Unravelling socioeconomic and regional differences in health and healthcare expenditures in the Netherlands

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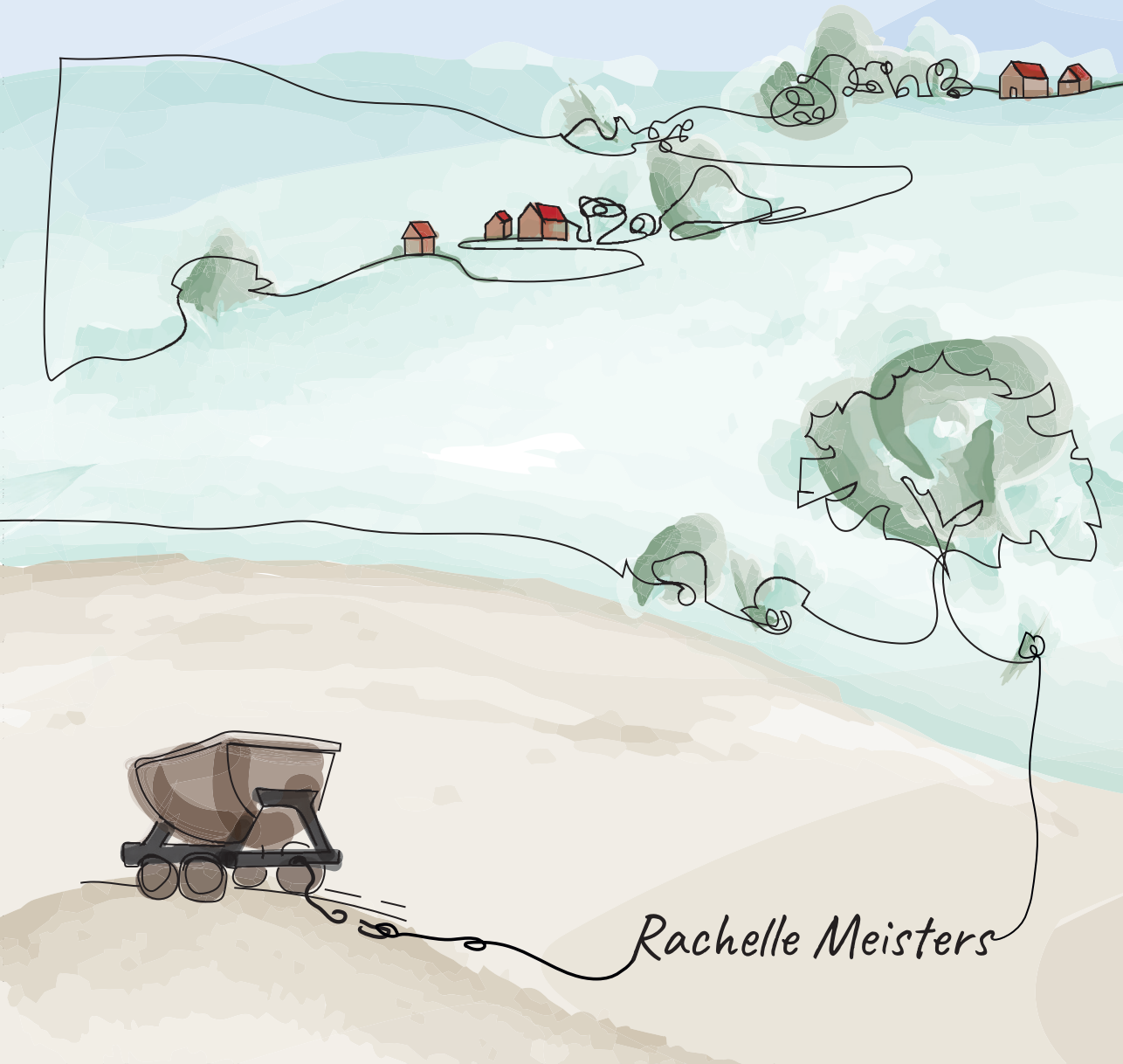

Rachelle Meisters

Stellingen

behorende tot het proefschrift

Unravelling socioeconomic and regional differences in health and healthcare expenditures in the Netherlands

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Rachelle Meisters, 2023

1. Eenzaamheid, moeite met rondkomen en regie over eigen leven zijn ook determinanten van gezondheid en van sociaaleconomische verschillen in gezondheid (dit proefschrift).

2. Onderliggende verklaringen voor regionale gezondheidsverschillen in Nederland betreffen zowel bekende (demografie, sociaaleconomische status en leefstijl) als minder bekende gezondheidsdeterminanten zoals eenzaamheid, moeite met rondkomen en regie over eigen leven (dit proefschrift).

3. Regionale verschillen in zorgkosten in Nederland kunnen verklaard worden aan de hand van demografie, sociaaleconomische status, leefstijl, eenzaamheid, regie over eigen leven en gezondheidsstatus, behalve de hogere huisartsconsultkosten in Zuid-Limburg (dit proefschrift).

4. De gezondheid van de Zuid-Limburgse bevolking wordt nog steeds negatief beïnvloed door de mijnsluitingen van meer dan 50 jaar geleden (dit proefschrift).

5. De gezondheidsimpact van beleidskeuzes dienen in alle beleidsterreinen te worden meegenomen.

6. Beleid en interventies gericht op het verkleinen van gezondheidsverschillen moeten verschillende determinanten van gezondheid op individueel- en op populatieniveau integraal meenemen.

7. Een data-infrastructuur die het gebruik en koppelen van geanonimiseerde data over meerdere aspecten van de samenleving mogelijk maakt - zonder de individuele privacy te schenden - is een aanjager van wetenschappelijk onderzoek ten behoeve van de samenleving.

8. De maatschappelijke impact van wetenschap kan worden bereikt door bijdrages aan beleidsontwikkelingen en laagdrempelige communicatie voor het brede publiek.

9. When you are curious, you find lots of interesting things to do (Walt Disney).

10. If I fly or if I fall, least I can say I gave it all (RuPaul).

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The research presented in this dissertation was conducted at the Care and Public Health Research Institute (CAPHRI), department of Health Services Research, Maastricht University. CAPHRI participates in the Netherlands School of Public Health and Care Research (CaRe), which has been acknowledged by the Royal Academy of Science (KNAW). This research was conducted within the Living Lab for Public Health (AWPG) and the Living Lab for Sustainable Care (AWDZ). The AWPG is a collaborative between the 16 municipalities in South Limburg, the regional Public Health Service (GGD Zuid Limburg), Maastricht University and the Maastricht University Medical Centre (MUMC+). The AWDZ is a collaborative of Maastricht University and MUMC+.

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Contents

Voor mijn grootouders

Chapter 1

General introduction

While global population health has improved over the past decades, not everyone has benefitted equally. The World Health Organization found that between 2000 and 2019, the global healthy life expectancy at birth increased from 58.3 to 63.7 years [1]. However, for low income populations the healthy life expectancy was still behind the global average with 56.7 years in 2019 [1]. The Organization for Economic Cooperation and Development found that across all 33 countries, the least educated were twice more likely to face poor health with 44% of people in the lowest education category reporting poor health versus 23% of people with highest education [2]. Inequalities in health reflect inequalities in society. Health inequalities do not arise by chance and are not a simple result of 'bad' genetics. They reflect differences in living conditions that accumulate over the life course [3]. Preventable health inequalities that still persevere in a society are simply unfair and putting them right is a matter of social justice [3]. In addition to the social and ethical aspects of health inequalities, health represents a fundamental resource and poor health wastes potential, cuts lives short and drains resources [4]. Whereas the overall health of populations in Europe has also improved over the last decades, great differences exist in health between and within countries and these differences are widening [4, 5].

This is also true for the Netherlands as it faces socioeconomic and regional health inequalities. The National Institute of Public Health and Environment (Dutch: Rijksinstituut voor Volksgezondheid en Milieu; RIVM) stated that on average, 21% of the Dutch adults report poor health in 2020 [6]. This percentage was lowest in the region Hollands Midden, with 18% and highest in the region of South Limburg, with 27% [6]. The region of South Limburg also has the highest percentage of people reporting at least one chronic disease (38% compared to 32% national average) [7]. Together with the region of Groningen, South Limburg has the lowest overall life expectancy at birth (80.0 years compared to 81.8 years national average) [8] and together with the region of Rotterdam, South Limburg also has the lowest healthy life expectancy (59.0 years compared to 62.4 years national average) [9]. Poorer health also results in draining resources as is shown in inequalities in healthcare expenditures. Healthcare expenditures (as covered by the basic insurance plan) were compared in 2018 on a municipal level. On average, €2625,- were spent on healthcare per Dutch adult per year [10]. However, spending differed greatly per municipality. The highest average cost were found in the South of Limburg, with €3625,- per person in the municipality Kerkrade and the lowest in the province of Flevoland, with €1813,- per person in the municipality Urk. This is a difference of €1700,- per adult per year. After taking into account age and gender, the difference still remained €1200,- between the municipalities with the highest and lowest healthcare expenditures (South Limburg, Heerlen: €3273,- and Gelderland, Rozendaal: €2074,-) [10]. These variations in cost may stem from

health inequalities (i.e. less healthy population consumes more health care services) but may also be caused by other factors such as availability and proximity of health care services or behavioral aspects in health care consumption. The health inequalities disadvantaging the population of the province of Limburg, and more specific, the region of South Limburg, have been common knowledge for the past decades. Substantial efforts have been made to understand why these health inequalities exist and persist [11].

The Limburg-factor

In 2015, the report 'Searching for the Limburg-factor' was published to shed light on the underlying mechanisms of these inequalities as a starting point for new provincial policy to turn the trend. The report aimed to bridge multiple domains in order to find and explore multi-faceted causes of the reported health inequalities in Limburg. Based on literature and expert opinions, the report listed the following domains as contributors to health disadvantages in Limburg: education, labor, mastery, historical burden, cultural environment, trust and societal participation, unhealthy lifestyles, and socioeconomic status (SES) [11]. The recommendations provided in the report helped to formulate new provincial policy, the so called Social Agenda Limburg, in 2016. In order to provide a baseline measurement, the Province commissioned a quantitative study in 2018. This study reported on a number of indicators covering each of the five main themes in the Social Agenda Limburg: education, labor and societal participation, health, upbringing, and social capital. The study showed that it was the region of South Limburg that was performing poorly in each of the five themes, specifically in health, labor and participation [12]. The region of North Limburg scored either average or above average in all domains [12]. Based on the two reports, further in-depth analyses were warranted to uncover determinants of health and potential mechanisms underlying health deficits in the South of Limburg.

Determinants of health

Various models have been developed to describe social determinants of health [13] such as the multilevel approach by Kaplan, Everson and Lynch [14], the Evans and Stoddart model [15], or the Dahlgren-Whitehead model [16]. What these models share in common is that they reflect multiple determinants of health, on macro, meso-, and micro levels that fall outside the traditional healthcare sector. For instance in sectors such as government (policies and societal norms), labor market (working conditions) and education. A more recent model is the Barton and Grant health map [17], which is an adaptation of the Dahlgren-Whitehead 'rainbow model' (represented by Figure 1.1).

