations are that SES influences health behavior, such as smoking, alcohol consumption, physical activity, obesity and nutrition (Marmot, 2010; Marmot, 2006).

Earlier in its history, public health was more concentrated around environmental and community characteristics when studying health and disease (Cummins et al., 2007; Diez-Roux, 1998; Macintyre and Ellaway, 2003). The idea that contexts shape individual health dates back to the Hippocratic traditions of medicine (Macintyre and Ellaway, 2003), thus studying contexts and neighborhoods is not new to public health research. Over the 20th century, however, the growing importance of chronic diseases shifted the scientific emphasis from environmental factors to individual-level factors (Diez-Roux, 1998). As a result, the idea that risk was individually determined dominated scientific work in the public health's sphere (Duncan et al., 1996). Health behavior was regarded as matters of individual free choice and was not seen as an integral parts of the social contexts in which people daily were engaged (Diez-Roux, 1998).

Since the mid 1990s researchers have again increasingly shown interest in how contexts, especially neighborhoods, influence individual health. The idea is that individual health is shaped and constrained by their contexts (Diez-Roux, 1998; Duncan et al., 1996). After years of dismissing the association between individual health and contexts, public health and epidemiology have reintroduced the importance of contexts and environments. It has been acknowledged that individuals are part of communities and large-scale environmental structures that mutually affect each other. People regularly engage in various social contexts scattered around in geographically distinct settings. Examples of such contexts could be the workplace, family, friends or the neighborhood. Regarding individual health as being determined not only by individual-level factors but also by social and physical influences, provides a more holistic and nuanced picture.

A number of reasons have been given for the emergence of this renewed arena in public health research (Diez Roux and Mair, 2010; Macintyre et al., 2002; Pickett and Pearl, 2001). Apart from a general shift towards encouraging non-individualistic approaches, methodologies and concepts, researchers have been reluctant to use ecological data because of the ecological fallacy (Diez-Roux, 1998; Macintyre et al., 2002). Also the growing acceptance of multilevel modeling along with the appropriate software now allows for the inclusion of both an individual-level and a neighborhood-level in one model. Furthermore, the discipline of public health is today using insights, theories and approaches that previously were exclusive to sociology, anthropology, psychology and geography, disciplines that have long studied neighborhoods and communities. The introduction of Geographic Information Systems (GIS) has also increased the interests in analyzing area-level effects on health outcomes (Diez Roux and Mair, 2010; Macintyre et al., 2002).

How neighborhoods affect health

Some of the earliest contemporary contributions to understand neighborhood effects on health showed that social disorganization was related to higher rates of hospitalizations for mental disorders (Farris and Dunham, 1965) and that poverty and residential instability was linked to infant mortality, low birth weight, tuberculosis and other health outcomes (Shaw and McKay, 1969).

With the introduction of multilevel statistical methods it became possible to separate effects attributable to individuals living in the neighborhoods from those attributable to the neighborhoods. An often made distinction is made between compositional and contextual effects. Compositional effect refers to the inhabitants of the neighborhoods, while the contextual effect has to do with the places.

A recent study has summarized the processes through which neighborhoods can contribute to health inequalities (Diez Roux and Mair, 2010): First, residential segregation by race, ethnicity and socioeconomic position affects the kind of resources that are allocated to and demanded in areas. The physical environment influences people’s health behavior through e.g. levels of traffic air pollution, availability of healthy food stores, fast-food restaurants, recreational resources, alcohol outlets and sports facilities, quality of the built environment etc. The social environment of neighborhoods affects peoples’ health through characteristics related to safety/violence, social connections/cohesion, local institutions and norms.

As an example of how the social environment of neighborhoods can affect individual health, inhabitants engage in verbal or non-verbal communication that is constrained by certain sets of norms, values and sanctions. If one daily sees people in the neighborhood bicycling, running and buying healthy food, the likelihood is higher that one notices and replicates this behavior (Auchincloss and Diez Roux, 2008). The importance of “weak ties” between neighbors defined as “unpretentious everyday contacts in the neighborhood” are stressed as important (Henning and Lieberg, 1996)

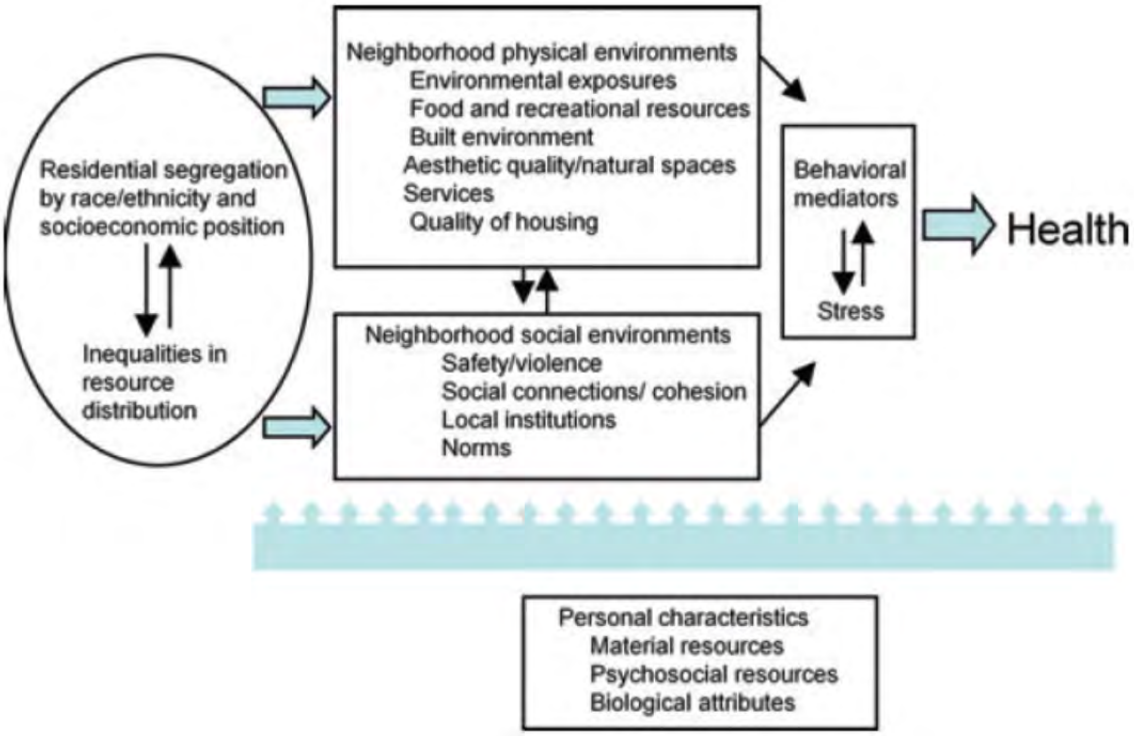


Figure 1

Schematic representation of the contribution of neighborhood environments to public health inequalities. Source: (Diez Roux and Mair, 2010).

Distinguishing between the effects of people and places has previously been criticized (Macintyre and Ellaway, 2003; Macintyre et al., 2002). For instance, is low qualification of inhabitants attributable to composition or context if the neighborhood is dominated by manual work places? This discussion has lead to a more dynamic view suggesting that neighborhoods affect people, e.g. by attracting certain socioeconomic groups, and that people affect neighborhoods, e.g. by attracting particular workplaces or shops. Regarding compositional and contextual influences as an intertwined relationship is therefore seen as a being less arbitrary (Cummins et al., 2007; Macintyre and Ellaway, 2003; Macintyre et al., 2002). The model pictured in Figure 1 (Diez Roux and Mair,

2010) has adopted this view by incorporating arrows pointing in both directions between the social and the physical environments. Also the ethnic and social composition of inhabitants is influenced by the social and physical environment. Individuals with higher SES, for instance, typically settle in more esthetically pleasing areas with less air- and noise pollution, better shopping facilities, better housing standards and less crime. Similarly, persons with lower SES are often restricted to live in areas with fewer opportunities to pursue a healthy life.

It could be questioned whether social cohesion should be regarded as a health indicator in itself, which it typically is, or if it should be treated as a filter between possible neighborhood influences and individual adaptation. A socially cohesive neighborhood can be seen as a place characterized by common values, social order, social solidarity, social networks and place attachment (Forrest and Kearns, 2001). In order for health behavior to be transferred between inhabitants, they typically need to engage in deeper and more meaningful social connections based on trust and shared values and norms, i.e. where social cohesion is high. Neighborhoods with high social cohesion are often linked to richer, well-functioning communities. However, social cohesion would also exist in neighborhoods consisting of e.g. ethnic minorities feeling excluded from society (Forrest and Kearns, 2001), who do not necessarily have positive health behaviors. Social cohesion could therefore result in both positive and negative health behavior. Earlier studies have not investigated whether social cohesion or social capital mediate neighborhood effects but have shown that low social cohesion is associated with higher mortality (Blomgren et al., 2004; Chaix et al., 2008; Martikainen et al., 2003).

Studies have also suggested that some social groups are more susceptible to neighborhood influences than others. The neighborhood is more important to blue-collar workers when it comes to making “strong social ties” than it is for people with white collar backgrounds (Henning and Lieberg, 1996). Similarly it has been suggested that unemployed inhabitants in poor areas (Forrest and Kearns, 2001), women (Stafford et al., 2005) as well as children, handicapped and elderly (Henning and Lieberg, 1996) are more susceptible to neighborhood influences, because they spend more time there. Despite increased spatial mobility and weakening place attachment a sociological study from 1999 suggests that, for older people, stability in residence is today more pronounced than it was in earlier generations and that “the relationship between people and places is perhaps even more important at the end of the 20^{th} century than it was at the beginning” (Phillipson et al., 1999, p. 740).

Altogether the links between neighborhoods and health is consistent. Nevertheless contemporary epidemiological studies often fail to recognize the possible influence form other contexts (Sampson, 2003). Family, friends, colleagues, fellow members of the sports club and media are also important arenas, but are rarely discussed in social epidemiological studies. As one of the most important modern sociologists Manuel Castells note:

> "People socialise and interact in their local environment, be it in the village, in the city, or in the suburb, and they build social networks among their neighbours. On the other hand, locally based identities intersect with other sources of meaning and social recognition, in a highly diversified pattern that allows for alternative interpretations" (Castells, 1997, p. 60).

Thus, it needs to be acknowledged that these "other sources of meaning", i.e. other contexts, influence individual health in a combination with neighborhoods.

Current evidence for the association between neighborhoods and health

Numerous epidemiological studies have demonstrated a link between neighborhood SES and health – also after taking account of individual level factors. Systematic reviews have shown that this pertains to mortality (Ellen et al., 2001; Pickett and Pearl, 2001; Riva et al., 2007; Yen et al., 2009), morbidity (Pickett and Pearl, 2001; Riva et al., 2007) and health behavior (Davison et al., 2008; Diez Roux and Mair, 2010; Pickett and Pearl, 2001; Pont et al., 2009; Riva et al., 2007). A recent meta-analysis also found a modest association between income inequality and mortality and self-rated health (Kondo et al., 2009).

Paper 1 in this thesis provides a thorough review of how individual mortality and cancer incidence are associated with various area-level factors. It also provides the results of the first meta-analysis conducted on the association between area-level SES (ALSES) and all-cause mortality. Methods and results appear in the next chapters.

Aims

The initial aim of this PhD project was to develop a relative deprivation index capable of measuring relative deprivation in Denmark and to examining if area-level effects could also be found in Denmark. Three studies had previously investigated area effects in Denmark. They found that high local unemployment was associated with higher mortality (Osler et al., 2003b), and that income inequality was not associated with either mortality (Osler et al., 2002) or with hospitalisations and death from ischemic heart disease (Osler et al., 2003a). However, they did not use multilevel modeling, which is seen as necessary in area-effect studies (Subramanian et al., 2003). The working hypothesis for the PhD was that the high economic redistribution in Denmark along with the universal access to education and health care would diminish social inequalities in health and that a Danish deprivation index therefore would require other measures than those used in the English deprivation indices. Additionally the expectation was that area-effects would be smaller than seen in international studies.

Before engaging in investigations of area-effects in Denmark and the Danish deprivation index, the literature was reviewed. Four previous reviews (Ellen et al., 2001; Pickett and Pearl, 2001; Riva et al., 2007; Yen et al., 2009) concluded that there is an association between ALSES and mortality. However, they were not based exclusively on studies using multilevel modeling, which, as mentioned, is essential if area effects are to be isolated from individual effects and if the clustering of individuals in areas should be accounted for (Subramanian et al., 2003; Subramanian and Kawachi, 2004). In addition they were not exclusively based on studies controlling for individual SES, which significantly increases the risk of overestimating the neighborhood effects (Pickett and Pearl, 2001). Given that neighborhood effect studies based on multilevel modeling started to appear in the mid 1990s and that the number of studies have increased markedly since 2001 (Riva et al., 2007), there was a need to update current knowledge with a systematic review solely based on studies that utilized multilevel analysis and controlled for at least one individual-level SES factor. Since this PhD project was part of a larger research project investigating area-effects on mortality and on cancer incidence, studies evaluating neighborhood influences on cancer incidence were also included. In addition to the systematic review, the number of studies allowed for a meta-analysis of how ALSES affected all-cause mortality. In sum the aim of the first paper therefore was

- to conduct a systematic review of multilevel studies controlling for individual SES to evaluate if neighborhoods affect mortality and cancer-specific incidence and to conduct a meta-analysis investigating the association between ALSES and all-cause mortality.

In the early phases of the research project it was decided to identify any possible area-effects in Denmark before constructing the relative deprivation index. The aim in paper 2 was therefore to investigate which of several available ALSES indicators that explained the most variation in all-cause mortality in Denmark in a multilevel model adjusting for individual demographic and socioeconomic factors. To do this, the effects of five factors were evaluated. These factors were the average parish-level education level, average disposable family income, proportion of unemployed, proportion semi- or unskilled workers, and proportion of disability pensioners. Three earlier studies suggested that different ALSES measures produce very different results (Bosma et al., 2001; Kravdal, 2007; Naess et al., 2005). The purpose of the analysis was to provide an overview of the effect of different ALSES measures to identify how best to account for ALSES, when a relative deprivation index was not available.

Additionally the aim was to examine the associations between population density, ALSES and all-cause mortality. Previous studies controlling for SES on both the individual level and the area level have shown that high population density is associated with increased mortality from ischemic heart disease (Chaix et al., 2006; Chaix et al., 2007a), lung cancer and chronic obstructive pulmonary disease (Chaix et al., 2006). Other studies have found that residence in rural areas was associated with lower all-cause mortality (Blakely et al., 2006) and higher alcohol-related mortality (Blomgren et al., 2004). The purpose of investigating ALSES and population density in the same model was to build on research suggesting the existence of an 'urban health penalty', i.e. that poor health is concentrated in highly urban areas because inhabitants are exposed to unhealthy physical and social environments (Freudenberg et al., 2005; Takano, 2003). By including both ALSES and population density in the same model, it was possible to evaluate if an urban penalty really exists and affects all-cause mortality, or if it is related to the socioeconomic composition of inhabitants. The aim in paper 2 was

- to investigate how best to measure ALSES with a single indicator and to conduct multilevel modeling investigating how ALSES and population density affect individual all-cause mortality.

In paper 3 the influence of area-level characteristics on breast, prostate and lung cancer incidence was investigated. Only two multilevel studies previously explored the association between breast cancer incidence and area-level factors. They found that inhabitants in urban (Robert et al., 2004) and high SES areas (Robert et al., 2004; Webster et al., 2008) were at higher risk. One study investigated the effect of neighborhoods on prostate cancer incidence and found that inhabitants in low SES neighborhoods were at higher risk (Sanderson et al., 2006). No multilevel studies have explored the influence of neighborhoods on lung cancer incidence. Using the same area-level factors as in paper 2 the aim therefore was to

- conduct multilevel modeling evaluating the effects of population density and ALSES on breast, lung and prostate cancer incidence.

In paper 4 the aim was to construct an empirically based deprivation index to identify deprived small-scale areas in Denmark. Internationally, the absence of individual data, has led researchers to use ecological measures to understand geographic variation in health outcomes. To capture different forms of deprivation and to make the ecological measure more reliable, previous studies have shown the benefits of combining several ecological variables into a deprivation index (Carstairs and Morris, 1989; Havard et al., 2008; Jarman, 1983; Juhasz et al., 2010; Messer et al., 2006; Noble M et al., 2004; Noble et al., 2008; Salmond et al., 1998; Townsend, 1987). The most well-known are the Townsend Index (Townsend, 1987), the Carstairs Index (Carstairs and Morris, 1989) and the English Indices of Multiple Deprivation (Noble M et al., 2004; Noble et al., 2008) which have been widely used in the UK. In Denmark and in the Nordic countries deprivation indices have not received the same attention and recognition. One of the main reasons is that the justification and practical use of deprivation indices diminishes when individual level data from public registers are available, as they are in Scandinavian countries. However, in area-effect studies such an index is useful because it is a multidimensional measure of ALSES. Additionally this index could be used to allocate health related resources. In sum, the aim of paper 4 was

- to construct an empirically based Danish deprivation index capable of explaining variation in health on a small-scale geographic level.

Materials and methods

Overview of data and methods in the four papers

Table 1 provides an overview of the aims, data and methods in the fours papers. In the following

Table 1
Overview of aims, methods and data in papers

	Paper 1	Paper 1	Paper 2	Paper 3	Paper 4	Paper 4
Aim	To investigate if areas have effect on mortality and cancer incidence	To estimate the effect of ALSES on all-cause mortality	To determine how best to measure ALSES and to evaluate the effects of ALSES and population density on all-cause mortality	To evaluate the effects of ALSES and population density on breast, prostate and lung cancer incidence	To construct a relative deprivation index for Danish parishes	To validate the index
Method	Systematic review	Meta-analysis and meta-regression	Frailty modeling	Frailty modeling	Principal component analysis	Frailty modeling
Data source	Multilevel studies investigating area-level effects on mortality or cancer incidence controlling for individual SES	Studies included in systematic review that investigates ALSES effects on all-cause mortality	Registry data from Statistics Denmark	Registry data from Statistics Denmark	Registry data from Statistics Denmark	Registry data from Statistics Denmark
Population	Adult populations in western societies	Adult populations in western societies	Ethnic Danes aged 30-81 years, present in Denmark in 2004 and 1995	Ethnic Danes aged 30-83 years, present in Denmark in 2004 and 1995	All individuals present in Denmark in 2005	As in paper 2
Study period	All times	All times	2004-2006	2004-2008	2005	2004-2006
Individual level data	(all studies controlled for age, sex and individual SES)	(all studies controlled for age, sex and individual SES)	Age, sex, marital status, highest attained education, disposable family income, occupation-based SES	As in paper 2	-	As in paper 2
Area level data	All area-effects investigated in studies	ALSES	Average education length, disposable income, proportion of unemployed, semi/unskilled workers, disability pensioners, population density, hemeroby	Proportion of unemployed, population density	See Table 2	IMSD index, Townsend index

sections more detailed descriptions are given.

Paper 1: Systematic review and meta-analysis

Guidelines for conducting systematic reviews provided by Centre for Reviews and Dissemination (NHS, 2009) were followed through the data collection. The PRISMA principles (Liberati et al., 2009) were used for reporting results.

Data collection and extraction

A pilot data collection was conducted upon which a final set of methods and inclusion criteria was developed. Studies were identified by searching Cochrane Library, Medline, Embase, Social Sciences Citation index and PsycInfo. Secondly, reference lists were scanned in existing reviews, publications were reviewed and authors were contacted for unpublished results. See paper 1 in the appendix for a complete list of search terms used.

Included studies were written in English, published in peer-reviewed journals, reported data from a primary study, were based on a random sample of an adult population from developed countries, used multilevel modeling, adjusted for at least one SES variable (income, education or occupation) at the individual level, used at least one area-level indicator and included either mortality or cancer incidence as the individual outcome.

In the first stage I removed duplicates together with another author and independently reviewed titles and abstracts to assess eligibility according to the inclusion criteria. When in doubt, full texts were assessed. Disagreements between reviewers were resolved by consensus (41 cases out of 766) and by consulting a third author (two cases). In a second phase full texts were independently assessed and studies were excluded with specific reference to inclusion criteria. Reviewers had five cases of disagreements out of the 59 full text assessments, which were resolved by consensus. Both reviewers independently extracted all relevant data from studies into a pilot tested coding scheme.

Systematic review

Based on the coding scheme, a systematic review of studies was conducted. For all studies overall estimates and confidence intervals were calculated for the area-level effect using weighted linear regression (Schlattman, 2009). A quality assessment of all reviewed studies was conducted using the standardized quality assessment tool for quantitative studies from the Effective Public Health Practice Project (EPHPP, 2007). This tool provides a systematic framework, recommended by the Cochrane Collaboration, for assessing selection bias, study design, confounders, blinding, data collection methods, withdrawals and drop-outs, intervention integrity and approaches to analyses. Although any quantitative study can be assessed with this tool, it was primarily developed for clinical studies. Since studies included in the systematic review were observational and based on registry-, census- or survey-data no assessment for blinding, withdrawals, dropouts or intervention integrity was conducted.

Meta-analysis and meta-regression

A meta-analysis of the association between ALSES and all-cause mortality was performed. Seven out of 18 studies used income as ALSES measure. Seven other studies used an index measure of ALSES which incorporated information on e.g. income, education, occupation, car access, house ownership or unemployment. The remaining four studies used the percentage of people with severe financial problems, the poverty rate, the percentage of manual workers and the percentage with primary education, respectively. All ALSES estimates in each study were combined into a single estimate using weighted linear regression (Schlattman, 2009) in order to calculate the effect of ALSES on mortality in lower SES areas compared to higher SES areas. The overall estimate was calculated by using a random effects approach, incorporating an estimate of variation between studies (DerSimonian and Laird, 1986). I^2 statistics was used to evaluate the between-study heterogeneity (Higgins and Thompson, 2004; Higgins et al., 2003).

A meta-regression was also performed. The outcome was estimates for mortality in lower SES areas compared to mortality in higher SES areas. Sex, age, number of covariates adjusted for, survey year, number of inhabitants in areas and welfare state regimes were used as covariates. The country investigated in each study was categorized as either liberal, conservative and social democratic after Gösta Esping-Andersen's theory on welfare state regimes (Esping-Andersen, 1990). ALSES was used as a quasi-metric variable ranging from 1 (high ALSES) to 9 (low ALSES). Only significant covariates were used in the final model. Estimates were weighted according to standard errors (Schlattman, 2009).

Papers 2 and 3: Frailty modeling

Design

The outcomes all-cause mortality and incidence from breast, prostate and lung cancer were analyzed in two separate papers. Although the data and study designs had many similarities, they also differed on a number of parameters.

Persons residing in Denmark January 1st 2004 were followed until December 31st 2006 (all-cause mortality) or December 31st 2008 (cancer-specific incidence). Individual characteristics were measured three years prior to the event of death and two years prior to a cancer diagnosis since persons can experience major life events in the before death and cancer diagnosis (e.g., job loss, income reduction or changes in marital status). For right censored individuals, individual characteristics were measured in 2002 (all-cause mortality) and in 2004 (cancer incidence). The analyses were conducted for persons between ages 30-81 (all-cause), 30-83 (breast cancer incidence) and 50-83 (prostate and lung cancer incidence). Younger individuals below 30 years were excluded to ensure that the majority had completed their educations while older individuals were excluded due to missing data on education. Prostate- and lung cancer incidence was measured from the age of 50 years since the number of diagnoses before this age is relatively low.

Parish level characteristics were measured in 1995 to allow for a latency period between neighborhood exposure and outcome. The study sample comprised those who resided in Denmark in 2004, when individual characteristics were measured and when parish-level characteristics were measured in 1995. To ensure a homogeneous study population, immigrants were excluded from the studies, because preliminary analyses indicated that their susceptibility to individual and parish-level SES differed from ethnic Danes.

Individual-level factors

All analyses included age, sex, marital status, education, income and occupation-based SES. Education, measured as the highest obtained education, was re-coded to the International Standard Classification of Education (ISCED) constructed by UNESCO in 1997 (UNESCO, 1997). Disposable income was calculated as the sum of annual gross income after taxation and interest per person in the household deflated to 2000 price levels and divided by the number of persons in the household elevated by a factor of 0.6. The elevation was done to account for the economic advantages of being more persons in a household. Marital status was dichotomized into cohabiting/married and single (including widows). Occupation-based SES was based on the six-class European Socio-Economic Classification (Rose and Harrison, 2007). Persons not employed were grouped into four additional categories: students; unemployed; disability pensioners, and old-age/early retirement pensioners. Pensioners and the unemployed were categorized due to their last held position if they had one after 1990 (pensioners) or within the last two years (unemployed).

Parish-level factors

Parishes (n=2,121) are the smallest geographical unit available in Danish registers. They have no political or administrative tasks. In 1995 they differed in size from 0.1 km^2 to 156.0 km^2 (median=16 km^2). Parish populations ranged from 8 to 20,442 persons of all ages (median=1,107). All factors were constructed as quartiles (528 parishes in each quartile). All parish-level SES factors were aggregated from individual-level data of inhabitants present in parishes in 1995. In paper 2 the following parish-level SES measures were evaluated: Average education length, average disposable income, the proportion of unemployed, the proportion of semi/unskilled workers and proportion of disability pensioners. Average education length in parishes was calculated for inhabitants aged 30-60 years. Average disposable income level was based on the same formula as individual disposable income but only for persons aged 20-60 years. The same age group was used for the proportion of unemployed, proportion of semi/unskilled workers and proportion disability pensioners.

Additionally population density (persons in all age groups/km^2) was used and compared to hemeroby (paper 2) since both concepts are dimensions of urbanicity. Hemeroby is a measure of the human impact on the landscape. Being developed especially within biology and nature conservation, the idea is to classify areas or even individual plant communities according to their "naturalness". A classification was used where landuse classes are assigned values from 0 (ahemerobic, no human impact) to 1 (metahemerobic, purely artificial) (Brentrup et al., 2002). Hemeroby scores were calculated on the basis of a digital land use map with a spatial resolution of 1:25,000 available at the National Environment Research Institute (Miljø- og Energiministeriet, 2009). The hemeroby of each parish was calculated as an area weighted average within the parish. In analyses with cancer incidence as outcome only the proportion of unemployed and population density were investigated.

Statistical analyses

Since ecologic studies often use aggregated individual data to the account for neighborhood characteristics it is not possible to distinguish between effects caused by the neighborhoods and effects attributable to the individuals that live in them. A multi-level statistical approach is required (Subramanian et al., 2003) because it includes data on both individual-level and area-level and takes account of the fact that individuals are nested within areas and therefore share the same risk of living in an area. Individuals within an area are not independent of each other. This is also the reason why standard regression model are not suitable for this purpose.

Hazard rates were estimated using shared frailty models allowing individuals to be nested within parishes and the intercept to vary between parishes. Shared frailty models are multilevel random effect models for survival data accounting for the presence of a latent multiplicative effect on the hazard function, the frailty. Individuals in the same parish-level share the same frailty thus generating dependence between individuals. The streg procedure in Stata 11.1 MP with the two-parameter Weibull survival distribution and a gamma frailty distribution was used to estimate the frailty variance and effect of individual-level and parish-level factors on all-cause mortality and cancer-specific incidence (Gutierrez, 2002). One of the advantages of frailty modeling is that it adds information about timing compared to ordinary multilevel logistic regression models. It makes it possible to account for censoring and to expand the analysis from solely focusing on a dichotomous outcome to also contain information about the time to the outcome.

In the investigation of how best to measure ALSES (paper 2) the frailty variance for all factors were compared. Smaller estimates equal more explained variance. Analyses for all-cause mortality were stratified on age because the combination of a complex analysis and a large data set proved to be too challenging for the statistical software.

Marginal modeling assessing the association between each of the four outcomes and each of the individual- and area-level factors (adjusted for age and sex) were conducted. Insignificant individual factors were omitted in further analysis. All individual factors were then evaluated in the same model (model 1). Secondly, each of the parish-level factors were examined while controlling for individual-level confounding. Significant individual-level factors and area-level factors were then included in the same model (model 2).