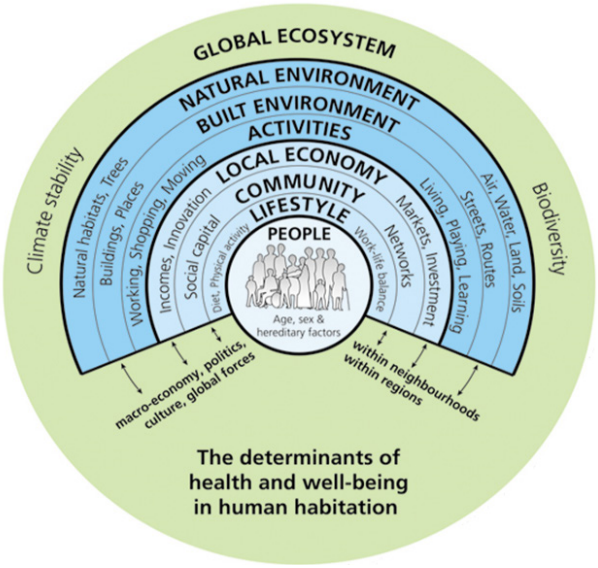

Figure 1. The health map by Barton and Grant 2006 [17], developed from the Dahlgren and Whitehead 1991 model of the determinants of health [16]

The determinants of health are layered in terms of environments and individuals are placed at its center. The center represents individual factors such as age and gender. The layers represent modifiable determinants such as lifestyle factors (first layer), social factors (second layer), income and investments (third layer) and living and working conditions (fourth layer). The fifth, sixth and seventh layers represent the overall societal environment in terms of built environment, the natural environment and the global ecosystem.

Research has linked each of these potentially modifiable layers to health inequalities. Health inequalities related to SES, in terms of education, income, and occupation (third layer) are well researched since the Whitehall studies [18] and the Black report [19]. Empirical studies have reported that lower SES groups face higher risks for poor health [20-23], chronic diseases [24, 25] and unhealthier lifestyles [26-29] (first layer). Also, unhealthier lifestyles (in terms of physical activity, alcohol consumption, smoking, dietary habits and/or body mass index [30]) have been linked to poorer health [31-33]. Research has shown however, that SES and lifestyle factors alone cannot fully explain observed health inequalities [27, 33].

As a part of the second layer, i.e., the community, loneliness has also received attention in health inequality research. Loneliness may be defined as i) perceiving a lack of communication or ii) having less (or lower-quality) relationships with others than desired or iii) lacking social support [34]. Research in older populations has shown that a lack of social support is related to poorer health [35, 36], lower life satisfaction [36], and

reduced physical functioning [37]. However, loneliness is not only a problem for older aged groups [38, 39]. In other age groups not limited to elderly, loneliness has been linked to poorer physical [40-43] and mental health [40, 44, 45], unhealthy behaviors [45, 46] and mortality [40, 47]. Although loneliness is closely related to other known determinants of health such as the first and third layer of Dahlgren and Whitehead framework [45], the extent of its contribution to explaining regional and socioeconomic health inequalities in the general population remained unclear.

Another well-known and extensively researched social determinant of health is income [48-50], part of the third layer. The relationship between income and health is most often studied in terms of absolute income. Studies have shown that people with lower absolute incomes have more difficulties maintaining a good health [48], are at higher risk of developing unhealthy behaviors [51] and mental health problems [52-54]. However, absolute income does not represent spending patterns, debts, expectations, aspirations or access to other economic resources [55]. Perceived income inadequacy does account for these other aspects of income and is therefore conceptually different to absolute income. This is also shown in research where people with low incomes do not always report income inadequacy [56], and people with similar absolute income levels reporting different levels of income adequacy [55]. Perceived income inadequacy can therefore affect one's health via other pathways from absolute income levels [56-58]. To complicate matters, mastery (the sense of personal control [59]) has been found to (partially) explain the associations between low absolute income, perceived income inadequacy and poor mental health [60, 61]. Health inequalities are well established by either absolute income or perceived income inadequacy. However, the interplay between both aspects of income on health and the role of demographic and socioeconomic confounders and mastery on these associations is not well known.

Regional variation in healthcare expenditures

As shown in the first part of this introduction, health inequalities are not only apparent in health measures, but also in healthcare expenditures. International studies have found that lower SES and poorer self-rated health [62, 63] and unhealthy behaviors [63, 64] are related to higher healthcare use, and therefore costs. Loneliness was also found as a contributor to more physician visits [45]. A recent review of cost of illness studies found that loneliness was related to higher healthcare costs in in three studies for older adults (samples were over 50, 60 or 75 years of age) [65]. However, for other age groups beyond older people, little is known about the associations of loneliness and different types of healthcare costs [65].

Regional variations in healthcare costs have been linked to both demand- and supply factors, where demand factors represent patient characteristics and supply represent characteristics for the healthcare market or healthcare providers [66]. Research based on movers in the Netherlands has linked 70% of regional variations in healthcare costs to demand factors [67]. A population health management study found that for patients with diabetes and depression, regional variations in healthcare costs in the Netherlands were mostly (for diabetes) or completely (for depression) explained by demand variables [68]. These studies have analyzed certain subpopulations in the Netherlands, and accounted for age, gender [67, 68], SES, and self-rated health [68]. However, as mentioned above, other determinants of health have also been linked to explaining healthcare costs. With these insights, more research is warranted in explaining regional variations in healthcare costs with a more extensive list of personal characteristics.

Aim and outline of this dissertation

The aim of this dissertation is to investigate the role of less established determinants of health in explaining socioeconomic and regional inequalities in health and variations in healthcare expenditures. First, this dissertation aimed to study less established determinants of health such as loneliness, income adequacy and mastery in a national setting to understand their role in socioeconomic health inequalities. Second, these determinants were added to a set of established determinants of health (demographic factors, SES, and lifestyle factors) in attempt to further explain the regional health inequalities and variations in healthcare expenditures in the Netherlands. For this aim, the following objectives were formulated:

1. What is the role of loneliness and perceived income inadequacy in socioeconomic health inequalities?
2. To what extent can social determinants of health explain regional health inequalities in the Netherlands?
3. To what extent can social determinants of health explain regional variations in healthcare expenditures in the Netherlands?

Chapters 2, 3 and 4 provide answers to the first objective in a national setting.

Chapter 2 explores the contribution of loneliness to the relationship between SES and health, measured as self-rated health, presence of at least one chronic disease and psychological distress. It reports the findings for the general adult population, and subgroups by age, gender, marital status and migration background. **Chapter 3** focuses on the associations of loneliness with different type of healthcare expenditures (total, GP consult, specialized, pharmaceutical and mental healthcare), also by different age groups. **Chapter 4** reports the associations of absolute income levels and perceived

income inadequacy (for different absolute income levels) with the same health outcomes from Chapter 2.

Chapters 5 and 6 cover the second and third objective and provide a regional perspective on health inequalities within the Netherlands. **Chapter 5** reports the findings on a study of regional variations for the same health outcomes studied in Chapter 2. **Chapter 6** shows the results of a study on regional variations in different types of healthcare care costs in line with Chapter 3.

Lastly, **Chapter 7** contains the general discussion of this dissertation with implications for policy and practice and directions for future research.

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Chapter 2

Is loneliness an undervalued pathway between socio-economic disadvantage and health?

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Abstract

Loneliness is a growing public health issue. It is more common in disadvantaged groups and has been associated with a range of poor health outcomes. Loneliness may also form an independent pathway between socio-economic disadvantage and poor health. Therefore, the aim of this study was to explore the contribution of loneliness to socio-economic health inequalities.

These contributions were studied in a Dutch national sample (n = 445,748 adults (≥19 y.o.)) in Poisson and logistic regression models, controlling for age, gender, marital status, migration background, BMI, alcohol consumption, smoking, and physical activity. Loneliness explained 21% of socioeconomic health inequalities between the lowest and highest socio-economic groups in self-reported chronic disease prevalence, 27% in poorer self-rated health, and 51% in psychological distress. Subgroup analyses revealed that for young adults, loneliness had a larger contribution to socioeconomic gaps in self-rated health (37%) than in 80+-year-olds (16%). Our findings suggest that loneliness may be a social determinant of health, contributing to the socioeconomic health gap independently of well-documented factors such as lifestyles and demographics, in particular for young adults. Public health policies targeting socioeconomic health inequalities could benefit from integrating loneliness into their policies, especially for young adults.

Introduction

Although average health and life expectancy in Western populations have been improving over the last few decades, not everyone in society has benefited equally. Health inequalities between and within countries still persist [1] and are a public concern from both an economic and social perspective. Health inequalities are well-documented in terms of differences in socioeconomic status (SES), which include differences in education, income, and occupation. Research on SES health inequalities was started by the Black report [2] and the Whitehall studies [3], and studies have since reported that lower-SES individuals tend to have poorer health [4,5], higher risks for chronic diseases [6,7], and unhealthier lifestyles. [8,9] According to Dahlgren and Whitehead [10], the determinants of health are layered with individual (age, gender) factors at the center, and layers of modifiable determinants such as lifestyle factors (first layer), social factors (second layer), living and working conditions (third layer), and the overall societal environment (fourth layer). Although most research has focused on socioeconomic and lifestyle factors, it is increasingly apparent that these factors alone cannot fully explain the observed inequalities [9,11].

As one of the social factors (the second layer), loneliness is a public health concern that is increasingly recognized in the context of poorer health [12,13]. Loneliness is defined as perceiving a lack of communication or having less (or lower-quality) relationships with others than desired [14] or lacking social support. A lack of social support has been found to negatively affect health [15,16], life satisfaction [16], and physical functioning [17] in elderly populations. Loneliness can be caused by a range of situations (physical isolation, moving, divorce, or the death of a significant person), internal factors (low self-esteem), personality factors (introversion), or it can be a symptom of a psychological disorder (depression) [18]. A growing number of people reporting feeling lonely has been documented in developed countries across the world. A cross-country study on loneliness and social isolation in the United States, the United Kingdom, and Japan reported that 22%, 23%, and 9% of the respondents felt lonely often or always, respectively. Loneliness is not limited to the elderly, as some studies found that the majority of the lonely were under the age of 50 and were more likely to be single or divorced [19,20]. Studies have shown that loneliness is correlated with mortality [12,21], as well as poorer physical [12,22] and mental health [12,23]. Lonely people were also more likely to engage in unhealthy behaviors [24,25] and visit physicians [25,26] and mental healthcare providers [26] more frequently. Although loneliness is closely interlinked with other known determinants of health [25], to date the extent of its contribution to socioeconomic health inequalities in the general population remains unclear. Socio-economic gaps are commonly attributed to unhealthy lifestyles among

disadvantaged groups. For example, lower-educated people might be less knowledgeable about healthy behaviors, are at higher risk of growing up in poorer neighborhoods with adverse peer influences, experiencing more stress (i.e., relational, financial, or work-related), and as a result are at higher risk of adverse health behaviors and poorer health. Since lifestyle factors alone cannot fully explain the observed inequalities, quantifying the impact of loneliness in health inequalities after considering the combined effect of (clusters of) other social determinants might therefore present possibilities for better targeted public health policies.

We also hypothesized that the impact of loneliness on socioeconomic health inequalities may vary across population groups (e.g., age, marital, or migration status) in light of an age-normative life-stage perspective, different life circumstances, and priorities [20]. In other words, loneliness may have a different impact on persons of different ages, depending on what is considered the 'norm' in society at different phases of life. Loneliness may interact differently with lower socio-economic status for divorced or widowed people [27], as well as persons with a migration background [28]. There is currently no consensus in the literature as to whether females or males are more susceptible to experiencing loneliness and its impact on health [25] and health inequalities. Therefore, the aim of this study was to use a comprehensive national population sample in order to (1) assess the contribution of loneliness in addition to lifestyle factors in the association between SES and health, and (2) explore whether the contribution of loneliness to the socio-economic health gradient differs across population groups, defined by age, gender, marital status, and migration background. Our findings should inform public health policies about the independent contribution of loneliness beyond the well-documented factors, in search of new modifiable social determinants to tackle the inequalities.

Materials and Methods

This is a cross-sectional study of associations between individual socioeconomic status, lifestyle-related factors, and loneliness with self-rated health, chronic disease, and psychological distress in the Netherlands for the year 2016.

Data and Sample

Data were obtained from two data sources: the Dutch Health Survey [29] and Statistics Netherlands. The Health Survey is commissioned by the municipalities and the Ministry of Health, Welfare, and Sport. In accordance with the Public Health Law, Dutch municipalities are required to assess local public health issues at least once every four years. In order

to do so, the Health Survey is implemented in collaboration with Statistics Netherlands, the Public Health Service, and The Dutch National Institute for Public Health and the Environment (RIVM). The Health Survey runs once every four years nationwide for people aged 19 years and older. The survey includes questions about respondents' general physical and mental health, daily activities, lifestyle, social contacts, participation in voluntary work, informal care, family life, SES, and housing and neighborhood conditions. Survey data are collected in a number of ways, including either by paper and pencil, internet, or interviews via telephone or face-to-face. The response rate for the Health Survey was 40% in 2016 [30], with a total of 445,748 complete responses. These data have been previously used to, for example, study the association of loneliness and healthcare costs in a nationally representative sample [26]. For more information regarding the content and distribution method of the Health Survey, we refer to [29].

The data provided by Statistics Netherlands consisted of the administrative data collected from the Personal Records Database and the Dutch Tax and Customs Administration data for the entire Dutch population. The former were collected by municipalities and provide information on citizens' age, gender, and migration background. The latter provided annual income records for each individual and household. Based on the pseudo-anonymized personal social security codes, the Health Survey data were linked with the Personal Records Database and the Dutch Tax and Customs Administration data for people aged 19 years and older in the secured environment managed by Statistics Netherlands. After merging the Health Survey sample with the administration data, 445,748 responses were retained in our sample.

Measures

Dependent Variables

Three outcome variables were used to operationalize health in this study, namely, 'having a chronic disease', 'self-rated health', and 'psychological distress'. The operationalization and sources of variables are listed in Supplementary Materials Table S1. The variable having at least one chronic disease was obtained from the question "Do you have one or more long-term diseases (expected duration 6 months or longer)" (answer options: yes or no). The dichotomous variable 'having a chronic disease' was categorized as either none or at least one. Self-rated health was measured using the question "In general, would you say your health is …". Answers were given on a five-point Likert scale with categories "excellent", "very good", "good", "fair", and "poor". The answer categories were dichotomized as "excellent, very good, good" or "fair, poor". Psychological distress was measured with the Kessler psychological distress scale (K10) [31]. The scores for these 10 questions were categorized as "none, low, or moderate" (scores between 10 and 29), or "high" (scores between 30 and 50) psychological distress [32].

Independent Variables

Loneliness

Loneliness was based on the score for the 11-item de Jong-Gierveld scale [14], a validated scale which has been applied in various (cross-) national samples. [24,25,33–37] Eleven statements are listed, based on various aspects of deprivation ("I wish I had a really close friend", "Often, I feel rejected", "I experience a sense of emptiness around me", "I miss having people around me"), companionship ("It makes me sad that I have no company around me", "I feel my circle of friends and acquaintances is too limited"), sociability ("There is always someone around that I can talk to about my day to day problems"), and meaningful relationships ("There are plenty of people that I can depend on if I'm in trouble", "There are enough people that I feel close to", "I can rely on my friends whenever I need them", "There are many people that I can rely on completely"). The statements are scored as 'yes', 'more or less' or 'no'.

Confounders

Lifestyle-related variables included body mass index (BMI), alcohol consumption, smoking, and physical activity, similarly to previous research [38]. We controlled for the demographic variables age, sex, migration background, and marital status, and for the mode of completing the survey. Proxies for socioeconomic status included the highest attained level of education, standardized household income quartile, and self-reported income adequacy. After performing all analyses for the three SES proxies separately and finding similar results, one SES construct was created in order to present the associations for socioeconomic health inequalities. To combine the three SES variables into one SES construct, they were standardized into z-scores ($z(x) = \frac{x - \text{mean}(x)}{\text{standard deviation}(x)}$) e.g., [39]. From the three z-scores, one overall mean score was calculated to represent the overall SES construct and was further divided into quartiles. The fourth quartile included persons with the highest SES and was taken as the reference group.

Statistical Analyses

The relative risks for adverse health outcomes were modelled in a series of logistic and robust Poisson regressions. The outcomes 'chronic disease' and 'self-rated health' were modelled in Poisson regressions with robust variance given so called 'common outcomes' (more than 10% cases). It is known that the odds ratios (OR) estimates given by logistic regressions do not appropriately approximate the relative risks (RRs) for such outcomes [40]. For the outcome 'psychological distress' (5% cases), logistic regressions were run. Per health outcome, four regressions were computed to assess the relationships between SES and health. Model 1 included the SES construct and demographic factors (age, gender, migration background, and marital status). Model 2 contained the SES construct, demographic factors, and lifestyle-related factors. Model 3 contained the

SES construct, demographic factors, and loneliness. Finally, in model 4 all factors were included. All models were adjusted for the mode of survey completion (paper, internet, phone, or face-to-face) and accounted for the complex survey design through survey weights. The contributions of factors were assessed by comparing the relative risk and odds ratios, and their percentage change ($\left(\frac{(\text{OR Model 1} - \text{OR Model X})}{(\text{OR Model 1} - 1)} \times 100\right)$, where X is 2, 3, or 4) as done in previous studies [41–43]. This method has been shown to result in similar findings as the counterfactual framework approach [43]. The interactions between the SES construct and (1) age, (2) gender, (3) migration background, and (4) marital status were tested to check whether the association of loneliness and the SES health gradient was different between subpopulations. Missing data were imputed by means of the multiple imputation by chained equations (MICE, 5 imputations, n = 445,748) method [44]. For the subgroup analyses, interaction effects were tested between the SES construct and age, gender, migration background, and marital status. For significant interaction effects, stratified models were run. Model assessments included goodness-of-fit tests and multicollinearity diagnostics. The significance level was set at alpha = 5%. Analyses were performed in Stata 16 [45].

Results

Descriptive Statistics

The mean (SD) age was 59.4 (16.9) years and 56% of the sample was female. Dutch-born respondents represented 88% of the sample, 9% of the respondents had a Western migration background, and 4% had a non-Western migration background. The majority of the participants were married or lived together (73%), 11% of the respondents were single, 10% were divorced, and 7% were widowed. Almost 40% of the people included in the sample reported having at least one chronic disease, 26% rated their overall health as fair or poor, and 5% of the respondents were at a high risk of experiencing psychological distress. Some loneliness was reported by 34% of the participants, 5% reported severe loneliness and 3% reported very severe loneliness (see Table 1). Model diagnostics are reported in Tables S2 and S3. Respondents from the lowest SES quartiles reported worse physical and mental health, unhealthier lifestyles, and were lonelier compared to higher SES quartiles (Table S4). The descriptive statistics per health outcome are listed in Table S5. Respondents with at least one chronic disease, poorer self-rated health, or a high risk for psychological distress were more often ((very) severely) lonely compared to their healthier counterparts.

Table 1. Sample characteristics (n = 445,748).

Variable		N (%)
Age	19–40	68,434 (15.4%)
	41–64	142,790 (32.0%)
	65–80	192,640 (43.2%)
	81+	41,884 (9.4%)
Gender	Male	204,095 (45.8%)
	Female	241,653 (54.2%)
Migration background	Dutch-born	389,298 (87.3%)
	Western background	38,445 (8.6%)
	Non-Western background	18,005 (4.1%)
Marital status	Married/co-habitant	313,285 (70.9%)
	Single	45,853 (10.4%)
	Widowed	30,593 (6.9%)
	Divorced	51,877 (11.7%)
Education	Primary school	30,981 (7.5%)
	Lower vocational	138,947 (33.5%)
	Middle vocational/secondary	125,981 (30.4%)
	Higher vocational/university	118,985 (28.7%)
Household income quartile	0–25%	64,825 (14.6%)
	26%–50%	122,251 (27.5%)
	51%–75%	125,196 (28.1%)
	76%–100%	132,739 (29.8%)
Self-reported income adequacy	Inadequate, major concerns	12,367 (3.0%)
	Inadequate, some concerns	43,640 (10.5%)
	Adequate, minor concerns	146,380 (35.1%)
	Adequate, no concerns	215,147 (51.5%)
SES Construct	Q1, lowest SES	103,316 (25.1%)
	Q2	102,502 (24.9%)
	Q3	103,322 (25.1%)
	Q4, highest SES	102,697(24.9%)
Physical activity	Sufficient	288,523 (70.1%)
	Insufficient	122,855 (29.9%)
Body Mass Index (BMI)	Underweight (<18.5)	5,410 (1.3%)
	Normal (18.5–25)	190,365 (44.8%)
	Overweight (25–30)	164,653 (38.8%)
	Obese (30>)	64,431 (15.2%)

table continues

Variable		N (%)
Alcohol consumption	Never	47,286 (11.4%)
	Regular consumption	335,675 (80.9%)
	Excessive	32,256 (7.8%)
Smoking	Never smoked	170,859 (40.6%)
	Former smoker	181,412 (43.2%)
	Current smoker	68,163 (16.2%)
Chronic disease	None	261,977 (59.9%)
	At least one	175,086 (40.1%)
Self-rated health	Fair, bad	125,043 (28.4%)
	(Very) good, excellent	315,079 (71.6%)
Psychological distress	No or low risk	411,536 (95.1%)
	High risk	21,362 (4.9%)
Mode of survey completion	Paper	221,433 (49.7%)
	Internet	223,657 (50.2%)
	Face-to-face	428 (0.1%)
	Telephone	230 (0.01%)
		Mean (sd)
Loneliness		3.1(2.9)

SES Construct: combination of education, household income quartile, and self-reported income adequacy. Self-reported variables: education, income adequacy, physical activity, BMI, alcohol consumption, smoking, loneliness, marital status, chronic disease, and self-rated health. Registry data variables: age, gender, migration background, and household income quartile.

Socioeconomic Status, Lifestyle, and Loneliness

The results of models 1–4 indicate that people with lower SES had higher odds of reporting the presence of at least one chronic disease, poor self-rated health, and a high risk for psychological distress (Table 2 and Figure 1). The differences between the SES groups were the largest for psychological distress, followed by self-rated health and chronic disease. That is, individuals in the lowest SES quartile had 8.93- times (95% CI 8.16–9.77) higher odds of reporting psychological distress, 3.26-times higher (3.17–3.35) odds of reporting poor health, and 1.75-times higher (1.72–1.79) odds of having at least one chronic disease. The RRs and ORs remained statistically significant for all SES quartiles in the complete model (model 4, adjusted for age, gender, migration background, marital status, SES, lifestyle-related factors, and loneliness). For example,

for the lowest SES quartile (Q1) the OR for high risk of psychological distress was 4.09 (3.72–4.51), for self-rated health the RR was 2.28 (2.21–2.34), and for chronic disease the RR was 1.45 (1.42–1.48), (Table 2).