Paper 4: Principal component analysis

Data

Socioeconomic indicators on the entire Danish population on January 1st 2005 (N=5,412,168) were obtained from Statistics Denmark. Persons without a parish code (0.4%) were omitted from the analysis. Individual data were aggregated to the parish-level. Apart from representing a church district parishes have no political or administrative tasks and in 2005 they differed in size from 0.1 km^2 to 156 km^2 (median=16 km^2). Parish populations of all ages ranged from 6 to 20,783 persons (median=1,132). Between 2005 and 2011 thirteen parishes were merged to seven new or already existing parishes, which was also done in the present analysis. The total dataset thus contains 5,391,995 persons in 2,113 parishes. Variables were selected based on previous studies that had included and evaluated them in international indices. The aim was furthermore to include variables covering deprivation domains suggested in the English Indices of Multiple Deprivation (Noble M et al., 2004; Noble et al., 2008). In addition, a demographic domain measured by the proportion of one-parent households and population density was included. In earlier studies the proportion of one-parent households have shown to be good indicators (Havard et al., 2008; Jarman, 1983; Juhasz et al., 2010). Population density was included since areas with high population density and high urbanicity have been associated with higher mortality in studies controlling for area-level socioeconomic deprivation (Chaix et al., 2006; Chaix et al., 2007a; Erskine et al., 2010). All variables evaluated and descriptions of how they were constructed are listed in Table 2.

Table 2

Definitions and deprivation domain of indicators evaluated in a principal component analysis

Domain	Indicator	Definition	Similar indicator used in previous study
Income	Low disposable income	% of inhabitants between 30 and 60 with disposable family income in the lowest quartile. Disposable family income was calculated as family gross income minus tax and interest divided by number of persons in the household elevated by a factor of 0.6.	(Hammer-Helmich et al., 2010; Havard et al., 2008; Juel, 2010; Juhasz et al., 2010; Messer et al., 2006; Noble M et al., 2004; Noble et al., 2008)
Employment	Manual workers	% of the total population between 30 and 60 years who’s occupation was categorized as either semi-skilled or unskilled workers in the European Socioeconomic Classification (Rose and Harrison, 2007)	(Carstairs and Morris, 1989; Havard et al., 2008; Jarman, 1983)
	Unemployment	% of inhabitants between 30 and 60 years who were unemployed	(Carstairs and Morris, 1989; Hammer-Helmich et al., 2010; Havard et al., 2008; Jarman, 1983; Juel, 2010; Juhasz et al., 2010; Messer et al., 2006; Noble M et al., 2004; Noble et al., 2008; Townsend, 1987)
Education, skills and training	Basic education	% of the total population between 30 and 60 years who’s highest attained education was categorized as basic in UNESCOs International Standard Classification of Education (UNESCO, 1997)	(Havard et al., 2008; Juhasz et al., 2010; Messer et al., 2006; Noble M et al., 2004; Noble et al., 2008)
Health deprivation and disability	Disability pensioners	% of inhabitants between 30 and 60 years who were on disability pension	(Hammer-Helmich et al., 2010; Juel, 2010)
Housing	Rented dwellings	% of inhabitants of all ages living in a rented dwelling	(Havard et al., 2008; Messer et al., 2006; Townsend, 1987)
	Overcrowding	% inhabitants of all ages living in a dwelling with more than one person per room	(Carstairs and Morris, 1989; Havard et al., 2008; Jarman, 1983; Juhasz et al., 2010; Messer et al., 2006; Noble M et al., 2004; Noble et al., 2008; Townsend, 1987)
	Access to car	% households with no car	(Carstairs and Morris, 1989; Havard et al., 2008; Juhasz et al., 2010; Messer et al., 2006; Townsend, 1987)
Demography	One-parent households	% of non-married and non-cohabiting inhabitants with a child living at the same address	(Havard et al., 2008; Jarman, 1983; Juhasz et al., 2010; Messer et al., 2006)
	Population density	Number of persons of all ages per square kilometer	
Crime	Inhabitants with a criminal record	Proportion of total population between 20 and 60 who had been convicted for theft, robbery, vandalism or violence.	(Noble M et al., 2004; Noble et al., 2008)

Mathematical and statistical transformation of data

A shrinkage technique (Noble M et al., 2004; Noble et al., 2008) was used to assure more reliable and robust proportions. In addition to proportions on the parish-level, proportions were also calculated on the municipality level. Parish-level proportions were moved towards the municipality-level proportions according to the standard error. The shrunken parish-level proportions were log-transformed to obtain normalized distributions and to reduce heterogeneity in score variance. Each score was then standardized to a z-score by subtracting the arithmetic mean of all observations from the individual observation and dividing by the standard deviation. The z-score denotes the relative position of the individual score in a distribution compared to the mean of all scores in the distribution.

Principal component analysis

To reduce the number of variables to a set of components and to determine their relative weight a principal component analysis was performed including a varimax (orthogonal) rotation and a scree test. The final sets of variables and components were determined upon the eigenvalue-one criterion, a scree test, the amount of common variance accounted for by each component and the interpretability criteria. Weights obtained in the principal component analysis (Table 7) were multiplied with the z-score for each indicator. The weighted z-scores for all variables were summarized into a final score for each component.

Application of index and comparison with the Townsend index

Parishes were sorted in quintiles according to their respective scores in the two components measuring material and socioeconomic deprivation – the index was therefore called the index of material and socioeconomic deprivation (IMSD). Proportions for all variables were calculated for the component quintiles and presented in Tables 8 and 9. Two maps depict the geographical variation in the two deprivation components (Figures 4 and 5). Standardized mortality ratios (SMRs) and 95% confidence intervals were calculated for each quintile by comparing the observed number of all age- and sex-specific deaths in 2004-2006 with the expected number of deaths based on age and sex specific deaths rates for the Danish population in the same period. SMRs for each of the two components were compared to the SMRs calculated for the Townsend index (Tables 10 and 11). In addition SMRs for a 3x3 matrix consisting of the two IMSD components were calculated (Table 12).

Throughout the analysis, the IMSD was compared to the Townsend index since it is the most well-known and used deprivation index in public health research. The shrinkage technique was also used in the calculation of the Townsend index. Unlike the original Townsend index, I calculated the proportion of unemployed only for persons between 30 and 60 years instead of 16+ years to reflect that many persons in Denmark study until the age of 30 and that the average age of withdrawal from the Danish labour market was 61 years in 2005 (Eurostat, 2011). The Townsend index presented in this study is therefore an adjusted version.

To evaluate how well the IMSD explained variation in all-cause mortality in Denmark, it was analysed in a shared frailty model (see methods for papers 2 and 3) controlling for individual age and sex using the STREG procedure in Stata 11.1 MP. All persons with residence in Denmark on January 1st 2004 were followed up for death or emigration, whichever came first, through 2006. The population was delimited to individuals younger than 81 years because data on education are missing for older age groups. Analyses were restricted to those older than 30 years to ensure that the majority had completed their educations. Residence as of January 1st 2004 determined the parish codes assigned to individuals. For a limited number of cases (N=152,950) parish codes were not available for 2004, but were assigned from 2005 and 2006 residence. To ensure a homogeneous study population first and second generation immigrants were excluded, because preliminary analyses indicated that their susceptibility to individual and parish-level SES differed from that of ethnic Danes. Furthermore persons with missing data were excluded, resulting in a dataset containing 2,741,157 persons, 91.8% of the total population between 30 and 81 years.

To evaluate to what extent the IMSD could be used as a proxy for individual-level SES factors four individual-level factors were used: Marital status, highest attained education, disposable income and occupation-based SES. For a description of how these factors were constructed see methods section for paper 2.

A null model estimated the total variation in all-cause mortality between Danish parishes. Then, as seen in Table 13, sex and age were added (model 1), together with the IMSD (model 2) and the Townsend index (model 3), respectively. These models analyzed the relative strength of the IMSD and the Townsend index. To evaluate to what extent the IMSD could be used as a proxy for individual-level SES factors, a fourth model was estimated containing the above mentioned individual factors (model 4) and variation was compared to model 2. Finally the IMSD (model 5) and the Townsend index (model 6) were added to model 4 in order to evaluate how well the indices accounted for any additional variation on the area level.

Results

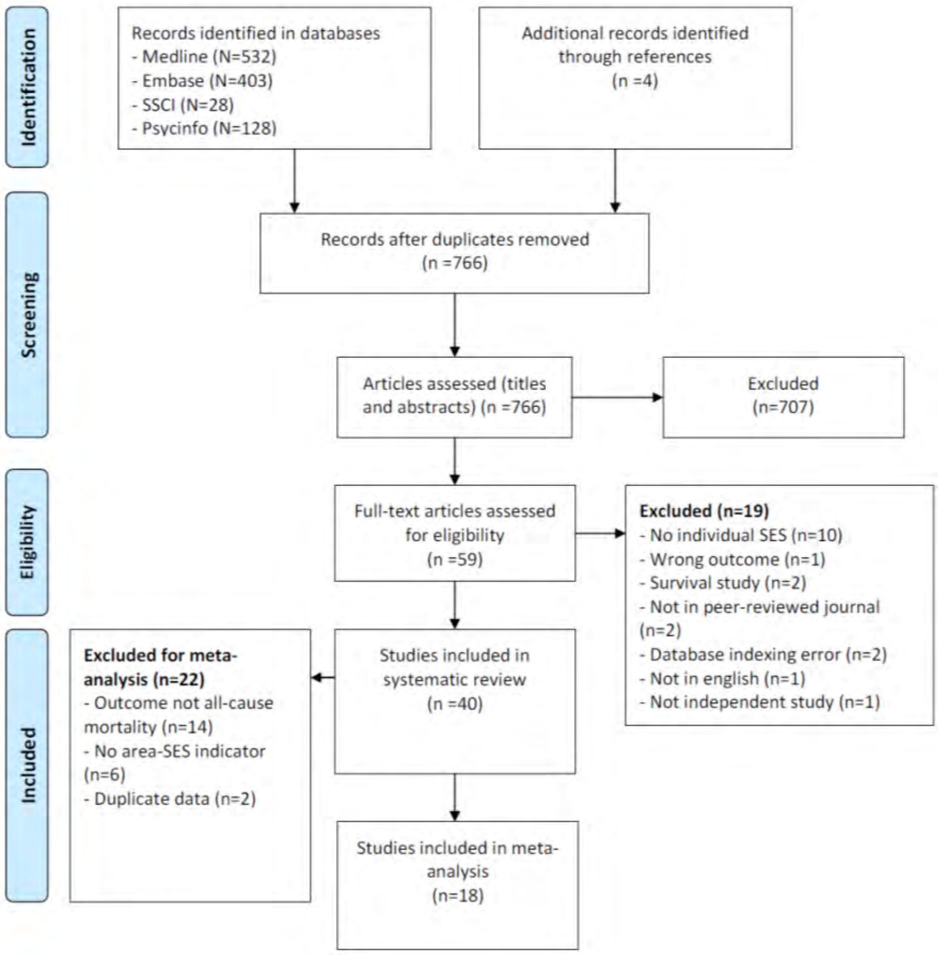
Paper 1: Synthesis of primary research

Data collection and assessment for risk of bias

Figure 2 depicts a flow diagram of identification, screening, eligibility assessment and inclusion of studies in the systematic review and in the meta-analysis. Out of 766 eligible studies a total of 40 publications were included in the systematic review and 18 studies in the meta-analysis.

Figure 2

Flow diagram of identification, screening, eligibility and inclusion of studies in systematic review and meta-analysis of multilevel investigations of area-effects on mortality and cancer-incidence



The overall quality of the reviewed studies was high given the strict study inclusion criteria. Only five studies received a moderate global rating. All remaining studies were rated strong, i.e. as having a low level of risk of bias. See paper 1 in the appendix for more elaborate results of the quality assessment.

Systematic review

The calculations of overall area-effects produced the following results: A significant ALSES effect was found in 24 studies (Anderson et al., 1997; Bentley et al., 2008; Blakely et al., 2006; Blomgren et al., 2004; Borrell et al., 2002; Chaix et al., 2008; Chaix et al., 2006; Chaix et al., 2007a, b; Curtis et al., 2004; Franzini and Spears, 2003; Jaffe et al., 2005a, b; Jerrett et al., 2003; Malmstrom et al., 2001; Mari-Dell'Olmo et al., 2007; Marinacci et al., 2004; Martikainen et al., 2003; Naess et al., 2007; Robert et al., 2004; Sanderson et al., 2006; Turrell et al., 2007; Webster et al., 2008; Yen and Kaplan, 1999), as well as for two studies with income inequality as outcome (Backlund et al., 2007; Waitzman et al., 1999). Nine studies did not find any significant effects for ALSES (Blakely et al., 2003; Bosma et al., 2001; Dahl et al., 2006; Jones et al., 2000; Kravdal, 2007; Lochner et al., 2001; Naess et al., 2005; Petrelli et al., 2006; Roos et al., 2004), two studies found no effect for income inequality (Henriksson et al., 2006, 2007), one study found no effect for air pollution (Jerrett et al., 2005) and for one study (LeClere et al., 1998) it was not possible to calculate an overall effect estimate due to insufficient information in the paper. See supplementary Table 1 in paper 1 in the appendix for the overall estimates calculated for each study.

In 22 of the 24 studies showing significant ALSES effects, mortality or prostate cancer incidence (Sanderson et al., 2006) was higher in lower SES areas. Only the two studies investigating breast cancer incidence found that high ALSES was associated with an increased risk of breast cancer (Robert et al., 2004; Webster et al., 2008).

Mixed results were found for income inequality effects on mortality. Four studies (Backlund et al., 2007; Dahl et al., 2006; Lochner et al., 2001; Waitzman et al., 1999) found that high income inequality was associated with increased mortality, whereas four other studies found no effect (Blakely et al., 2003; Blomgren et al., 2004; Franzini and Spears, 2003; Henriksson et al., 2006). One study found that a high level of income inequality had a protective effect for high-level non manual workers and an adverse effect for unskilled manual workers (Henriksson et al., 2007).