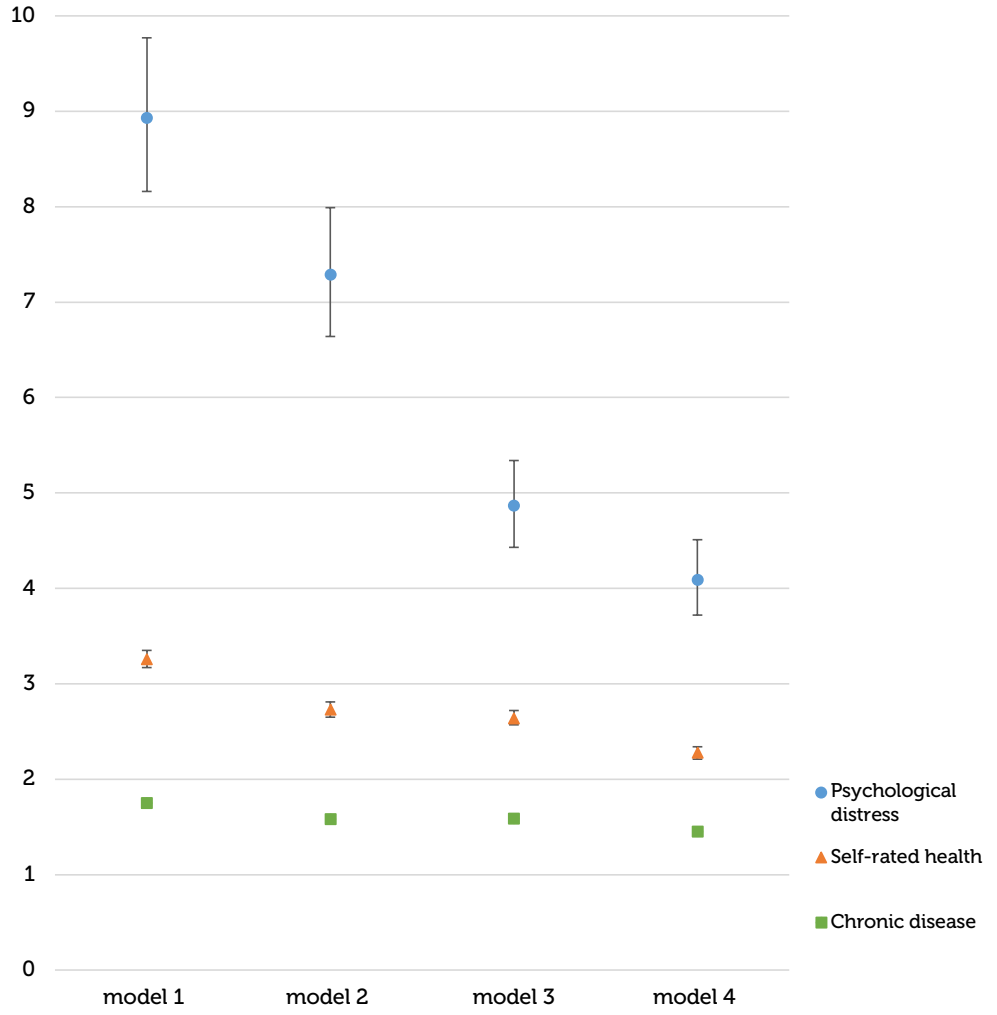

Figure 1. Odds ratios of having (1) high risk for psychological distress, (2) poor self-rated health, and (3) at least one chronic disease for individuals in the lowest SES group compared to the highest SES group. ORs (95% CI) (lowest SES group (Q1) vs. highest SES group (Q4)) in model 1 (demographic and SES factors), model 2 (demographic, SES factors, and loneliness), and model 3 (demographic, SES, lifestyle factors, and loneliness) for psychological distress (blue), self-rated health (orange), and chronic disease (green).

Table 2. Associations between socioeconomic groups and the three health outcomes, adjusted for demographic factors, lifestyle, and loneliness (n = 445,748).

RR/OR (95% CI) % Reduction	Model 1 (SES)	Model 2 (SES + Lifestyle-Related Factors)		Model 3 (SES + Loneliness)		Model 4 (SES + Lifestyle-Related + Loneliness)	
Chronic disease (RR)							
Q1 lowest SES	1.75 (1.72–1.79)	1.58 (1.55–1.61)	23%	1.59 (1.55–1.62)	21%	1.45 (1.42–1.48)	40%
Q2	1.30 (1.27–1.32)	1.22 (1.20–1.25)	27%	1.24 (1.21–1.26)	20%	1.17 (1.15–1.20)	43%
Q3	1.14 (1.11–1.16)	1.10 (1.07–1,13)	29%	1.11 (1.09–1.14)	21%	1.08 (1.05–1.11)	43%
Q4 highest SES	Ref	Ref		Ref		Ref	
Self-rated health (RR)							
Q1 lowest SES	3.26 (3.17–3.35)	2.73 (2.65–2.81)	23%	**2.64 (2.57–2.72)**	27%	2.28 (2.21–2.34)	43%
Q2	2.01 (1.94–2.07)	1.83 (1.78–1.89)	18%	**1.81 (1.76–1.87)**	20%	1.68 (1.63–1.73)	33%
Q3	1.46 (1.41–1.51)	1.39 (1.34–1.43)	15%	**1.39 (1.35–1.44)**	15%	1.33 (1.29–1.38)	28%
Q4 highest SES	Ref	Ref		Ref		Ref	
Psychological distress (OR)							
Q1 lowest SES	8.93 (8.16–9.77)	7.29 (6.64–7.99)	21%	4.87 (4.43–5.34)	51%	4.09 (3.72–4.51)	61%
Q2	3.24 (2.94–3.57)	2.94 (2.67–3.25)	13%	2.29 (2.07–2.53)	42%	2.12 (1.91–2.34)	50%
Q3	1.85 (1.67–2.05)	1.75 (1.58–1.94)	12%	1.58 (1.42–1.76)	32%	1.51 (1.36–1.68)	40%
Q4 highest SES	ref	ref		ref		Ref	

RR: risk ratio; OR: odds ratio; CI: confidence interval, all ORs significant at p-value < 0.01; SES construct: combination of standardized z-scores ($z(x) \frac{x-\text{mean}(x)}{\text{standard deviation}(x)}$) for education, household income, and income adequacy. All models were adjusted for age, gender, migration background, marital status, and the mode of survey completion. RR and OR percentage reductions were calculated as: $\left(\frac{(\text{OR Model1} - \text{OR Model2})}{(\text{OR Model1} - 1)} \times 100\right)$.

When chronic disease was the outcome, the RR for the lowest vs. highest SES group decreased by 21% with the addition of loneliness and 40% when the model was adjusted for lifestyle-related factors and loneliness (Table 2). Similarly, for self-rated health, the RR for individuals in the lowest SES quartile was reduced by 27% with the addition of loneliness. With both lifestyle-related factors and loneliness, the RR for the lowest (vs. highest) SES group was reduced by 43%, from 2.73 to 2.28. For psychological distress, loneliness accounted for a 51% reduction in the OR for the lowest vs. the highest SES group. Together, loneliness and lifestyle resulted in a reduction of 61% (Table 2 and Figure 1). As a robustness check, we ran our models with each of the SES variables separately, which yielded similar results, see Tables S6–S9.

Analyses in Age and Gender Strata

To assess whether sub-group analyses were warranted, interaction effects were tested between SES and age, gender, migration status, and marital status for all three outcomes. Interaction effects between SES and all four demographic factors were significant when chronic disease or self-rated health were an outcome. For psychological distress, interactions with age, gender, and migration status were observed. For gender and migration status, the direction and magnitude of the SES gradient, as well as the relative role of lifestyles and loneliness, remained similar compared to the general population (Tables S10 and S11). Loneliness had a slightly larger role in explaining the socioeconomic health gradient in single (24% for chronic disease and 31% for self-rated health) and divorced respondents (24% and 29%), compared to married (21% and 27%) and widowed respondents (22% for both outcomes) (Table S12). For the youngest age group (19–40 years old), loneliness was relatively more important in explaining socio-economic differences in self-rated health and psychological distress, compared to older adults. When accounting for loneliness, the difference between the lowest and highest SES group in self-rated health was reduced by 37% among young adults vs. 16% in the 80+ age category. For psychological distress, this difference was reduced by 55% and 27% for the youngest and oldest age group, respectively. See Table 3 for the results of model 3 (loneliness) in the complete sample and the four age groups, and Table S13 for the results of all age groups in all models.

Table 3. Associations for the complete sample and four age groups with the three health outcomes, adjusted for demographic factors, SES, and loneliness (model 3).

RR/OR (95% CI) (% reduction)	Complete sample (n = 445,748)		Age group 19–40 (n = 68,434)		Age group 41–64 (n = 142,790)		Age group 65–80 (n = 192,640)		Age group 81+ (n = 41,884)	
Chronic disease (RR)										
Q1 lowest SES	**1.59 (1.55–1.62)**	21%	**1.83 (1.72–1.95)**	27%	**1.73 (1.68–1.79)**	22%	**1.27 (1.25–1.30)**	21%	**1.10 (1.06–1.15)**	29%
Q2	**1.24 (1.21–1.26)**	20%	**1.29 (1.20–1.37)**	26%	**1.29 (1.25–1.33)**	17%	**1.08 (1.06–1,10)**	27%	1.00 (0.96–1.04)	
Q3	**1.11 (1.09–1.14)**	21%	**1.12 (1.05–1.20)**	25%	**1.15 (1.11–1.19)**	12%	1.01 (0.99–1.04)		0.99 (0.95–1.03)	
Q4 highest SES	Ref		ref		Ref		ref		ref	
Self-rated health (RR)										
Q1 lowest SES	**2.64 (2.57–2.72)**	27%	**2.95 (2.70–3.23)**	37%	**2.96 (2.83–3.09)**	28%	**2.11 (2,05–2.18)**	20%	**1.53 (1.46–1.61)**	16%
Q2	**1.81 (1.76–1.87)**	20%	**1.88 (1.71–2.06)**	27%	**1.90 (1.81–1.99)**	18%	**1.56 (1.51–1.61)**	14%	**1.29 (1.22–1.35)**	9%
Q3	**1.39 (1.35–1.44)**	15%	**1.43 (1.29–1.58)**	19%	**1.43 (1.36–1.50)**	12%	**1.25 (1.21–1.29)**	14%	**1.17 (1.10–1.23)**	6%
Q4 highest SES	Ref		ref		Ref		ref		ref	
Psychological distress (OR)										
Q1 lowest SES	**4.87 (4.43–5.34)**	51%	**3.92 (3.32–4.61)**	55%	**5.83 (5.09–6.67)**	51%	**5.18 (4.48–5.98)**	40%	**4.95 (3.86–6.33)**	27%
Q2	**2.29 (2.07–2.53)**	42%	**2.06 (1.73–2.47)**	64%	**2.52 (2.18–2.91)**	40%	**2.32 (2.00–2.70)**	32%	**2.72 (2.11–3.51)**	18%
Q3	**1.58 (1.42–1.76)**	32%	**1.49 (1.24–1.79)**	36%	**1.64 (1.41–1.90)**	29%	**1.66 (1.40–1.96)**	27%	**1.65 (1.22–2.23)**	21%
Q4 highest SES	ref		Ref		Ref		ref		ref	

RR: risk ratio; OR: odds ratio; CI: confidence interval; SES construct: combination of standardized z-scores ($z(x)=\frac{x-\text{mean}(x)}{\text{standard deviation}(x)}$) for education, household income, and income adequacy. All models are adjusted for gender, migration background, marital status, and the mode of survey completion. RR and OR percentage reductions were calculated as: $\left(\frac{(\text{OR Model1}-\text{OR Model2})}{(\text{OR Model1}-1)}\times 100\right)$. RR's and ORs with $p < 0.05$ are presented in bold.