Five studies tested whether social cohesion or social capital in neighborhoods was associated with mortality. Three studies (Blomgren et al., 2004; Chaix et al., 2008; Martikainen et al., 2003) found that low social cohesion was associated with higher mortality while two studies (Blakely et al., 2006; Turrell et al., 2007) found no association for social capital.

Two studies (Jerrett et al., 2005; Jerrett et al., 2003; Naess et al., 2007) found that high levels of air pollution was associated with excess mortality, while a third study found a border line significant effect of 1.11 (0.99-1.25). One study found urban areas to be associated with higher breast cancer incidence (Robert et al., 2004) and one Finnish study found that a high level of urbanization had a protective effect on alcohol-related mortality (Blomgren et al., 2004). Two Swedish studies found that high population density had a negative effect on individual mortality and that ALSES had a stronger effect in densely populated areas (Chaix et al., 2006; Chaix et al., 2007a).

Five studies allowed for more than one area-level in their analyses. Three of these found that all investigated area levels contributed to mortality outcomes (Bentley et al., 2008; Franzini and Spears, 2003; Turrell et al., 2007). One study found variation in all-cause mortality only at the highest (regional) level (Jones et al., 2000) and one reported no effect from any area levels on all-cause or cause-specific mortality (Blakely et al., 2003). Thus, incorporating more area-levels seem to increase precision of where area-level effects occur.

One study found that area-level deprivation experienced in childhood was associated with mortality over 40 years later (Curtis et al., 2004) while the other found an increased effect of neighborhood context when allowing for a 10-year latency period (Webster et al., 2008). These findings suggest that it is appropriate to allow for a time lag between the influence of the neighborhood and the event of either mortality or morbidity. This effect, however, could be due to individual circumstances in this period, since one study found that a significant area-effect disappeared when early life deprivation was controlled for at the individual level, demonstrating the importance of incorporation of a life-course perspective (Naess et al., 2005). None of the studies investigated how length of residence affected mortality or cancer incidence.

Meta-analysis

In Figure 3 it is seen that the overall relative risk for all-cause mortality for inhabitants in lower SES areas compared to inhabitants from higher SES areas adjusted for individual SES was RR=1.07 (95% CI=1.04-1.10).

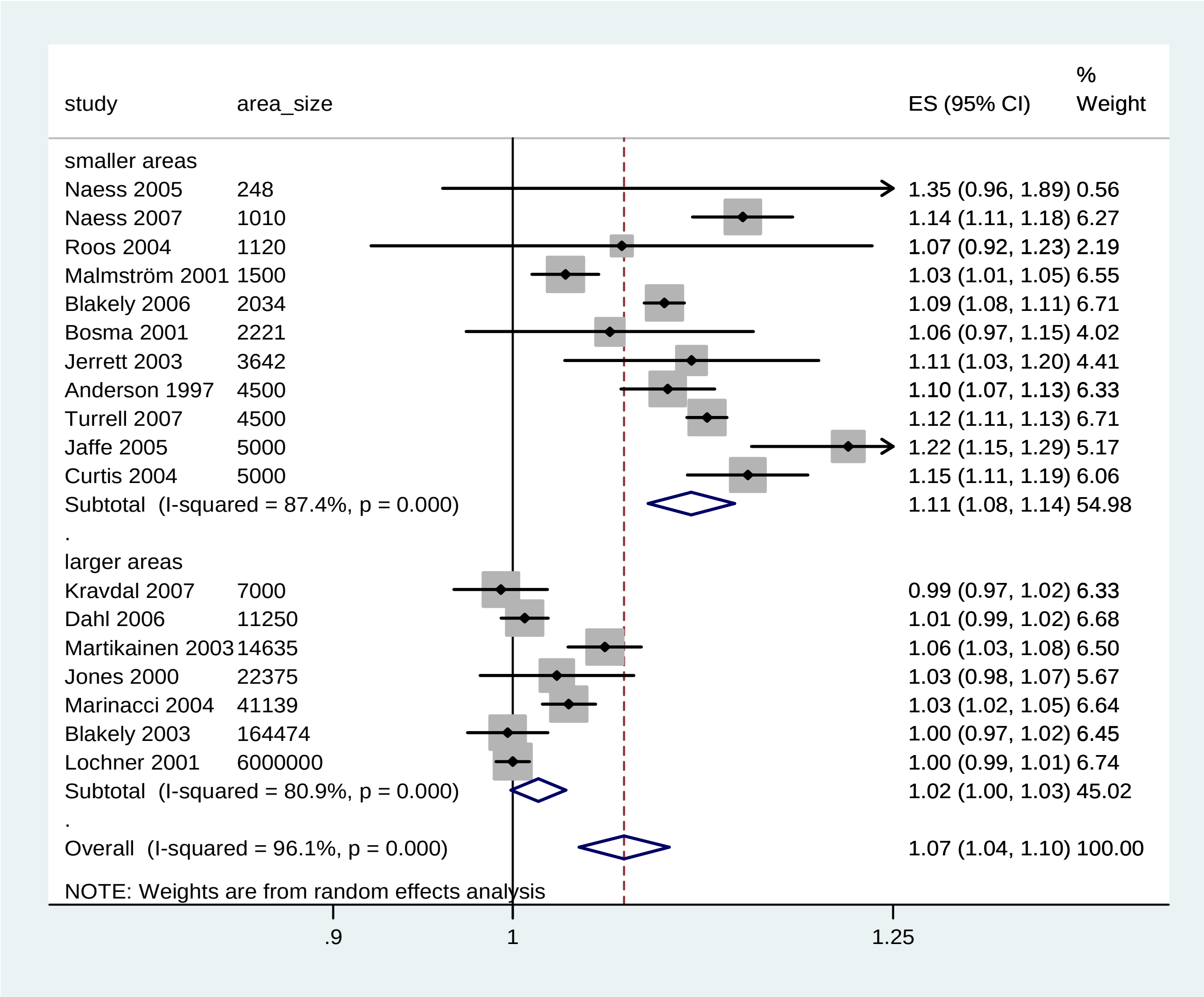


Figure 3: Results of meta-analysis: relative risks for mortality in low-SES areas compared to high-SES areas and between-study heterogeneity, studies grouped according to number of inhabitants per area unit (<7000 or ≥7000)

This demonstrates that the ALSES has an independent effect on all-cause mortality, even after controlling for individual SES. Figure 3 also shows that the effect of ALSES is stronger when the number of inhabitants in the analyzed areas is smaller. In studies investigating area units with few inhabitants the effect of ALSES is RR=1.11 (95% CI=1.08-1.14) while the effect in studies analyzing areas with many inhabitants is RR=1.02 (95% CI=1.00-1.03). However, strong evidence of heterogeneity between studies was observed even within the subgroups of studies analyzing areas with few inhabitants (I^2 = 87.4%, P<0.001) or area units with many inhabitants (I^2 = 80.9%, P<0.001) indicating that there is significant variation in ALSES effects between the studies that could be caused by differences in study designs or study populations. A meta-regression was therefore conducted to investigate if these differences could account for the observed heterogeneity.

Table 3

Meta-regression results (random effects model) of the effect of area SES on mortality (outcome: estimate of mortality in relative lower SES areas in comparison to highest SES area)

	Beta	(SE)	RR	95% CI
Sex (reference: women)				
men	0.021	(0.008)	1.02	(1.004-1.04)
Both*	-0.044	(0.024)	0.96	(0.91-1.00)
Age (in decades)	-0.021	(0.004)	0.98	(0.97-0.99)
Area SES	0.046	(0.005)	1.05	(1.04-1.06)
Age* area SES	-0.014	(0.005)	0.99	(0.98-0.99)
Smaller area units analyzed (<7000 inhabitants per area)	0.096	(0.022)	1.10	(1.06-1.15)
Variance between studies	0.001	(0.0007)		

* no sex-specific estimates were provided

The meta-regression analyses showed that the effect of ALSES on mortality was higher for men and for younger age groups (Table 3). Areas with lower SES had higher mortality than areas with higher SES. The effect of ALSES on mortality is stronger in studies using area units with few inhabitants than in studies with many inhabitants per area unit.

No effect of welfare state models was found. Although estimates suggest that effects are larger in liberal welfare states they remained insignificant and therefore do not explain the heterogeneity between the studies. After adjusting for sex and age the odds ratio of mortality in areas with lower SES compared to those with higher SES attenuated to OR=1.05 (95% CI:1.04-1.06) in studies analyzing larger area units and OR=1.10 (95%CI: 1.06-1.15) for studies using smaller area units. There was still significant variance between studies, after adjusting for the covariates. No evidence of publication bias was found (p=0.363 in Begg-Test).

Papers 2 and 3: Area-effects in Denmark

Individual age, sex, marital status, education, disposable family income and occupation-based SES were significantly related to the four outcomes. Only for prostate cancer incidence individual education became insignificant when included with other individual factors.

Table 4

Effect of parish-level factors (not mutually adjusted) on individual all-cause mortality between 2004 and 2006 among ethnic Danes aged 30-81 years, stratified by age group, estimated in a Frailty model adjusted for individual characteristics

	Age 30-49		Age 50-64		Age 65-81	
	Hazard ratio (95%CI)		Hazard ratio (95%CI)		Hazard ratio (95%CI)	
Education level						
Highest	1	(ref)	1	(ref)	1	(ref)
High	1.01	(0.95-1.06)	0.97	(0.94-1.01)	0.96	(0.94-0.98)
Low	0.95	(0.88-1.02)	0.91	(0.87-0.95)	0.91	(0.89-0.94)
Lowest	0.89	(0.82-0.97)	0.90	(0.86-0.95)	0.92	(0.89-0.95)
Variation	0.0075		0.0132		0.0088	
Disposable income						
Highest	1	(ref)	1	(ref)	1	(ref)
High	0.92	(0.87-0.99)	0.97	(0.94-1.02)	0.98	(0.95-1.01)
Low	0.94	(0.88-1.00)	0.95	(0.91-0.99)	0.98	(0.95-1.00)
Lowest	1.02	(0.95-1.08)	1.04	(1.00-1.08)	1.05	(1.02-1.08)
Variation	0.0056		0.0133		0.0084	
Proportion of disability						
Highest	1.00	(0.94-1.07)	1.04	(1.00-1.08)	1.06	(1.03-1.08)
High	1	(ref)	1	(ref)	1	(ref)
Low	0.91	(0.85-0.97)	0.98	(0.94-1.03)	0.99	(0.96-1.01)
Lowest	0.98	(0.91-1.05)	0.97	(0.93-1.02)	0.98	(0.96-1.01)
Variation	0.0074		0.0136		0.0086	
Proportion of routine workers						
Highest	0.93	(0.87-1.00)	0.95	(0.90-0.99)	0.94	(0.91-0.96)
High	0.97	(0.91-1.04)	0.94	(0.90-0.98)	0.95	(0.92-0.98)
Low	0.97	(0.92-1.03)	0.97	(0.94-1.01)	0.96	(0.93-0.98)
Lowest	1	(ref)	1	(ref)	1	(ref)
Variation	0.0082		0.0141		0.0094	
Proportion of unemployed						
Highest	1.02	(0.96-1.09)	1.05	(1.01-1.10)	1.05	(1.03-1.08)
High	1	(ref)	1	(ref)	1	(ref)
Low	0.96	(0.90-1.02)	0.96	(0.93-1.00)	0.97	(0.94-0.99)
Lowest	0.93	(0.86-1.00)	0.94	(0.90-0.98)	0.94	(0.91-0.96)
Variation	0.0072		0.0129		0.0079	
Population density						
Highest	1	(ref)	1	(ref)	1	(ref)
High	0.87	(0.82-0.93)	0.90	(0.86-0.92)	0.88	(0.86-0.90)
Low	0.85	(0.78-0.93)	0.83	(0.79-0.87)	0.87	(0.85-0.90)
Lowest	0.84	(0.76-0.94)	0.80	(0.76-0.86)	0.86	(0.83-0.89)
Variation	0.0052		0.010		0.0057	

Variation was estimated from the frailty model including individual variables and the variable itself. Models including individual variables only had the following variation: 0.0081 (30-49 year olds), 0.0139 (50-64 year olds) and 0.0095 (65-81 year olds).

For the youngest age group disposable family income explained the most variation (variation estimate is lowest) among the ALSES factors (population density not included) while for the two older age groups the proportion of unemployed was a better measure (Table 4). Thus, in subsequent analyses the average disposable family income and population density were included for the youngest age group, whereas for the older age groups, the proportion of unemployed and population density were used as parish-level characteristics.

As seen in Table 5 individuals between 30 and 49 years living in areas with the lowest population density had reduced mortality risks, HR=0.85 (95% CI=0.76-0.95), compared to those living in areas with the highest population density. ALSES had no effect on all-cause mortality for this age group. Population density had similar effects for individuals aged 50-64 years and 65-81 years;

HR=0.81 (95% CI=0.76-0.86) and HR=0.86 (95% CI=0.83-0.89). The results also indicate that there is no significant gradient associated with the effect of population density; only residence in the most densely populated areas increases mortality.

Table 5

Hazard ratio and 95%CI of individual factors (model 1) plus parish-level factors (model 2) on individual all-cause mortality in Denmark in 2004 and 2006 for Danes stratified on age, estimated in a Frailty model adjusted for all factors in the same model

	Age 30-49		Age 50-64		Age 65-81	
	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
Individual level						
Sex						
Men	1.61 (1.53-1.70)	1.61 (1.53-1.69)	1.86 (1.80-1.91)	1.85 (1.80-1.91)	1.87 (1.83-1.90)	1.87 (1.84-1.91)
Women	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Age						
30-34	0.22 (0.20-0.24)	0.22 (0.20-0.23)				
35-39	0.34 (0.32-0.37)	0.34 (0.32-0.36)				
40-44	0.59 (0.56-0.62)	0.59 (0.56-0.62)				
45-49	1 (ref)	1 (ref)				
50-54			1 (ref)	1 (ref)		
55-59			1.45 (1.40-1.50)	1.45 (1.40-1.50)		
60-64			1.97 (1.91-2.04)	1.97 (1.91-2.04)		
65-69					1 (ref)	1 (ref)
70-74					1.66 (1.62-1.70)	1.66 (1.62-1.70)
75-81					2.69 (2.63-2.75)	2.68 (2.62-2.74)
Marital status						
Married or cohabiting	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Single	2.05 (1.94-2.16)	2.00 (1.90-2.11)	1.53 (1.49-1.58)	1.50 (1.45-1.54)	1.42 (1.40-1.45)	1.41 (1.39-1.44)
Education						
Basic	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Non-tertiare	0.91 (0.86-0.96)	0.91 (0.86-0.96)	1.01 (0.98-1.04)	1.00 (0.97-1.03)	0.97 (0.95-0.99)	0.96 (0.94-0.98)
Tertiare	0.74 (0.68-0.81)	0.74 (0.68-0.81)	0.93 (0.88-0.98)	0.93 (0.88-0.97)	0.94 (0.91-0.98)	0.94 (0.91-0.97)
SES						
Salariat	0.59 (0.54-0.65)	0.58 (0.52-0.64)	0.71 (0.67-0.75)	0.70 (0.67-0.74)	0.93 (0.90-0.97)	0.93 (0.90-0.96)
Intermediate employee	0.71 (0.65-0.78)	0.70 (0.64-0.76)	0.84 (0.80-0.88)	0.83 (0.79-0.87)	0.92 (0.90-0.95)	0.91 (0.89-0.94)
Small employers and self-employed	0.56 (0.47-0.65)	0.57 (0.48-0.67)	0.54 (0.49-0.58)	0.55 (0.51-0.60)	0.74 (0.71-0.76)	0.76 (0.73-0.79)
Lower white collar	0.70 (0.63-0.77)	0.69 (0.62-0.76)	0.84 (0.79-0.89)	0.84 (0.79-0.89)	0.94 (0.91-0.98)	0.94 (0.90-0.97)
Skilled manual	0.85 (0.78-0.93)	0.86 (0.79-0.93)	0.85 (0.81-0.89)	0.85 (0.81-0.89)	0.95 (0.92-0.98)	0.95 (0.92-0.97)
Semi/unskilled	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Unemployed	1.91 (1.73-2.11)	1.85 (1.67-2.05)	1.01 (0.93-1.09)	1.00 (0.93-1.07)	0.90 (0.86-0.94)	0.90 (0.86-0.94)
Disability pensioners	4.13 (3.85-4-43)	4.06 (3.78-4.36)	2.53 (2.44-2.63)	2.51 (2.41-2.60)	1.51 (1.46-1.56)	1.51 (1.45-1.56)
Students	1.15 (0.87-1.51)	1.11 (0.84-1.47)	0.85 (0.67-1.08)	0.84 (0.66-1.07)	0.72 (0.27-1.93)	0.72 (0.27-1.93)
Pensioners			0.77 (0.44-1.35)	0.77 (0.44-1.36)	1.14 (1.11-1.17)	1.14 (1.11-1.17)
Disposable income						
Highest	0.59 (0.54-0.64)	0.58 (0.53-0.63)	0.59 (0.56-0.61)	0.58 (0.56-0.61)	0.66 (0.63-0.68)	0.65 (0.63-0.67)
High	0.58 (0.54-0.62)	0.57 (0.54-0.62)	0.74 (0.71-0.77)	0.74 (0.71-0.77)	0.76 (0.74-0.78)	0.76 (0.74-0.78)
Low	0.72 (0.68-0.76)	0.72 (0.68-0.76)	0.93 (0.89-0.96)	0.93 (0.89-0.96)	0.91 (0.89-0.92)	0.90 (0.89-0.92)
Lowest	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Parish level						
Population density						
Highest		1 (ref)		1 (ref)		1 (ref)
High		0.88 (0.83-0.94)		0.91 (0.87-0.94)		0.89 (0.87-0.91)
Low		0.86 (0.78-0.94)		0.83 (0.79-0.88)		0.88 (0.85-0.90)
Lowest		0.85 (0.76-0.95)		0.81 (0.76-0.86)		0.86 (0.83-0.89)
Disposable income						
Highest		1 (ref)				
High		0.94 (0.88-1.01)				
Low		0.96 (0.90-1.03)				
Lowest		1.01 (0.95-1.08)				
Proportion of unemployed						
Highest				1.05 (1.01-1.09)		1.05 (1.02-1.07)
High				1 (ref)		1 (ref)
Low				0.97 (0.93-1.00)		0.97 (0.95-0.99)
Lowest				0.96 (0.92-1.00)		0.96 (0.93-0.98)
Variation	0.0081	0.0036	0.0139	0.0096	0.0095	0.0050
SE	0.0058	0.0055	0.0026	0.0022	0.0013	0.0009
P (Variation=0)	0.0700	0.2480	0	0	0	0

Variation in unadjusted model was 0.0574 (30-49 year olds), 0.0676 (50-64 year olds) and 0.0224 (65-81 year olds).

For the middle- and older age group, living in the most deprived areas was also associated with higher mortality HR:1.05 (1.01-1.09) and HR:1.05 (1.02-1.07). These effects were found in addition to those of population density, i.e. while adjusting for population density. Contrary to the effects of population density, however, there was a clear gradient between the degree of parish-level deprivation and mortality: Higher levels of neighborhood deprivation were associated with higher mortality.

Individual factors explained 86%, 79% and 58% of all frailty variation for the youngest, middle and oldest age groups respectively. Adding area-level factors to the model further reduced unexplained frailty variation so that 94%, 86% and 78% of the variation was explained for the three age groups. This clearly indicates that the importance of individual factors decreases with age and that area-effects become more important with higher ages. It is therefore important to consider both individual and area effects, especially for persons in the oldest age group.

The analyses of cancer incidence were not stratified on age. Analyses showed that there was a reduced risk of breast cancer in areas with lowest population density HR:0.93 (95% CI=0.86-0.99) compared to areas with the highest density. Parish-level SES proved to have no effect. This was also found when population density was not included in the same model. For prostate cancer higher risk among inhabitants in affluent areas HR:1.14 (95% CI=1.08-1.21) were found compared to those living in deprived areas. No effect was found for of population density. Lung cancer risk was lower in the least densely populated areas HR:0.80 (95% CI=0.74-0.85) and in affluent areas HR:0.88 (95% CI=0.84-0.92) compared to risks in densely populated and deprived areas. Results appear in Table 6.

Table 6

Hazard ratio and 95% CI of significant individual factors (model 1) plus significant parish-level factors (model 2) on breast, prostate and lung cancer incidence between 2004 and 2008, estimated in a Frailty model adjusted for all factors in the same model

	Breast cancer incidence		Prostate cancer incidence		Lung cancer incidence	
	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
Individual level						
Sex						
Men					1 (ref)	1 (ref)
Women					0.71 (0.69-0.74)	0.71 (0.69-0.73)
Age						
30-34	1.00 (ref)	1.00 (ref)				
35-39	2.19 (1.89-2.54)	2.20 (1.90-2.55)				
40-44	4.17 (3.64-4.78)	4.20 (3.66-4.81)				
45-49	6.76 (5.92-7.72)	6.81 (5.96-7.78)				
50-54	8.36 (7.33-9.53)	8.41 (7.38-9.59)	1.00 (ref)	1.00 (ref)		
55-59	10.67 (9.37-12.14)	10.73 (9.43-12.21)	2.91 (2.63-3.23)	2.91 (2.63-3.23)	1.56 (1.46-1.68)	1.56 (1.46-1.67)
60-64	13.21 (11.60-15.04)	13.27 (11.65-15.10)	6.69 (6.08-7.39)	6.68 (6.06-7.36)	2.32 (2.17-2.48)	2.31 (2.16-2.47)
65-69	13.99 (12.26-15.96)	14.05 (12.31-16.00)	11.44 (10.37-12.60)	11.39 (10.33-12.55)	3.01 (2.82-3.22)	3.00 (2.81-3.21)
70-74	12.61 (11.03-14.44)	12.67 (11.07-14.49)	14.14 (12.81-15.60)	14.09 (12.76-15.54)	3.92 (3.67-4.20)	3.90 (3.65-4.17)
75-79	12.79 (11.14-14.68)	12.82 (11.16-14.71)	15.12 (13.68-16.72)	15.08 (13.64-16.67)	3.88 (3.61-4.17)	3.83 (3.57-4.12)
80-83	11.68 (10.07-13.55)	11.69 (10.07-13.56)	12.59 (11.28-14.06)	12.56 (11.25-14.02)	2.79 (2.56-3.04)	2.75 (2.52-2.99)
Marital status						
Married or cohabiting	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Single	0.97 (0.93-1.00)	0.96 (0.93-0.99)	0.80 (0.77-0.84)	0.81 (0.77-0.84)	1.12 (1.09-1.16)	1.09 (1.06-1.14)
Education						
Basic	1 (ref)	1 (ref)			1 (ref)	1 (ref)
Non-tertiare	1.13 (1.09-1.17)	1.12 (1.08-1.17)			0.88 (0.85-0.91)	0.87 (0.83-0.90)
Tertiare	1.08 (1.03-1.14)	1.08 (1.02-1.13)			0.74 (0.70-0.79)	0.74 (0.69-0.78)
SES						
Salariat	1.21 (1.14-1.29)	1.21 (1.13-1.29)	1.09 (1.02-1.16)	1.09 (1.04-1.15)	0.76 (0.71-0.81)	0.75 (0.70-0.80)
Intermediate employee	1.13 (1.07-1.19)	1.12 (1.06-1.18)	1.05 (0.99-1.11)	1.04 (0.98-1.11)	0.82 (0.78-0.87)	0.81 (0.77-0.85)
Small employers and self-employed	0.90 (0.78-1.04)	0.90 (0.78-1.04)	1.17 (1.10-1.25)	1.18 (1.10-1.25)	0.58 (0.53-0.64)	0.62 (0.57-0.68)
Lower white collar	1.00 (0.94-1.05)	1.00 (0.94-1.05)	1.06 (0.97-1.15)	1.06 (0.97-1.15)	0.90 (0.84-0.96)	0.89 (0.84-0.95)
Skilled manual	1.01 (0.88-1.16)	1.01 (0.88-1.16)	1.01 (0.96-1.06)	1.01 (0.96-1.06)	0.97 (0.92-1.03)	0.97 (0.92-1.02)
Semi/unskilled	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Unemployed	1.16 (1.08-1.24)	1.15 (1.07-1.24)	1.23 (1.08-1.40)	1.23 (1.08-1.39)	0.91 (0.84-0.98)	0.90 (0.84-0.98)
Disability pensioners	1.09 (1.03-1.16)	1.09 (1.03-1.15)	0.73 (0.67-0.80)	0.73 (0.67-0.80)	1.24 (1.17-1.30)	1.22 (1.16-1.28)
Students	0.95 (0.77-1.19)	0.94 (0.76-1.18)	1.50 (1.02-2.24)	1.51 (1.02-2.24)	0.62 (0.42-0.90)	0.60 (0.41-0.88)
Pensioners	0.96 (0.88-1.05)	0.96 (0.88-1.05)	1.09 (0.96-1.24)	1.09 (0.96-1.24)	0.77 (0.72-0.84)	0.78 (0.72-0.84)
Disposable income						
Highest	1.08 (1.03-1.14)	1.08 (1.02-1.14)	1.54 (1.46-1.63)	1.52 (1.44-1.61)	0.57 (0.54-0.61)	0.57 (0.53-0.61)
High	1.05 (1.00-1.11)	1.05 (1.00-1.11)	1.24 (1.18-1.31)	1.23 (1.17-1.30)	0.81 (0.77-0.85)	0.80 (0.76-0.84)
Low	1.04 (0.99-1.08)	1.04 (0.99-1.08)	1.13 (1.09-1.19)	1.13 (1.08-1.18)	1.02 (0.98-1.06)	1.01 (0.98-1.05)
Lowest	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Parish level						
Population density						
Highest		1 (ref)				1 (ref)
High		0.95 (0.91-0.99)				0.87 (0.84-0.91)
Low		0.93 (0.88-0.98)				0.82 (0.77-0.86)
Lowest		0.93 (0.86-1.00)				0.80 (0.74-0.85)
Proportion of unemployed						
Highest				1 (ref)		1 (ref)
High				1.05 (1.00-1.11)		0.94 (0.90-0.98)
Low				1.08 (1.02-1.14)		0.91 (0.87-0.95)
Lowest				1.14 (1.08-1.21)		0.88 (0.84-0.92)
Variation	0.0045	0.00396	0.0197	0.01883	0.0104	0.00454
SE	0.0026	0.00256	0.0042	0.00416	0.0031	0.00259
P (Variation=0)	0.0310	0.04700	0	0	0	0.02800

The estimated frailty variance in empty models was 0.0212 for breast cancer incidence, 0.0307 for prostate cancer incidence and 0.0311 for lung cancer incidence

Individual-level factors were able to explain 79%, 36% and 66% of the frailty variation for breast, prostate and lung cancer incidence respectively. By adding significant parish-level factors these figures increased to 81%, 39% and 85%. This demonstrates that individual-level indicators are important when explaining variation in breast and lung cancer incidence and much less so for prostate cancer incidence. Area characteristics have a small additional effect for breast and prostate cancer incidence, while they are of greater importance for lung cancer incidence.

Paper 4: A Danish deprivation index

A two-dimensional index was chosen because the two components accounted for relatively small proportions of the total variance; 36% and 30%, respectively. The only variable omitted from the final index was ‘overcrowding’.

The ten remaining variables were included in both components with different weights. As seen in Table 7 seven variables had high loadings (>0.40) on the first component (called here “the material deprivation component”). Higher scores on the material component are primarily associated with lower proportion of car owners, higher proportion of inhabitants in rented dwellings, higher population density, higher proportions of unemployment, of criminal records, of one-parent families, and lower proportion of manual workers. Six variables had high loadings on the second component (called here “the socioeconomic status component”). Higher scores on this component are therefore primarily associated with higher proportions of inhabitants with low education, low disposable income, a criminal background and higher proportions of disability pensioners, unemployed people and manual workers.