Discussion

The aims of this study were to (1) assess the relative contribution of loneliness to the association between SES and chronic disease, self-rated health, and psychological health and (2) explore whether the interplay between loneliness, socio-economic status, and health is different across population subgroups divided by age, gender, migration background, and marital status. We observed that loneliness can further explain the socio-economic gradients in health, independent of lifestyle, demographics, and migration background. In other words, our findings suggest that low-SES individuals are more often lonely, which could partially explain why they report poorer health. Importantly, in young adults the role of loneliness in socioeconomic health inequalities was more pronounced compared to that observed in older people. To our knowledge, our study is the first to quantify the relative contribution of loneliness to socio-economic gradients across a range of important health outcomes.

In line with previous research, loneliness was found to be associated with poorer physical [12,22] and mental health [12,23,25]. In addition to these known associations, this study showed that loneliness can be seen as an additional pathway between SES and health, independent of demographic and lifestyle factors. Building on an age-normative perspective [20], this study found that loneliness accounted for relatively larger socioeconomic health inequalities for younger people.

Our findings could inform public health policies about the independent contribution of loneliness beyond the well-documented factors, in search of new modifiable social determinants to tackle inequalities. Public health policies aiming to reduce the health gradient could benefit from recognizing loneliness as a potential pathway from socio-economic disadvantage to poor health. So far, EU public health policy has focused on reducing the health gap by promoting healthy lifestyles in terms of nutrition, physical activity, alcohol, tobacco, and drug consumption, without specifically mentioning loneliness or other social factors [46]. In 2013, Mackenbach et al. assessed the 10 major contributors to health gains with the aim of evaluating European public health policies, and loneliness was not considered among the major contributors [47]. In the Netherlands, policies that have been introduced in the past decades to reduce socioeconomic health inequalities were mostly focused on lifestyle, with an emphasis on individual responsibility [48]. One of the most recent health policies, the National Prevention Agreement, focuses on three major lifestyle factors—smoking, overweight, and excessive alcohol consumption [49]. These policies are mainly focused on individual change, as are most common interventions targeting loneliness, for example, befriending interventions, educational programs, leisure or skills development

programs, psychological therapy, and social facilitations. [50] However, loneliness may also be targeted with more upstream policies by targeting other 'causes of the causes' [1]. These policies would be implemented on a population level by addressing unequal opportunities and social exclusionary processes related to proper employment, education, public spaces, and housing and neighborhood conditions, as part of the third and fourth levels of Dahlgren and Whitehead's determinants of health [10]. The UK appears to be one of the few countries integrating loneliness into public health policy-making for the general population, with a Minister for Loneliness appointed in January 2018, and its first cross-government loneliness strategy released in October of that year.

Current national policies that do target loneliness focus mainly on elderly populations [51]. One of the strengths of this study is that the large sample allowed us to explore differences between subpopulations and revealed the relative importance of loneliness in the context of health inequalities in the youngest age group. If elderly populations might to some extent be more accepting of feelings of loneliness as part of their life phase, in line with the age-normative perspective [20], younger-aged low-SES groups may struggle more with loneliness in their overall well-being. This could imply that public health policies targeting loneliness may benefit from expanding the target group to include younger adults. The UK strategy is not focused on older age groups only as, for example, it also aims to embed the remediation of loneliness into primary and secondary school classes. By 2023, all general practitioners in the UK will refer lonely or socially isolated patients to 'community activities and voluntary services' [52]. While the effects of these policies remain to be seen, evidence points at potential benefits of integrating social factors into public health agendas to offer opportunities to level socioeconomic inequalities in diverse population groups.

Although this study accounted for loneliness to help further explain socio-economic inequalities beyond demographic and lifestyle factors, part of the health gap still remains. The risk ratios between the lowest and highest SES groups remained 1.45 for chronic disease, 2.28 for self-rated health, and 4.09 for psychological distress. Other individual (e.g., genetic) and environmental factors (e.g., housing or neighborhood environment) [53] could explain socioeconomic health differences further. Future research should explore the role of loneliness in the context of these other individual and environmental factors on the pathway from socioeconomic disadvantage to poor health.

Our findings should be interpreted in view of a few limitations. First, the cross-sectional design hinders the drawing of any causal inferences. Future research with a longitudinal design is warranted to explore the causal relationships and direction of

the relationships between loneliness, SES, and health. Second, the Health Survey might suffer from selection bias, as the most socially disadvantaged individuals tend not to participate in survey research [54]. Despite deliberate oversampling of disadvantageous groups by the Health Survey, only 12.8% of the respondents belonged to the lowest income quartile. Similarly, only 12.1% of the respondents had a migration background, as opposed to the national average of 22.1% in 2016 [55], possibly because the Health Survey is administered in Dutch only. Though the analyses used weighted data to balance out underrepresented groups, the associations of loneliness and SES health inequalities reported in this study are likely to represent a conservative estimate. Third, although health was operationalized in three ways that captured various dimensions of the concept, each operationalization used only a single indicator as a dependent variable in our models. Future research should explore multiple indicators for each operationalization of health, as well as different ways of operationalizing health. For example, the presence of at least one chronic disease as an outcome does not distinguish the type of the disease. Different types of chronic diseases may be associated differently with SES, lifestyle-related factors, and loneliness. For example, diabetes, respiratory, and cardiac diseases may be more related to SES and lifestyle-related factors, whereas mental diseases may be more strongly related to SES and loneliness. In this study, socioeconomic health inequalities were more pronounced in psychological and self-rated health compared to the presence of chronic disease(s), which may be attributed to the fact that self-rated health and psychological health are a more sensitive proxy to well-being than the presence of at least one chronic condition. These differences remain to be explored in future research.

Conclusions

In conclusion, our findings revealed that loneliness is independently associated with socioeconomic inequalities on top of demographic and lifestyle-related factors. While current public health policies tend to focus predominantly on lifestyle and address loneliness specifically in elderly populations, our results suggest that public health policies may benefit from more integrated approaches. In addition to lifestyle interventions, tackling loneliness, especially for youth, has the potential to reduce socioeconomic health inequalities.

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Appendix 1

Table S1. Categories, operationalization, and sources of dependent and independent variables

Variable	Category	Coded	Source
Age	19-40	0	Statistics Netherlands
	41-64	1	Statistics Netherlands
	65-80	2	Statistics Netherlands
	81+	3	Statistics Netherlands
Sex	male	0	Statistics Netherlands
	female	1	Statistics Netherlands
Migration status	Dutch born	0	Statistics Netherlands
	Western migration background	1	Statistics Netherlands
	Non-western migration background	2	Statistics Netherlands
Marital status	married or living together	0	Health survey
	single	1	Health survey
	divorced	2	Health survey
	widowed	3	Health survey
Education	Primary school	3	Health survey
	Lower vocational	2	Health survey
	Middle vocational/ secondary	1	Health survey
	Higher vocational/ university	0	Health survey
Household income quartile	0-25%	3	Statistics Netherlands
	26-50%	2	Statistics Netherlands
	51-75%	1	Statistics Netherlands
	76-100%	0	Statistics Netherlands
Self-reported income adequacy	Inadequate, major concerns	3	Health survey
	Inadequate, some concerns	2	Health survey
	Adequate, minor concerns	1	Health survey
	Adequate, no concerns	0	Health survey
Physical activity	Insufficient	1	Health survey
	Sufficient	0	Health survey
Body Mass Index (BMI)	Underweight (<18,5)	1	Health survey
	Normal (18,5-25)	0	Health survey
	Overweight (25-30)	2	Health survey
	Obese (30>)	3	Health survey

table continues

Variable	Category	Coded	Source
Alcohol consumption	Never	0	Health survey
	Regular consumption	1	Health survey
	Excessive	2	Health survey
Smoking	Never smoked	0	Health survey
	Former smoker	1	Health survey
	Current smoker	2	Health survey
Loneliness	Score 0-11	n/a	Health survey
Chronic disease	None	0	Health survey
	At least one	1	Health survey
Self-rated health	(very) good, excellent	0	Health survey
	fair, bad	1	Health survey
Psychological distress	No or low risk (score 10-29)	0	Health survey
	High risk (score 30-50)	1	Health survey
Mode of survey completion	Paper	0	Health survey
	Internet	1	Health survey
	Face-to-face interview	2	Health survey
	Telephone interview	3	Health survey

Table S2. Goodness-of-fit tests per health outcome and model.

Health outcome	Goodness-of-fit test	Model 1		Model 2		Model 3		Model 4	
		F	p-value	F	p-value	F	p-value	F	p-value
Chronic disease	Deviance	280641	1.00	243286.9	1.00	271587.1	1.00	231737.3	1.00
	Pearson	242381.1	1.00	210064.2	1.00	237570.5	1.00	206915.2	1.00
Self-rated health	Deviance	256432.6	1.00	215575	1.00	239907.2	1.00	199533.8	1.00
	Pearson	289834.5	1.00	252750.8	1.00	280249	1.00	242259.9	1.00
Psycho-logical distress	Pearson	0.58	0.82	0.36	0.95	10.42	0.00*	7.80	0.00*

*goodness of fit statistics have been shown to be conservative in complex models in large sample sizes so these test statistics should be interpreted with caution.

Table S3. Variance Inflation Factors (VIF) per independent variable.

Variable	Category	VIF	1/VIF
Age	41-64	2.94	0.34
	65-80	3.78	0.26
	81+	1.64	0.61
Sex	n/a	2.06	0.49
Migration status	Western migration background	1.10	0.91
	Non-western migration background	1.13	0.89
Marital status	Single	1.32	0.76
	Divorced	1.15	0.87
	Widowed	1.39	0.72
SES Construct	Q1, lowest SES	2.10	0.48
	Q2	1.92	0.52
	Q3	1.88	0.53
Physical activity	Insufficient	1.46	0.68
Body Mass Index (BMI)	Underweight (<18,5)	1.03	0.97
	Overweight (25-30)	1.92	0.52
	Obese (30>)	1.40	0.71
Alcohol	Regular consumption	6.11	0.16
consumption	Excessive	1.59	0.63
Smoking	Former smoker	2.32	0.43
	Current smoker	1.49	0.67
Loneliness	n/a	2.05	0.49
Mode of survey completion	Internet	2.29	0.44
	Face-to-face interview	1.02	0.98
	Telephone interview	1.01	0.99

Table S4. Percentages of adverse health outcomes by SES quartile.