Table 7

Rotated factor pattern from principal component analysis of indicators for the two-dimensional IMSD and weights used in the adjusted Townsend index

Indicator	Material component	Socioeconomic status component	Townsend Index
No access to a car	0.91	0.03	1
Rented dwellings	0.90	0.02	1
Population density	0.83	-0.37	
One-parent households	0.64	-0.04	
Criminal records	0.40	0.43	
Manual workers	-0.47	0.63	1
Unemployment	0.60	0.54	1
Basic education	-0.23	0.89	
Disability pensioners	0.31	0.79	
Low disposable income	-0.12	0.78	

Overall the two components measure different dimensions that can explain differences in mortality. Whereas the material component captures the domains of housing and demography, the SES component concentrates on education, income and health. That both components measure one-dimensional concepts, is confirmed by the Cronbach’s alpha which is 0.81 for the material component and 0.79 for the SES component. The material component is highly correlated with the Townsend index (r=0.88), while the SES component is not correlated (r=0.01).

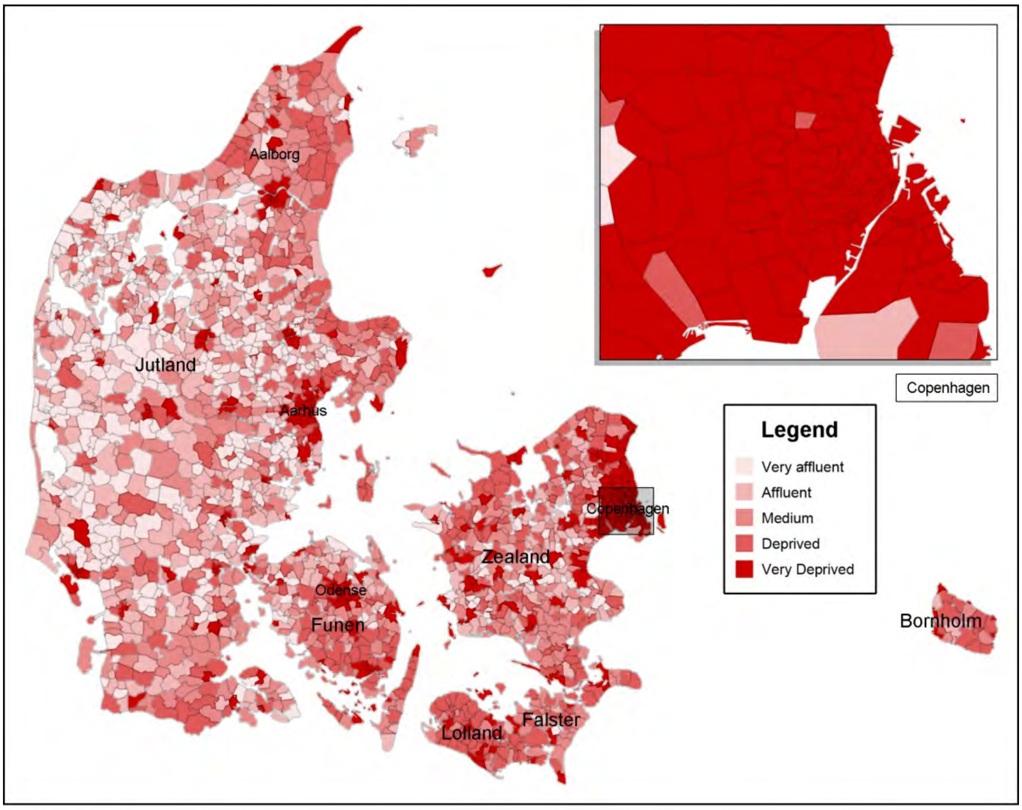


Fig. 4
Area-level deprivation related to material deprivation component of the IMSD in Danish parishes in 2005, enlargement of the Copenhagen area.

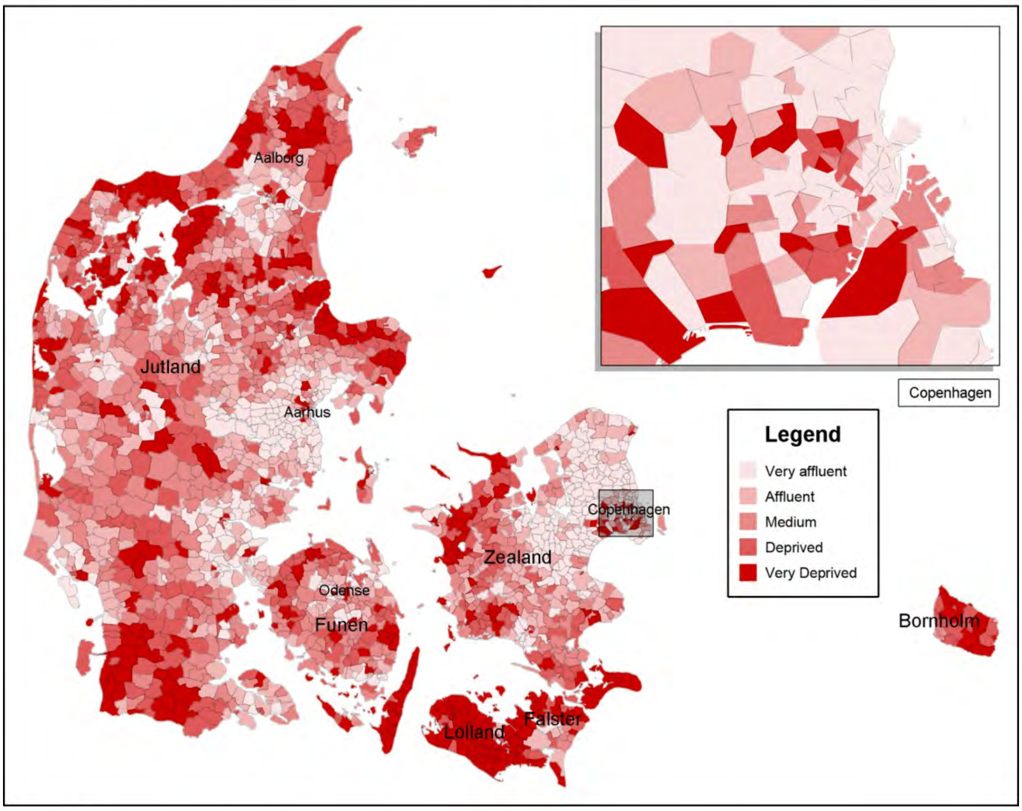


Fig. 5
Area-level deprivation related to socioeconomic status component of IMSD in Danish parishes in 2005, enlargement of the Copenhagen area.

The most materially deprived areas were found in the areas around Copenhagen, Aarhus, Odense and Aalborg (the four largest cities in Denmark) while the more materially affluent areas generally were found in mid and western Jutland (Fig 4). Apart from high scores on population density, urban areas generally score high on the material deprivation component because cars are less needed in urban areas and because rental housing is also more common. Thus, material deprivation in cities can be explained with infrastructure and urbanicity and has less to do with general low material standards. In the SES component the affluent areas are concentrated around the two largest cities, Copenhagen and Aarhus, while the more deprived areas are found in northern and southern Jutland, western Zealand, Lolland, Falster and Bornholm (Fig 5). The enlargement of Figure 5 shows that the capital area generally is characterized by affluent parishes, but that there are deprived areas located in the north-western parts of inner Copenhagen and in the southern suburbs.

Table 8

Proportion of inhabitants in quintiles of parishes by the material deprivation component of the IMSD

	Very affluent	Affluent	Medium	Deprived	Very deprived
Number of parishes	422	423	422	423	423
Number of inhabitants	310,533	432,331	580,118	1,003,127	3,065,789
Inhabitants per km2	33.7	45.0	55.7	105.7	833.1
Proportion of inhabitants					
With no access to a car	9.4	12.9	16.6	22.1	45.8
In rented dwellings	9.4	12.6	16.5	21.2	53.9
In one-parent households	3.2	4.0	4.7	5.4	6.7
With criminal records	0.2	0.3	0.4	0.5	0.8
With manual jobs	16.9	15.7	15.4	13.4	11.5
On unemployment benefits	6.9	7.7	8.4	8.7	12.5
With basic education	27.0	26.2	26.9	25.4	23.6
On disability pension	3.8	4.1	4.9	5.7	6.8
With low disposable income	10.4	9.6	9.7	8.7	9.6

Table 9

Proportion of inhabitants in quintiles of parishes by the socioeconomic status component of the IMSD

	Very affluent	Affluent	Medium	Deprived	Very deprived
Number of parishes	422	423	422	423	423
Number of inhabitants	1,787,229	1,021,337	967,143	835,673	780,516
Inhabitants per km2	291.4	129.1	95.0	86.1	92.0
Proportion of inhabitants					
With no access to a car	32.9	32.8	33.5	36.2	41.1
In rented dwellings	33.3	35.0	36.2	40.8	50.4
In one-parent households	5.5	5.7	5.7	6.0	7.1
With criminal records	0.4	0.6	0.7	0.8	1.1
With manual jobs	9.0	13.5	15.1	15.6	16.7
Being unemployed	8.4	9.4	10.3	12.8	15.5
With basic education	16.9	24.1	27.6	30.3	35.2
On disability pension	3.6	5.6	6.6	7.5	9.7
With low disposable income	7.0	8.4	9.8	11.6	14.1

A clear gradient is seen for the variables loading on each of the components (Tables 8 and 9). For instance, for the material component, the proportions of inhabitants without a car or the proportions living in rented dwellings are five to six times higher in the deprived areas compared to the more affluent parishes. It is seen that the proportions in the education, income and health domains differ relatively little in this component. For the SES component, however, the proportion of inhabitants with low education or low disposable income is twice as high in very deprived parishes compared the very affluent.

Table 10

SMRs among men in Danish parishes in 2004-2006 by level of material and socioeconomic deprivation of the IMSD and adjusted Townsend index score

	Very low	Low	Medium	High	Very high
IMSD, material deprivation	0.79 (0.76-0.82)	0.84 (0.82-0.87)	0.90 (0.88-0.92)	0.96 (0.94-0.97)	1.06 (1.05-1.07)
IMSD, socioeconomic deprivation	0.88 (0.87-0.89)	0.98 (0.96-0.99)	1.00 (0.98-1.02)	1.04 (1.02-1.06)	1.14 (1.12-1.16)
Townsend index	0.81 (0.79-0.84)	0.84 (0.82-0.86)	0.90 (0.88-0.92)	0.97 (0.96-0.99)	1.07 (1.06-1.08)

Table 11

SMRs among women in Danish parishes in 2004-2006 by level of material and socioeconomic deprivation of the IMSD and adjusted Townsend index score

	Very low	Low	Medium	High	Very high
IMSD, material deprivation	0.83 (0.80-0.87)	0.89 (0.86-0.92)	0.97 (0.95-0.99)	0.98 (0.97-1.00)	1.01 (1.00-1.02)
IMSD, socioeconomic deprivation	0.90 (0.90-0.92)	1.00 (0.99-1.02)	1.00 (0.98-1.01)	1.02 (1.01-1.04)	1.08 (1.06-1.10)
Townsend index	0.84 (0.81-0.87)	0.91 (0.89-0.94)	0.96 (0.94-0.98)	0.97 (0.96-0.99)	1.02 (1.01-1.03)

SMRs for the material component, the socioeconomic component and for the Townsend index are lower in affluent areas and higher in deprived areas both for men (Table 10) and for women (Table 11). Differences in mortality are more pronounced for men than for women. Table 12 shows how SMRs are related to a matrix of the two IMSD components. For men it is seen that higher SMRs are found in parishes that are deprived on both dimensions (SMR=1.17) and lowest in parishes that are both materially and socioeconomically affluent (SMR=0.79). With increasing scores in any of the two components SMR gradually increases. The same pattern is evident for women, but men appear to be more sensitive to the two dimensions.

Table 12

Distribution of SMR among men and women in Denmark in 2005 in parishes characterised by level of material and socioeconomic deprivation of the IMSD

	Men Socioeconomic status						Women Socioeconomic status					
	Deprived		Medium		Affluent		Deprived		Medium		Affluent	
Material status												
Deprived	1.16	(1.14-1.17)	0.94	(0.91-0.98)	0.89	(0.84-0.94)	1.08	(1.07-1.10)	1.00	(0.96-1.03)	0.86	(0.80-0.92)
Medium	1.07	(1.05-1.08)	0.93	(0.90-0.96)	0.80	(0.76-0.83)	1.03	(1.01-1.04)	0.98	(0.95-1.00)	0.86	(0.82-0.90)
Affluent	0.94	(0.93-0.95)	0.87	(0.85-0.89)	0.79	(0.76-0.82)	0.94	(0.93-0.95)	0.95	(0.92-0.97)	0.85	(0.81-0.88)

Table 13 shows that frailty modelling including sex, age and IMSD explained 76 percent of the variation in all-cause mortality, compared to 69.6 percent explained by a model with age, sex and the Townsend index, which suggests that the IMSD is the better measure than the Townsend index. Additional analyses showed, however, that the Townsend index explained more variation (69.6%, model 3) than a model with age, sex and the material component only (67.9%) as well as than a model with age, sex and the SES component only (60.9%) (results not shown). This stresses the need to use both IMSD components as one index.