Category	Variables		SES Q1, lowest	SES Q2	SES Q3	SES Q4, highest	p-value
Outcome variables	Chronic disease	At least one	40%	36%	32%	30%	<0.01
	Self-rated health	Bad, fair	34%	26%	21%	18%	<0.01
	Psychological distress	High risk	7%	7%	6%	6%	<0.01
Lifestyle-related factors	Physical activity	Insufficient	35%	32%	34%	35%	<0.01
	Body Mass Index (BMI)	Overweight (BMI:25-30)	38%	36%	35%	33%	<0.01
		Obese (BMI>30)	18%	15%	13%	11%	
	Alcohol consumption	Excessive	7%	8%	7%	7%	<0.01
	Smoking	Former smoker	38%	35%	32%	30%	<0.01
		Current smoker	20%	22%	21%	20%	
Loneliness	Lonely	Some, severe, very severe	48%	44%	41%	40%	<0.01

SES Construct: combination of education, household income quartile and self-reported income adequacy. Based on weighted, multiple-imputed data.

Table S5. Percentages of unhealthy lifestyle behaviors and loneliness by health outcome.

			Chronic disease		Self-rated health		Psychological health		p-value
Category	**Variables**		**none**	**At least one**	**(very) good**	**fair, (very) bad**	**No or low risk**	**High risk**	
Lifestyle-related factors	**Physical activity**	Insufficient	33%	37%	31%	44%	33%	50%	<0.01
	Body Mass Index (BMI)	Overweight (BMI:25-30)	34%	40%	34%	37%	35%	32%	<0.01
		Obese (BMI>30)	10%	21%	10%	25%	13%	22%	
	Alcohol consumption	Excessive	7%	7%	7%	7%	7%	8%	<0.01
	Smoking	Former smoker	30%	40%	32%	37%	34%	26%	<0.01
		Current smoker	21%	21%	20%	25%	20%	36%	
Loneliness	**Lonely**	Some, severe, very severe	37%	53%	36%	65%	40%	87%	<0.01

Based on weighted, multiple-imputed data.

Tables S6-S8 separate SES measures.

Table S6. Associations between education, demographic, lifestyle-related factors, loneliness, and health outcomes (n = 445,748).

OR (95% CI) and % decrease	Model 1 (SES-model)	Model 2 (SES + Lifestyle)		Model 3 (SES + loneliness)		Model 4 (SES + lifestyle + loneliness)	
Chronic Disease							
Primary school	**1.49 (1.46-1.53)**	**1.30 (1.26-1.33)**	39%	**1.38 (1.34-1.41)**	22%	**1.22 (1.19-1.26)**	55%
Lower vocational	**1.27 (1.24-1.29)**	**1.16 (1.14-1.18)**	41%	**1.20 (1.18-1.23)**	26%	**1.11 (1.09-1.13)**	59%
Middle vocational/ secondary	**1.14 (1.12-1.16)**	**1.08 (1.06-1.10)**	43%	**1.11 (1.09-1.13)**	21%	**1.06 (1.04-1.08)**	57%
Higher vocational/ university	ref	ref		ref		ref	
Self-rated health							
Primary school	**2.51 (2.43-2.60)**	**1.97 (1.91-2.04)**	36%	**2.14 (2.07-2.21)**	25%	**1.76 (1.70-1.82)**	50%
Lower vocational	**1.92 (1.86-1.97)**	**1.66 (1.61-1.71)**	28%	**1.73 (1.68-1.77)**	21%	**1.53 (1.49-1.58)**	42%
Middle vocational/ secondary	**1.44 (1.40-1.48)**	**1.32 (1.29-1.36)**	27%	**1.36 (1.32-1.40)**	18%	**1.27 (1.23-1.31)**	39%
Higher vocational/ university	ref	ref		ref		ref	
Psychological distress							
Primary school	**4.83 (4.39-5.32)**	**3.54 (3.20-3.91)**	34%	**3.43 (3.11-3.78)**	37%	**2.69 (2.43-2.98)**	56%
Lower vocational	**2.60 (2.42-2.79)**	**2.13 (1.98-2.29)**	29%	**1.96 (1.82-2.11)**	40%	**1.68 (1.56-1.81)**	58%
Middle vocational/ secondary	**1.65 (1.54-1.77)**	**1.47 (1.37-1.58)**	28%	**1.41 (1.31-1.52)**	37%	**1.29 (1.19-1.38)**	55%
Higher vocational/ university	ref	Ref		ref		ref	

Based on weighted, multiple-imputed data. OR's in bold are significant, $p<0.05$

Table S7. Associations between household income quartile, demographic, lifestyle-related factors, loneliness and health outcomes (n = 445,748).

OR (95% CI) and % decrease	Model 1 (SES-model)	Model 2 (SES + Lifestyle)		Model 3 (SES + loneliness)		Model 4 (SES + lifestyle + loneliness)	
Chronic Disease							
0-25%	**1.56 (1.53-1.59)**	**1.44 (1.41-1.47)**	21%	**1.43 (1.40-1.46)**	23%	**1.34 (1.31-1.37)**	39%
26-50%	**1.30 (1.28-1.32)**	**1.22 (1.20-1.25)**	27%	**1.23 (1.21-1.26)**	23%	**1.17 (1.15-1.19)**	43%
51-75%	**1.13 (1.11-1.15)**	**1.10 (1.08-1.12)**	23%	**1.10 (1.08-1.12)**	23%	**1.07 (1.05-1.09)**	46%
76%-100%	ref	Ref		Ref		ref	
Self-rated health							
0-25%	**2.40 (2.34-2.47)**	**2.07 (2.01-2.12)**	24%	**2.01 (1.96-2.06)**	28%	**1.78 (1.73-1.83)**	44%
26-50%	**1.85 (1.80-1.89)**	**1.67 (1.63-1.71)**	21%	**1.65 (1.61-1.69)**	24%	**1.52 (1.48-1.55)**	39%
51-75%	**1.37 (1.34-1.41)**	**1.31 (1.27-1.34)**	16%	**1.30 (1.26-1.33)**	19%	**1.25 (1.22-1.28)**	32%
76%-100%	ref	ref		Ref		ref	
Psychological distress							
0-25%	**4.64 (4.29-5.02)**	**3.86 (3.57-4.17)**	21%	**2.94 (2.71-3.18)**	47%	**2.53 (2.33-2.74)**	58%
26-50%	**2.69 (2.49-2.91)**	**2.38 (2.21-2.57)**	18%	**1.96 (1.82-2.12)**	43%	**1.78 (1.65-1.93)**	54%
51-75%	**1.72 (1.58-1.86)**	**1.61 (1.49-1.75)**	15%	**1.44 (1.33-1.56)**	39%	**1.38 (1.27-1.50)**	47%
76%-100%	ref	ref		ref		ref	

Based on weighted, multiple-imputed data. OR's in bold are significant, p<0.05

Table S8. Associations between income adequacy, demographic, lifestyle-related factors, loneliness and health outcomes (n = 445,748).

OR (95% CI) and % decrease	Model 1 (SES-model)	Model 2 (SES + Lifestyle)		Model 3 (SES + loneliness)		Model 4 (SES + lifestyle + loneliness)	
Chronic disease							
Inadequate, major concerns	**2.17 (2.12-2.23)**	**1.96 (1.90-2.01)**	18%	**1.86 (1.81-1.91)**	26%	**1.71 (1.66-1.75)**	39%
Inadequate, some concerns	**1.66 (1.63-1.69)**	**1.55 (1.52-1.58)**	17%	**1.52 (1.49-1.55)**	21%	**1.44 (1.41-1.47)**	33%
Adequate, minor concerns	**1.29 (1.26-1.31)**	**1.24 (1.22-1.26)**	17%	**1.24 (1.22-1.26)**	17%	**1.20 (1.19-1.22)**	31%
Adequate, no concerns	ref	ref		ref		Ref	
Self-rated health							
Inadequate, major concerns	**3.34 (3.24-3.44)**	**2.72 (2.64-2.81)**	26%	**2.42 (2.34-2.49)**	39%	**2.04 (1.98-2.11)**	56%
Inadequate, some concerns	**2.35 (2.30-2.41)**	**2.08 (2.03-2.13)**	20%	**1.95 (1.90-2.00)**	30%	**1.77 (1.72-1.81)**	43%
Adequate, minor concerns	**1.56 (1.53-1.59)**	**1.47 (1.44-1.50)**	16%	**1.44 (1.42-1.47)**	21%	**1.38 (1.35-1.40)**	32%
Adequate, no concerns	ref	ref		ref		ref	
Psychological distress							
Inadequate, major concerns	**14.24 (13.10-15.48)**	**11.45 (10.48-12.51)**	21%	**6.72 (6.15-7.36)**	57%	**5.62 (5.12-6.18)**	65%
Inadequate, some concerns	**4.82 (4.48-5.18)**	**4.25 (3.95-4.58)**	15%	**2.89 (2.67-3.11)**	51%	**2.62 (2.42-2.84)**	58%
Adequate, minor concerns	**2.13 (1.99-2.28)**	**2.02 (1.89-2.17)**	10%	**1.68 (1.57-1.80)**	40%	**1.62 (1.51-1.73)**	45%
Adequate, no concerns	ref	ref		ref		ref	

Based on weighted, multiple-imputed data. OR's in bold are significant, $p<0.05$

Table S9 SES measures modelled simultaneously.

Table S9. Associations between SES, demographic, lifestyle-related factors, loneliness, and health outcomes (n = 445,748).