Table 13

Hazard ratio and 95% CI of all-cause mortality between 2004 and 2006 in Denmark in six different frailty models adjusted for all factors in the same model

	Model 1 (age and sex)		Model 2 (model 1 + IMSD)		Model 3 (model 1 + Townsend)		Model 4 (model 1 + individual factors)		Model 5 (model 4 + IMSD)		Model 6 (model 4 + Townsend)	
Individual level												
Sex												
Men	1.54	(1.52-1.56)	1.54	(1.52-1.56)	1.54	(1.53-1.56)	1.93	(1.90-1.96)	1.93	(1.91-1.97)	1.94	(1.91-1.97)
Women	1	(ref)	1	(ref)	1	(ref)	1	(ref)	1	(ref)	1	(ref)
Age												
30-34	1.00	(ref)	1.00	(ref)	1.00	(ref)	1.00	(ref)	1.00	(ref)	1.00	(ref)
35-39	1.64	(1.50-1.80)	1.64	(1.50-1.80)	1.65	(1.50-1.80)	1.62	(1.48-1.78)	1.63	(1.49-1.79)	1.63	(1.49-1.79)
40-44	2.85	(2.61-3.10)	2.85	(2.62-3.11)	2.86	(2.62-3.12)	2.87	(2.63-3.13)	2.88	(2.64-3.14)	2.88	(2.64-3.14)
45-49	5.13	(4.73-5.56)	5.13	(4.73-5.56)	5.15	(4.75-5.58)	5.24	(4.83-5.68)	5.26	(4.85-5.70)	5.26	(4.85-5.70)
50-54	7.95	(7.35-8.60)	7.95	(7.35-8.60)	7.98	(7.38-8.63)	8.20	(7.58-8.87)	8.23	(7.60-8.90)	8.23	(7.61-8.91)
55-59	11.98	(11.09-12.93)	11.97	(11.09-12.93)	12.02	(11.13-12.98)	11.96	(11.07-12.92)	11.99	(11.10-12.95)	12.01	(11.12-12.97)
60-64	18.96	(17.57-20.47)	18.94	(17.55-20.44)	19.04	(17.64-20.55)	16.68	(15.45-18.00)	16.70	(15.47-18.03)	16.73	(15.50-18.06)
65-69	31.10	(28.83-33.54)	31.00	(28.74-33.43)	31.21	(28.93-33.66)	24.39	(22.61-26.32)	24.40	(22.61-26.32)	24.45	(22.66-26.38)
70-74	52.42	(48.62-56.51)	52.14	(48.36-56.21)	52.55	(48.74-56.65)	43.27	(40.12-46.66)	43.14	(40.00-46.52)	43.27	(40.13-46.66)
75-81	89.50	(83.07-96.44)	88.82	(82.43-95.70)	89.55	(83.11-96.48)	72.39	(67.15-78.04)	72.88	(66.67-77.49)	72.16	(66.94-77.80)
Marital status												
Married or cohabiting							1	(ref)	1	(ref)	1	(ref)
Single							1.49	(1.47-1.51)	1.47	(1.45-1.49)	1.47	(1.45-1.49)
Education							1	(ref)	1	(ref)	1	(ref)
Basic							0.97	(0.96-0.99)	0.96	(0.95-0.98)	0.96	(0.95-0.98)
Non-tertiare							0.90	(0.88-0.93)	0.90	(0.87-0.92)	0.90	(0.87-0.92)
Tertiare												
SES												
Salariat							0.83	(0.81-0.86)	0.83	(0.81-0.86)	0.83	(0.81-0.86)
Intermediate employee							0.89	(0.87-0.91)	0.88	(0.86-0.90)	0.89	(0.86-0.91)
Small employers and self-employed							0.70	(0.68-0.72)	0.72	(0.69-0.74)	0.71	(0.69-0.74)
Lower white collar							0.89	(0.87-0.92)	0.89	(0.86-0.92)	0.89	(0.87-0.92)
Skilled manual							0.91	(0.89-0.93)	0.91	(0.89-0.93)	0.91	(0.89-0.93)
Semi/unskilled							1	(ref)	1	(ref)	1	(ref)
Unemployed							1.05	(1.01-1.08)	1.04	(1.01-1.08)	1.05	(1.01-1.08)
Disability pensioners							2.23	(2.18-2.28)	2.21	(2.16-2.26)	2.22	(2.17-2.27)

Students						1.03	(0.86-1.24)	1.02	(0.85-1.22)	1.02	(0.86-1.22)
Pensioners						1.11	(1.09-1.14)	1.11	(1.09-1.14)	1.11	(1.09-1.14)
Disposable income											
Highest						1	(ref)	1	(ref)	1	(ref)
High						1.24	(1.21-1.27)	1.24	(1.21-1.27)	1.24	(1.21-1.27)
Low						1.54	(1.50-1.57)	1.54	(1.50-1.58)	1.54	(1.50-1.57)
Lowest						1.66	(1.62-1.70)	1.67	(1.63-1.71)	1.66	(1.62-1.70)
Deprivation Index											
IMSD, material deprivation											
Very affluent		1	(ref)					1	(ref)		
Affluent		1.03	(0.99-1.08)					1.03	(0.99-1.08)		
Medium		1.10	(1.06-1.15)					1.09	(1.05-1.14)		
Deprived		1.14	(1.10-1.19)					1.13	(1.09-1.17)		
Very deprived		1.34	(1.29-1.39)					1.29	(1.24-1.33)		
IMSD, social location											
Very affluent		1	(ref)					1	(ref)		
Affluent		1.08	(1.05-1.12)					0.98	(0.95-1.01)		
Medium		1.13	(1.09-1.16)					0.98	(0.96-1.01)		
Deprived		1.16	(1.13-1.20)					0.99	(0.96-1.01)		
Very deprived		1.22	(1.19-1.26)					1.00	(0.98-1.03)		
Townsend											
Very affluent				1	(ref)					1	(ref)
Affluent				1.03	(0.99-1.08)					1.02	(0.98-1.06)
Medium				1.09	(1.04-1.13)					1.05	(1.01-1.09)
Deprived				1.17	(1.13-1.22)					1.11	(1.08-1.15)
Very deprived				1.35	(1.30-1.41)					1.26	(1.22-1.30)
Variation	0.03612	0.01811		0.02292		0.01814		0.00999		0.01008	
SE	0.00214	0.00138		0.00157		0.00147		0.00101		0.00102	
P (Variation=0)	0	0		0		0		0		0	
Explained variation compared to null model (%)	52.2	76.0		69.6		76.0		86.8		86.7	

The estimated frailty variance in empty models was 0.07548, SE=0.00364, P=0

Comparing model 2 with model 4 shows that the IMSD explains as much variation in all-cause mortality as a model consisting of individual SES factors (both 76%). Finally, including individual-level SES factors and the IMSD in the same model proved to be the best fitting model by explaining 86.8% of all variation in all-cause mortality (model 5), closely followed by a model including individual factors and the Townsend index which explained 86.7% (model 6). This shows that the IMSD and the Townsend index are both good measures of area-level effects, i.e. effects that are attributable to the neighbourhoods in which people live. It is seen, however, that the effect of the SES component in model 5 is greatly attenuated compared to model 2, suggesting that the SES component is explained by individual factors. The material component remains a relatively strong predictor after inclusion of individual factors.

Discussion

Main study findings

In paper 1 the systematic review found a significant association between ALSES and mortality in 21 out of 30 multilevel studies controlling for individual SES. Living in affluent areas significantly reduced mortality. There also appeared to be evidence for a relation between high mortality and low social cohesion, whereas no effect was found in studies investigating social capital. Studies examining the effect of income inequality on mortality were inconclusive. Prostate cancer risk (Sanderson et al., 2006) was also lower in higher SES areas. Only the two studies investigating breast cancer incidence found that high ALSES was associated with an increased risk of breast cancer (Robert et al., 2004; Webster et al., 2008).

The meta-analysis showed that the relative risk of death (all-cause) was RR=1.05 (1.04-1.06) in areas with low SES compared to areas with high SES. Results in paper 2 confirmed this effect by finding that the hazard ratio in low SES areas was HR=1.05 (1.01-1.09) for individuals aged 50-64 years and HR=1.05 (1.02-1.07) for individuals aged 65-81 years. Although no such effect was found for the 30-49 old age groups, the results in this thesis consistently suggest that the socioeconomic environment affects individual all-cause mortality beyond the effect of individual level factors.

In addition to the effect of ALSES it was found that also population density was associated with mortality as well as with breast- and lung cancer incidence (papers 2 and 3). Reduced mortality (HR between 0.81 and 0.86) and reduced risk of breast (HR between 0.93 and 0.95) and lung cancer (HR between 0.80-0.87) was found for individuals living in the least densely populated areas. Generally the results suggest that there is no significant gradient associated with the effect of population density; only residence in the most densely populated areas increases mortality.

In paper 4 a Danish area-based deprivation index capable of measuring material and socioeconomic deprivation was constructed. There were clear gradients in SMRs in both dimensions: SMRs for men were 1.06 (1.05-1.07) and 1.14 (1.12-1.16) in areas deprived on the material and socioeconomic dimension, respectively, while SMRs in more affluent areas were 0.79 (0.76-0.82) and 0.88 (0.87-0.89). The same pattern existed among women although the effects were smaller.

The index was better at explaining variation in all-cause mortality compared to the Townsend index (76% vs. 69.6% of frailty variation) and was able to account for as much variation as individual SES factors could (76% of frailty variation).

Area effects and mortality

The found effect of ALSES in papers 1 and 2 confirms results found in previous studies (Anderson et al., 1997; Blakely et al., 2006; Jaffe et al., 2005b; Jerrett et al., 2003; Malmstrom et al., 2001; Marinacci et al., 2004; Martikainen et al., 2003; Naess et al., 2007; Turrell et al., 2007). This could be a result of shared social norms, sanctions and value sets existing among inhabitants in areas which directly or indirectly influence individual health behavior. For instance, since smoking is more common in low SES groups, inhabitants in low SES neighborhoods might be influenced by fellow inhabitants to replicate this behavior if they regularly see people smoking in the neighborhood. The premise for this pathway, however, is that social ties exist between inhabitants and that the social environment allows health behavior to be transferred (Diez Roux and Mair, 2010; Forrest and Kearns, 2001). Earlier studies also have found that low levels of neighborhood social cohesion are associated with higher mortality (Blomgren et al., 2004; Chaix et al., 2008; Martikainen et al., 2003) indicating that positive social neighborhood characteristics such as common values, social order, solidarity, high social capital and place attachment can affect health positively. This effect persisted when individual-level and neighborhood-level SES was controlled for. Two studies, however, found no link between social capital and mortality (Blakely et al., 2006; Turrell et al., 2006). Social capital relates to trust, reciprocity, altruism, social integration, participation, and membership between people. It should be noted that theoretical considerations, operationalizations and types of measurement differ substantially between studies investigating the influence of social neighborhood characteristics. Altogether however, it seems likely that the association between ALSES and mortality could be at least partly caused by the social environment in the neighborhood.

The effect of ALSES could also be attributable to the physical environment since individuals with higher SES typically settle in more esthetically pleasing areas with less air- and noise pollution, better shopping facilities, better housing standards and less crime. Similarly, persons with lower SES are financially restricted to live in areas with fewer opportunities to pursue a healthy life. Research has found, for instance, that low SES areas are more exposed to air pollution (Naess et al., 2007) and that availability and access to fast-food restaurant is better here (Block et al., 2004; Cummins et al., 2005; Macintyre et al., 2005; Pearce et al., 2007). However, recent research in

Denmark shows that deprived areas in Copenhagen had fewer fast-food outlets (Svastisalee, 2011) and in New Zealand no association between access to fast-food outlets and diet was found (Pearce et al., 2009).

Availability of alcohol outlets is also concentrated in deprived areas (LaVeist and Wallace, 2000; Morland et al., 2002; Pollack et al., 2005) and since it has been found that consumption of alcohol is higher in neighborhoods with higher concentrations and shorter distances of outlets (Connor et al., 2010; Kavanagh et al., 2011) this suggests a link between ALSES and mortality. Another study, however, found no association between better access and increased intake of alcohol (Scribner et al., 2000). Furthermore it has been found that heavy drinking is associated with residence in wealthier neighborhoods (Pollack et al., 2005) and not in the more deprived. Overall the causal pathways from ALSES to mortality remain somewhat blurred and differing cultural contexts between studies also complicate the picture.

In addition to the effect of the socioeconomic environment, an effect of population density was found. Densely populated areas had increased mortality. This mirrors the findings of two Swedish studies (Chaix et al., 2006; Chaix et al., 2007a). The effect of population density could be attributable to several mediating factors, including that people in urban areas are more exposed to air pollution (Blomgren et al., 2004; Jerrett et al., 2003; Waitzman et al., 1999), noise pollution (van Kempen et al., 2002) or stress (Diez Roux and Mair, 2010). Other studies have found that inhabitants have worse diets (Moore et al., 2009) and have higher levels of smoking (Chuang et al., 2005) if they live in neighborhoods with higher densities of fast-food restaurants and stores selling cigarettes, respectively. Since distances in cities to these facilities are typically shorter and the densities are higher, these factors could may explain why inhabitants in areas with high population density have an increased risk of all-cause mortality. A systematic review of the association between physical environments and physical activity also advocates for policies supporting physical activity in urban areas (Kahn et al., 2002). Furthermore, cultural and ethnic differences between people living in urban areas and those living in more rural or suburban parts could affect the health behavior of the inhabitants.

On the other hand, studies investigating the association between access to food stores and diet have found that inhabitants in neighborhoods with easier access to supermarkets and other shops selling healthy food products have a healthier diet and lower BMI (Larson et al., 2009; Moore et al., 2008). As mentioned, studies have also generated mixed conclusions on the link between alcohol outlets and alcohol consumption. This conflicts with the idea that cities only are exponents for unhealthy behavior. Nevertheless results in this thesis confirm the existence of an ‘urban penalty’ regardless of both individual-level and ALSES. This suggests that mediating processes between population density and all-cause mortality should be given more attention in the future.

Area effects and cancer incidence

Results in paper 3 showed that also breast, prostate and lung cancer incidence is affected by the neighborhood environment, when taking account of individual-level confounding. Population density had an effect on breast cancer incidence among Danish women, whereas ALSES had no effect. This contrasts with the findings of a previous study finding that both ALSES and urbanization had an effect (Robert et al., 2004) and another finding that higher SES was associated with higher breast cancer incidence but not urbanization (Webster et al., 2008). One of the reasons of the different results could be that paper 3 adjusted for three individual SES factors while the two earlier studies adjusted for only education. Thus, in previous studies the found effects of ALSES could be attributable to residual confounding and not to true area-level effects. Similarly, the effect of population density in paper 3 is not very strong and could be caused by insufficient control for individual-level factors other than SES. As first suggested by Robert et al. (Robert et al., 2004), the found excess risk of breast cancer in densely populated areas could partly be a result of better access to mammography screening in urban areas. In addition, cultural differences between inhabitants in urban and rural areas or the easier access to alcohol in urban areas could also increase the risk of breast cancer.