OR (95% CI) and % decrease	Model 1 (SES-model)	Model 2 (SES + Lifestyle)		Model 3 (SES + loneliness)		Model 4 (SES + lifestyle + loneliness)	
Chronic Disease							
Education							
primary school	**1.26 (1.23-1.30)**	**1.15 (1.11-1.18)**	42%	**1.22 (1.18-1.25)**	15%	**1.12 (1.08-1.15)**	54%
lower vocational	**1.13 (1.11-1.15)**	**1.06 (1.04-1.08)**	54%	**1.10 (1.08-1.13)**	23%	**1.05 (1.02-1.07)**	62%
middle vocational/ secondary	**1.06 (1.04-1.08)**	**1.02 (1.00-1.04)**	67%	**1.05 (1.03-1.07)**	17%	1.01 (0.99-1.03)	83%
Higher vocational/ university	Ref	Ref		Ref		Ref	
Household income quartile							
0-25%	**1.18 (1.15-1.21)**	**1.16 (1.13-1.19)**	11%	**1.15 (1.12-1.18)**	17%	**1.13 (1.10-1.16)**	28%
26-50%	**1.08 (1.06-1.10)**	**1.06 (1.04-1.08)**	25%	**1.06 (1.04-1.09)**	25%	**1.05 (1.03-1.07)**	38%
51-75%	**1.03 (1.01-1.05)**	**1.02 (1.00-1.04)**	33%	**1.02 (1.01-1.04)**	33%	1.02 (0.99-1.04)	33%
76% - 100%	Ref	ref		Ref		Ref	
Income adequacy							
Inadequate, major concerns	**1.95 (1.90-2.01)**	**1.82 (1.76-1.87)**	14%	**1.71 (1.66-1.76)**	25%	**1.61 (1.56-1.66)**	36%
Inadequate, some concerns	**1.54 (1.51-1.57)**	**1.47 (1.44-1.51)**	13%	**1.44 (1.40-1.47)**	19%	**1.38 (1.35-1.41)**	30%
Adequate, minor concerns	**1.23 (1.21-1.25)**	**1.21 (1.19-1.23)**	9%	**1.20 (1.18-1.22)**	13%	**1.18 (1.16-1.20)**	22%
Adequate, no concerns	ref	ref		Ref		ref	

table continues

OR (95% CI) and % decrease	Model 1 (SES-model)	Model 2 (SES + Lifestyle)		Model 3 (SES + loneliness)		Model 4 (SES + lifestyle + loneliness)	
Self-rated health							
Education							
primary school	**1.88 (1.81-1.95)**	**1.59 (1.53-1.65)**	33%	**1.74 (1.68-1.81)**	16%	**1.51 (1.45-1.56)**	42%
lower vocational	**1.55 (1.51-1.59)**	**1.41 (1.37-1.45)**	25%	**1.48 (1.44-1.52)**	13%	**1.36 (1.32-1.40)**	35%
middle vocational/ secondary	**1.25 (1.22-1.29)**	**1.19 (1.15-1.22)**	24%	**1.23 (1.19-1.26)**	8%	**1.17 (1.13-1.20)**	32%
Higher vocational/ university	ref	ref		Ref		Ref	
Household income quartile							
0-25%	**1.43 (1.39-1.47)**	**1.38 (1.34-1.42)**	12%	**1.35 (1.31-1.39)**	19%	**1.31 (1.27-1.35)**	28%
26-50%	**1.27 (1.24-1.31)**	**1.25 (1.21-1.28)**	7%	**1.23 (1.20-1.27)**	15%	**1.21 (1.18-1.24)**	22%
51-75%	**1.14 (1.11-1.17)**	**1.13 (1.10-1.16)**	7%	**1.12 (1.09-1.15)**	14%	**1.11 (1.08-1.14)**	21%
76% - 100%	Ref	ref		Ref		Ref	
Income Adequacy							
Inadequate, major concerns	**2.61 (2.53-2.70)**	**2.28 (2.20-2.35)**	20%	**1.99 (1.93-2.05)**	39%	**1.78 (1.72-1.83)**	52%
Inadequate, some concerns	**1.95 (1.90-2.01)**	**1.81 (1.76-1.86)**	15%	**1.68 (1.64-1.72)**	28%	**1.58 (1.54-1.62)**	39%
Adequate, minor concerns	**1.39 (1.36-1.42)**	**1.35 (1.32-1.38)**	10%	**1.31 (1.29-1.34)**	21%	**1.28 (1.25-1.31)**	28%
Adequate, no concerns	ref	ref		ref		ref	
Psychological distress							
Education							
primary school	**3.04 (2.74-3.37)**	**2.49 (2.24-2.77)**	27%	**2.57 (2.31-2.85)**	23%	**2.19 (1.97-2.44)**	42%
lower vocational	**1.81 (1.68-1.95)**	**1.62 (1.50-1.74)**	23%	**1.55 (1.44-1.68)**	32%	**1.42 (1.31-1.53)**	48%
middle vocational/ secondary	**1.28 (1.19-1.38)**	**1.20 (1.12-1.29)**	29%	**1.18 (1.10-1.28)**	36%	**1.12 (1.04-1.21)**	57%
Higher vocational/ university	ref	ref		Ref		Ref	

table continues

OR (95% CI) and % decrease	Model 1 (SES-model)	Model 2 (SES + Lifestyle)		Model 3 (SES + loneliness)		Model 4 (SES + lifestyle + loneliness)	
Household income quartile							
0-25%	**1.71 (1.57-1.87)**	**1.63 (1.49-1.78)**	11%	**1.43 (1.31-1.57)**	39%	**1.38 (1.26-1.51)**	46%
26-50%	**1.39 (1.28-1.51)**	**1.36 (1.25-1.47)**	8%	**1.22 (1.12-1.33)**	44%	**1.20 (1.10-1.31)**	49%
51-75%	**1.25 (1.15-1.35)**	**1.23 (1.13-1.34)**	8%	**1.15 (1.06-1.25)**	40%	**1.14 (1.05-1.24)**	44%
76% - 100%	ref	ref		Ref		Ref	
Income Adequacy							
Inadequate, major concerns	**10.22 (9.36-11.17)**	**8.92 (8.11-9.76)**	14%	**5.41 (4.93-5.95)**	52%	**4.80 (4.36-5.30)**	59%
Inadequate, some concerns	**3.75 (3.47-4.04)**	**3.49 (3.23-3.77)**	9%	**2.45 (2.26-2.66)**	47%	**2.32 (2.13-2.52)**	52%
Adequate, minor concerns	**1.83 (1.71-1.96)**	**1.79 (1.67-1.92)**	5%	**1.52 (1.42-1.64)**	37%	**1.50 (1.39-1.61)**	40%
Adequate, no concerns	ref	ref		ref		Ref	

Based on weighted, multiple-imputed data. OR's in bold are significant, $p<0.05$

Chapter 3

Does loneliness have a cost? A population-wide study of the association between loneliness and healthcare expenditure

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Abstract

Objectives

Loneliness has been associated with unhealthy behavior, poorer health, and increased morbidity. However, the costs of loneliness are poorly understood.

Methods

Multiple sources were combined into a dataset containing a nationally representative sample (*n* = 341,376) of Dutch adults (18+). The association between loneliness and total, general practitioner (GP), specialized, pharmaceutical, and mental healthcare expenditure was tested using Poisson and Zero-inflated negative binomial models, controlling for numerous potential confounders (i.e., demographic, socioeconomic, lifestyle-related factors, self-perceived health, and psychological distress), for four age groups.

Results

Controlling for demographic, socioeconomic, and lifestyle-related factors, loneliness was indirectly (via poorer health) associated with higher expenditure in all categories. In fully adjusted models, it showed a direct association with higher expenditure for GP and mental healthcare (0.5 and 11.1%, respectively). The association with mental healthcare expenditure was stronger in younger than in older adults (for ages 19–40, the contribution of loneliness represented 61.8% of the overall association).

Conclusion

Loneliness contributes to health expenditure both directly and indirectly, particularly in younger age groups. This implies a strong financial imperative to address this issue.

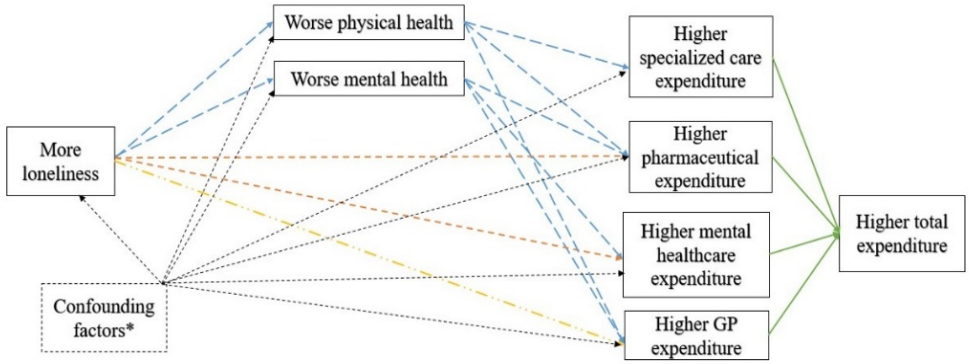
Introduction

In recent years, loneliness has become a growing public health issue. Approximately 10% of European citizens (18+) feel left out of society and the problem is greater for unemployed and low-income groups [1]. While most modern Western societies perceive loneliness as a problem of old age [2], it is a growing problem in younger age groups [2, 3]. Extensive research has related poor health to loneliness [4], and conversely, loneliness to unhealthy behaviors [3, 5], worse physical [6-10] and mental health [3, 10], and increased morbidity and mortality [10]. In addition to the social effects of loneliness, it can thus also have a considerable impact on the ever-increasing healthcare costs of most Western countries [11]. While it is imperative for well-informed policy decisions, such economic consequences of loneliness remain poorly understood.

Despite the growing awareness of loneliness as a health issue [1] and the increasing pressure on healthcare resources, research on the healthcare costs that could be attributed to loneliness is scarce. A recent review by Mihalopoulos et al (2019) identified 12 relevant studies conducted in the last 10 years [12]. Four of these studies were cost of illness studies, which assessed various combinations of inpatient, outpatient, medical, non-medical (residential care, social services, administrative costs), or indirect costs (informal care) associated with loneliness in older adults [13-16]. While most of these found that loneliness was associated with excess healthcare costs, one reported that it is associated with lower inpatient healthcare expenditure, suggesting that loneliness might act as a barrier to accessing healthcare [16]. Four economic evaluation studies reported that interventions addressing loneliness may provide good value for money [12]. Another five return on investment studies of loneliness interventions studied various non-monetary values, making results difficult to compare and validate [12]. While some evidence thus suggests that lonely older people do have higher health care costs, little is known about other population groups [12]. Furthermore, most studies focused on a limited amount of expenditure categories (e.g. only inpatient hospital care), control for a limited amount of confounding variables, and utilize relatively small samples [12].

The present study addresses the question “what is the relation between loneliness and healthcare expenditure?” using a large, nationally representative, sample of the general adult (18+) population. We strive to understand the association with health expenditures in the context of a broad range of potential confounding variables that are known to have an association with healthcare expenditure. As the impact of loneliness might differ between age groups and expenditure categories, we investigate the association between loneliness and general practitioner (GP), pharmaceutical, mental healthcare,

specialized, and total curative healthcare expenditure in four different age groups (i.e. 19-40, 41-64, 65-80, and 81 years and older). Given the relation between loneliness and worse physical [6-10] and mental health [3, 10], we expect that loneliness is indirectly (i.e. through poorer health) associated with higher expenditure in all expenditure categories (hypothesis 1). Furthermore, we expect loneliness to be directly associated with higher a) mental healthcare and b) pharmaceutical expenditure (hypothesis 2a-b) because individuals could perceive loneliness as a mental health condition in itself, which can be treated by a mental healthcare provider or using pharmaceuticals. Additionally, lonely individuals may visit easily accessible and free-of-charge GP's more often in search of social interactions [17]. Therefore, we expect loneliness to be directly associated with higher GP expenditure (hypothesis 3). Lonely individuals of older age may lack support networks and thus seek relief for their loneliness through increased contacts with their GP's, as opposed to their younger counterparts. Therefore, we expect differences in the associations between loneliness and GP expenditures between age groups (hypothesis 3a). For other costs categories, no a priori hypothesis was made for directions of differences by age as prior research is scarce. Explorative analyses will be undertaken. Lastly, we expect that the net effect of the previous hypotheses will result in a direct and an indirect increase of total healthcare expenditure (hypothesis 4). The hypothesized relationships in this study are visualized in Figure 1. The results of our work should provide insight to public health policy-makers who seek to understand the impact of loneliness on healthcare expenditure and economic aspects of programs targeting at alleviating loneliness.