For prostate cancer incidence a gradient was found, demonstrating that risk is reduced with increasing ALSES deprivation, which contradicts the findings of a previous study (Sanderson et al., 2006). So far, the reasons for higher prostate cancer incidence in affluent areas are unclear. Better access to screening for prostate specific antigen (PSA) could be an explanation. Other explanations could be that men in more affluent areas encourage each other to be tested or that doctors in affluent areas more frequently advise patient to be tested because many other inhabitants require this.

Increased risk of lung cancer incidence was found in densely populated areas and in areas with low SES. Although no previous multilevel studies have tested the influence of area characteristics on lung cancer incidence, two studies have found associations between higher risk of lung cancer mortality in areas of low SES (Bentley et al., 2008) or high population density (Chaix et al., 2006), whereas a third found no association for ALSES (Martikainen et al., 2003). While it is well known that smoking is related to lung cancer as the dominant causal factor, more recent studies also demonstrate a link between lung cancer and traffic-related air pollution (Pope et al., 2002; Raaschou-Nielsen et al., 2010). Therefore it seems likely that some of the excess lung cancer risk found in densely populated areas may be related to higher levels of air pollution in urban areas. Similarly a study has demonstrated that smoking prevalence in several European countries, including Denmark, is higher in urban communities (Idris et al., 2007). A number of studies have also found associations between lower SES areas and higher levels of smoking (Chuang et al., 2005; Diez Roux et al., 2003; Duncan et al., 1999; Karvonen et al., 2008). It has been hypothesized that social influences between inhabitants in neighborhoods can account for the some of the variation in smoking between neighborhoods, e.g. through norms and acceptance towards smoking (Karvonen et al., 2008). It has also been suggested that higher density and shorter distances to convenience stores are associated with higher levels of smoking (Chuang et al., 2005). These factors could therefore explain the higher risks of lung cancer in areas with low SES. Additionally a study has found that low SES areas are more exposed to air pollution (Naess et al., 2007), which also could explain the found effect.

Material and socioeconomic deprivation in Denmark

The IMSD proved to be better than the Townsend index at explaining variation in all-cause mortality when applied to Danish parishes in a multilevel model controlling for age and sex. Whereas a strong correlation was found between the Townsend index and the material component, analyses showed that there was no association between Townsend and the SES component. The strong association with material conditions can be seen as a result of the fact that car and house ownership as well as unemployment have large weights in this component, at the same time as they constitute three quarters of the Townsend index. That the SES component is not related to the Townsend index reflects that the SES component is measuring something not contained in the Townsend index. While the Townsend index is constructed to measure material deprivation, the IMSD has an additional component devoted to socioeconomic deprivation. This reveals the importance of including education, income and occupation in a Danish deprivation index and points to why the IMSD performs better than the Townsend index.

It was found that the Townsend index and each of the two IMSD components were less sensitive to variation in all-cause mortality than individual SES factors. However, including both IMSD components in the same frailty model explained as much frailty variation as the individual SES factors. On one hand this confirms results in previous studies that have pointed to the relevance of using aggregated variables in the absence of individual-level variables (Carstairs and Morris, 1989;

Havard et al., 2008; Jarman, 1983; Juhasz et al., 2010; Krieger, 1992; Messer et al., 2006; Noble M et al., 2004; Noble et al., 2008; Salmond et al., 1998; Townsend, 1987) but conflicts with the well-demonstrated results of studies finding that individual-level SES variables are more accurate and produce stronger effects than aggregate measures (Geronimus and Bound, 1998; Greenwald et al., 1994; Hanley and Morgan, 2008; Soobader et al., 2001).

Introducing individual-level SES factors into a model containing age, sex and the IMSD showed that the effect of the IMSD SES component disappeared while the material component kept its effect sizes. This indicates that the material component measures true area-level effects whereas the SES component functions as a proxy for individual SES factors. However, even though the present study evaluates a large population that does not suffer from selection bias on either the individual or the area-level, it is not recommend using the IMSD or any of its components as proxies for individual SES since then it is not possible to isolate individual SES effects from area-level effects. By controlling for individual SES, however, the IMSD components serve as good indicators of area-level effects.

Parishes scoring high on the material deprivation component were mostly concentrated around the capital area and other large cities. Since large weights are given to car and house ownership and that urban parishes have higher proportions of rented housing (Statistikbanken, 2011) and inhabitants are less dependent on cars, it explains why urban parishes score high on this component. A previous study confirms that home ownership is confounded by urban/rural characteristics (Gilthorpe and Wilson, 2003). More rural areas such as northern Jutland, southern Funen, Lolland, Falster, western Zealand and Bornholm also are characterized as materially deprived. A hypothesis could be that socioeconomic deprivation increases together with the proportions of inhabitants not owning cars, and perhaps also with unemployment. Therefore these parishes score higher on the material component. Yet, the effect of the material component was attenuated relatively little by adding individual SES factors. This suggests that the material component is unaffected by socioeconomic deprivation and that material deprivation might be attributable rather to area-level deprivation, such as lack of job opportunities. However, since this is not the reason for the high material deprivation levels in the larger cities, this indicates that there are likely various reasons for levels of material deprivation, as so measured. It is therefore recommend that any comparisons between urban and rural parishes regarding the material component be done cautiously.

The relationships between individual-, ecological- and area effects

Papers 2-4 use both individual and ecological measures to say something about individual-, ecological-, and area-effects. To avoid misinterpretations of these concepts and effects a short discussion of their relationship and strengths is needed.

In paper 4 ecological measures - the deprivation indices - are used to describe the level of deprivation in areas. However, these measures cannot be used to infer anything about the individuals living in them (Diez-Roux, 1998). This would be an example of the ecological fallacy, since a highly educated person with a high income easily can live in a deprived area. Ecological studies are subject to the ecological fallacy when they are used to explain relationships at the individual level (Mackenbach, 2000). Using ecological factors to say something about the context in which individuals live, however, is possible as long as the statistical model controls for individual factors also. If no adjustment is made on the individual level it remains unclear whether the effect is attributable to the area or to the composition of inhabitants in the area (Subramanian et al., 2003). For these very reasons it was recommended not to use the IMSD as a proxy for individual SES even though the IMSD was able to explain as much variation in all-cause mortality as individual SES factors.

It should remain clear, however, that individual factors are the dominant risk factors. In paper 2 the individual level accounted for 86%, 79% and 58% of all variation in all-cause mortality for Danish inhabitants aged 30-49 years, 50-64 years and 65-81 years respectively. Adding ecological factors increased explained variation to 94%, 86% and 78% for the same age groups. The influence of area-level factors is therefore relatively modest compared to the demographic and socioeconomic factors on the individual level. Results also indicate that individual level factors explain more variation in all-cause mortality for younger individuals than for older generations.

Analyses conducted with breast, prostate and lung cancer incidence as outcome showed that the individual level factors accounted for 79%, 36% and 66% of the variation, respectively, while adding area-level factors increased these numbers to 81%, 39% and 85%. Again individual factors explain much more variance than the area level. Although individual demographic and socioeconomic factors seem to have relatively little influence on prostate cancer incidence, their impact is still far greater than area-level factors. For lung cancer incidence it is seen that area-level factors do have a substantial impact.

Measuring area-level SES in a Scandinavian country

As stated in the in the aims of the thesis, the working hypothesis was that social inequalities on the area level would be less pronounced in Denmark or in other Scandinavian countries because of the extensive economic redistribution and universal access to education and health care.

Results from the meta-regression (paper 1) suggest that the hypothesis can be rejected, since it was shown that types of welfare state regimes had no influence on the relation between ALSES and all-cause mortality. Thus, in Scandinavian countries, having the social democratic welfare state model, ALSES effects were not significantly different from ALSES effects in countries with liberal or conservative welfare state regimes.

ALSES effects found in paper 2 were similar to those found in the meta-analysis, in paper 1. The associations in Denmark also seemed equal to those in studies conducted in liberal countries, although the analysis presented in paper 2 controlled for three SES factors on the individual level. Since a previous review (Pickett and Pearl, 2001) has concluded that area-level effects are likely to be stronger when fewer SES factors are adjusted for on the individual level, it is unlikely that ALSES effects are smaller in Denmark compared to countries characterized by conservative and liberal welfare state regimes. However, the design of the studies in paper 2 and paper 3 are relatively unique because they incorporated a latency period of about ten years between neighbourhood exposure and outcome. Secondly, individual level SES factors were measured 2-3 years prior to death and cancer diagnosis, which is not common either. These design differences could amplify the effect sizes in the present studies compared to other studies.

Still, on the individual level the results in papers 2 and 3 confirm results in previous investigations showing that socioeconomic inequality in mortality (Mackenbach et al., 1997) and cancer incidence and survival (Dalton et al., 2008) exit in Denmark despite the redistributive efforts.

Validating the deprivation index for Denmark proved that material deprivation as measured in the Townsend index was not sufficient to capture variation all-cause mortality on the area-level. Adding a socioeconomic dimension improved the strength of the index significantly. However, this does not suggest that Denmark is particularly sensitive to socioeconomic condition, since other contemporary indices (Havard et al., 2008; Juhasz et al., 2010), including English Indices of Multiple Deprivation (Noble et al., 2008) have also incorporated similar measures.

Overall I found no evidence suggesting that economic redistribution or universal access to education or health care produces smaller socioeconomic effects in Denmark.

Strengths and limitations

Paper 1

While systematic reviews and especially meta-analyses are highly ranked research methods the study also has drawbacks. This pertains to the number of searched databases and search terms used in the retrieval. Conducting a pilot and having searched four databases have contributed to a solid data collection and limited any possible errors in this phase. Data extraction and qualitative analysis is also subject to possible subjective interpretations, but by having two researchers individually code the individual studies this bias should is reduced. In the assessment of risk of bias it was showed that the reviewed studies are of very high overall quality. However, it is a limitation that studies varied as to cause of mortality, control for individual SES, age range, geographical scale and statistical method. This together with the high level of heterogeneity between studies as assessed by the meta-analysis and meta-regression suggest that the results should be treated with caution. One particular weakness is that studies in the meta-analysis used different measures of ALSES, which also might contribute to the heterogeneity.

Paper 2 and 3

A common strength in papers 2 and 3 is the size of the study populations. In all analyses register data on nearly the entire Danish population in relevant age groups is included. This significantly reduces selection bias (Chaix et al., 2011) and increases reliability. It is also a particular strength that both individual education, disposable family income and occupation-based SES was adjusted for, which significantly reduced the risk of residual confounding by individual SES (Macintyre and Ellaway, 2003). Moreover it is a strength that the studies have incorporated a latency period between neighborhood exposure and outcome and that they take account of the fact that major life changes are likely to occur shortly before death or a cancer diagnosis. However, in the analyses of cancer incidence data were not available on a number of important individual-level confounders such as, for breast cancer, menopause, age at first child and family history of breast cancer, or for prostate cancer, the use of PSA testing. Thus, there is a risk that the area-level effects are overestimated because individual factors have not been sufficiently controlled for. It would also have added important information to the study on the area level if information was available about spatial distributions of places that test for breast and prostate cancer. A common disadvantage in paper 2 and paper 3 is also that they only include one area-level. Other area levels might account for some of the found parish-level effects (for instance on the municipal level).

Paper 4

The IMSD is not as straightforward to use as the Townsend (Townsend, 1987) or Carstairs (Carstairs and Morris, 1989) indices as they consist of only one dimension with four unweighted standardized variables. Parishes can therefore be described by only one score whereas the IMSD requires two. However, while the Townsend and Carstairs indices only use variables belonging to the housing and employment domains, the IMSD encompasses a wider range of domains which are acknowledged to be associated with deprivation. This is also a particular strength compared to the existing Danish indices (Hammer-Helmich et al., 2010; Juel, 2010). Measuring deprivation as a two-dimensional entity also enables users of the index to describe deprivation on both the material dimension and the SES dimension, which is the most appropriate way to use this index.

A further advantage of this index is that it is developed at a much more detailed resolution than the two existing Danish indices (2,113 parishes vs. 98 municipalities) which ensures more homogeneous areas with respect to the characteristics of the inhabitants. For instance, with this index it is possible to detect and acknowledge the large variation in SES within the municipality of Copenhagen. This facilitates identification of small-scale areas that are particularly deprived.

Conclusion and perspectives

This thesis shows that area-level socioeconomic characteristics and population density are risk factors for mortality and cancer incidence beyond the effect of individual demographic and socioeconomic factors. In addition a relative deprivation index has been constructed that can identify parishes in Denmark by their level of material and socioeconomic deprivation.

Conclusions drawn from this thesis suggest a number of implications. Firstly, policy areas traditionally thought of as unrelated to public health could contribute to reducing morbidity and mortality (Schoeni et al., 2008). Shifting focus from concentrating on individual health behavior to also investing in low SES areas would have several advantages. The infrastructural circumstances for inhabitants would improve, which in itself would reduce morbidity and mortality. It could attract higher socioeconomic groups to these areas, which possibly would imply a number of positive influences with regard to the social and physical environment. Some researchers have suggested looking at housing policy (Diez Roux and Mair, 2010; Van Lenthe, 2006). Avoiding large-scale public housing complexes as well as situating public housing in more affluent areas could reduce high concentrations of low SES groups and thereby have positive health impacts. Utilizing the IMSD would help identifying deprived areas.

The IMSD also provides policy makers with a tool to allocate health-related attention and resources. Identifying deprived neighbourhoods could enable health professionals in planning area-specific health interventions. It has been examined how the IMSD performs only with regard to all-cause mortality. Future research can examine how well the IMSD relates to cause-specific mortality as well as to morbidity and to health behaviour indicators. Danish epidemiological studies can also benefit from using the IMSD when investigating or controlling for ALSES.

The hope is that future epidemiological research will welcome the challenges in disentangling the mediators between high population density and ill-health. In research concentrating on developing countries the excess risk of living in areas with high urbanicity is conceptualized ‘the urban health penalty’ (Freudenberg et al., 2005; Vlahov et al., 2005). Consistent with the few other multilevel analyses of the phenomenon, this thesis suggests that these concepts are also true for western societies. Investigations into whether the effect of population density is related to known risk factors (such as smoking, air pollution, distance and density of shops selling products associated with ill health) or if it is related to cultural differences between urban residents and more rural residents could contribute substantially in understanding and reducing health inequalities.

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