Hypothesis 1: loneliness is indirectly related to higher expenditure through poorer physical and mental health (blue arrows)
Hypothesis 2a and b: loneliness is directly related to higher pharmaceutical and mental healthcare expenditure (orange arrows)
Hypothesis 3: loneliness is directly related to higher GP expenditure (yellow arrow)
Hypothesis 4: net effect of the previous hypotheses will result in a direct and an indirect increase of total healthcare expenditure (green arrows)

* Confounding factors considered in this study are age, gender, migration background, marital status, education, income level, and income inadequacy.

Figure 1. Hypothesized relationships between loneliness and healthcare expenditures.

Methods

Setting

We use a time-lagged design to study associations between loneliness and healthcare expenditure in the Netherlands in 2016 and 2017. Roughly, 31 billion euros were spent on curative care through compulsory health insurance schemes in the country in 2016 [18]. This amounts to approximately €1800 per capita, or 4.3% of the Dutch GDP, ranking the Netherlands 13th of the 32 OECD countries on curative health expenditure [18]. Dutch citizens are insured for general practitioner (GP) services, specialized care, pharmaceuticals, and mental healthcare amongst others through compulsory basic health insurance [19].

Data sources and linkage

Our dataset combines individual-level data from two sources covering the year 2016 and one source covering 2017. Firstly, we used the *Health Survey of the Public Health Service 2016*. It is a nationwide survey completed every four years by adults aged 19 years and older (n=457,150). It covers various subjects including socioeconomic status (SES), social contacts, lifestyle, and general (physical and mental) health [20]. It is completed by either paper and pencil, internet, telephone or face-to-face interviews. Secondly, we used data provided by *Statistics Netherlands for 2016*. These data included two administrative databases: the Personal Records Database (PRB) and the Dutch Tax and Customs Administration data. The PRB is managed by municipalities and provided information about citizen's age, gender, and migration background. The Dutch Tax and Customs Administration data provided income records for each citizen, for both the personal and household level. Thirdly, we used the 2017 *Dutch healthcare claims dataset* provided by Vektis, the healthcare information center. It is a national dataset of reimbursed individuals' claims covered by the basic insurance package in a given year. These data have previously been used to explore associations of neighborhood disadvantage with healthcare expenditure [21]. All datasets were linked via pseudonymized personal social security codes in the secured environment of Statistics Netherlands. After data linkage, our sample included 341,376 respondents.

Measures

Dependent variables

We used five dependent variables. These are 1) GP, 2) mental healthcare, 3) pharmaceutical, 4) specialized healthcare, and 5) total healthcare expenditure for the year 2017. Total healthcare expenditure is the sum of all expenditure individuals incurred under the basic health insurance plan. This includes expenditure for primary care, mental health care, pharmaceutical care, and hospital care (these four accounted for 88% of

total expenditure in 2017), as well as several smaller expenditure categories such as dental-, paramedic-, obstetric-, geriatric-, cross-border care, and ambulance costs [19]. In the Netherlands, GP expenditure consists of an annual enrolment fee per individual and a fee-for-service component. We use the fee-for-service component as our GP expenditure variable (i.e. expenditure associated with GP consultations). Specialized care expenditure include expenditure for specialized in-patient and outpatient clinics including in-hospital medication and excluding mental health hospitals. Pharmaceutical expenditure includes all prescription pharmaceuticals provided outside the hospital. Mental healthcare expenditure includes expenditure for basic and specialized (long and short-term) mental health services care in ambulatory or hospital settings.

Independent variable

The main factor of interest in this study is loneliness, a self-reported measure based on the 11-item de Jong Gierveld scale [22], taken from the Health Survey. Work by van Tilburg & de Jong Gierveld [23] based cutoff scores on individual's self-assessed level on loneliness in order to keep cutoff scores more in line with individuals own perception rather than arbitrary cutoff scores. Loneliness is subsequently categorized as follows: "not lonely" (scores between 0 and 2, reference group), "somewhat lonely" (scores between 3 and 8), "severe loneliness" (scores of 9 or 10), and "very severe loneliness" (score of 11).

Potential confounders

Potential confounders included demographic, SES, lifestyle-related factors and general health measures. The *demographic factors* were age (19-40 as the reference group, 41-64, 65-80, and 81 years and older), gender (binary variable with male as the reference group), migration background (Dutch-born as the reference group, western migration background, and non-western migration background), and marital status (self-reported as "living together or married" as the reference group, "single", "widowed", or "divorced"). The three former variables were taken from the BRP, while the latter was taken from the Health Survey. The *SES-variables* were individuals' highest level of completed education (higher vocational education or university degree as the reference group, secondary or middle vocational education, lower vocational education, and primary education), self-reported income adequacy ("adequate, no concerns" as the reference group, "adequate, minor concerns", "inadequate, some concerns", and "inadequate, major concerns"), and standardized household income based on the number of members in the household (divided it into quartiles based on the entire Dutch population, with highest quartile as reference group). The two former measures were taken from the Health Survey and the latter from the Dutch Tax Authority.

The *lifestyle-related factors* include Body Mass Index (BMI), alcohol consumption, smoking behavior, and physical activity level. These were all taken from the Health Survey and are self-reported measures. BMI was categorized in "normal" (between 18.5 and 25, reference group), "underweight" (less than 18.5), "overweight" (between 25 and 30), and "obese" (over 30) [24]. Alcohol consumption consists of three mutually exclusive categories; "never consuming alcohol" (reference group), "regular alcohol consumption", or "excessive alcohol consumption" (more than 21 alcoholic beverages a week for men and more than 14 for women). The norms for alcohol consumption are based on the guidelines by the Dutch Health Council. Smoking habits were categorized as "never smoked before" (reference group), "former smoker", and "current smoker". Physical activity was dichotomized as being sufficient (at least 30 minutes of reasonably intensive activity [like walking] per day for at least five days a week, or a minimum of 20 minutes intense activity [like running] per day for at least three days a week, reference group) or insufficient based on the Dutch Health Council's guidelines for sufficient physical activity [25].

General health indicators were also self-reported measures from the Health Survey: self-reported health, chronic disease, and psychological distress. Self-rated health was based on the following question; "*In general, would you say your health is …"*. Answer categories include "excellent", "very good", "good", "fair" and "poor". The measure was dichotomized as either "excellent, [very] good" health (reference group) or "fair or poor" health [26]. Having at least one chronic disease was based on the question "*Do you have one or more long-term diseases (expected duration 6 months or longer)".* Answers were either no (i.e. no chronic disease) (reference group) or yes (i.e. at least one chronic disease). Psychological distress was measured with the Kessler psychological distress scale (K10) [27]. The scores for these 10 questions were categorized as "none or low" (scores between 10 and 15, reference group), "moderate" (scores between 16 and 29), or "high" (scores between 30 and 50) psychological distress.

Lastly, as mode of completing the survey (internet, paper and pencil, telephone or face-to-face interviews) can impact the answers [28], it was adjusted for in each model.

Statistical Analyses

The survey sample was weighted to represent the overall Dutch population, based on age, gender, ethnicity and urbanization levels. The regression analyses accounted for survey design.

Healthcare expenditure data are often skewed and/or contain excessive zeros, requiring specific analytical approaches [29]. Vuong and Zero-Inflated Poisson likelihood-ratio

tests guided the choice of final model [30]. We consequently performed our analyses using Poisson (for total expenditure) and zero-inflated negative binomial (ZINB) regressions (for GP, specialized, pharmaceutical, and mental healthcare expenditure). In ZINB regressions, the output is two-fold. The first part provides the Incidence Rate Ratio (IRR) for non-zero expenditure, assuming a Poisson distribution. Second, the inflated part of the output represents the odds of incurring zero expenditure (vs any expenditure). For this study, the IRR represents the expected expenditure incurred for a lonely person (somewhat, severe or very severely lonely), divided by the expected expenditure incurred for a non-lonely person, accounting for covariates.

For each expenditure category, six models were computed by adding new covariates at each step. That is, expenditure were first modelled with loneliness as the only predictor in model 1. Next, demographic variables were added in model 2, SES variables were added in model 3, lifestyle variables were added in model 4, self-perceived health variables (self-rated health and chronic disease) were added in model 5, and the psychological distress variable was added in model 6, which represents the fully adjusted model. The mode of completing the survey was included in all models 1 through 6. To determine the need for subgroup analyses, we tested for interaction effects between loneliness and age in the different expenditure categories. Lastly, to estimate expenditure of loneliness, marginal expenditure estimates were obtained from the models with all covariates held constant at their average value. These were than extrapolated to the entire Dutch population for the year 2017. The significance level was set at alpha=5%. All analyses were performed in Stata 15 [31].

Results

Descriptive statistics

Table 1 reports the descriptive statistics. The mean (SD) age was 59.3 (16.9) years and 52.7% of the sample was female. The prevalence of loneliness was 41.8%, with 33.5% of the respondents experiencing some loneliness, 5.4% severe, and 2.9% very severe loneliness. Chronic diseases were reported at least once for 39.3% of the sample, and 26.1% reported their health as (very) bad or fair. Over half of the population reported none or low psychological distress (60.7%), 34.8% reported moderate, and 4.5% high psychological distress. Loneliness was prevalent in all age groups, however more common in older age groups. The prevalence of loneliness was 34.8% in 19-40 year-olds, 39.7% in 41-64 year-olds, 43.7% in 65-80 year-olds and 57.4% for respondents of 81 years and older, see Table 2.

Table 1. Sample characteristics (*n* = 341,376)

Sample Characteristics		N (%)
Age§	19-40	55,817 (16.4%)
	41-64	118,814 (34.8%)
	65-80	143,231 (42.0%)
	81+	23,514 (6.9%)
Gender§	Male	161,576 (47.3%)
	Female	179,800 (52.7%)
Migration background§	Dutch-born	300,426 (88.0%)
	Western migration background	28,697 (8.4%)
	Non-Western migration background	12,253 (3.6%)
Marital	Married/co-habitant	248,688 (72.8%)
status§	Single	36,338 (10.6%)
	Widowed	23,533 (6.9%)
	Divorced	32,817 (9.6%)
Migration background§	Dutch-born	300,426 (88.0%)
	Western migration background	28,697 (8.4%)
	Non-Western migration background	12,253 (3.6%)
Marital	Married/co-habitant	248,688 (72.8%)
status§	Single	36,338 (10.6%)
	Widowed	23,533 (6.9%)
	Divorced	32,817 (9.6%)
Education*	Primary school	19,897 (5.8%)
	Lower vocational	106,023 (31.1%)
	Middle vocational/ secondary	107,937 (31.6%)
	Higher vocational/ university	107,519 (31.5%)
Household income quartile§	0-25%	43,471 (12.7%)
	26-50%	86,582 (25.4%)
	51-75%	99,759 (29.2%)
	76-100%	111,564 (32.7%)
Self-reported income adequacy*	Inadequate, major concerns	9,690 (2.8%)
	Inadequate, some concerns	34,973 (10.2%)
	Adequate, minor concerns	117,764 (34.5%)
	Adequate, no concerns	178,949 (52.4%)
Physical activity*	Insufficient	96,417 (28.2%)
	Sufficient	244,959 (71.8%)

table continues

Sample Characteristics		N (%)
BMI*	Underweight (<18,5)	4,260 (1.2%)
	Normal (18,5-25)	155,082 (45.4%)
	Overweight (25-30)	131,625 (38.6%)
	Obese (30>)	50,409 (14.8%)
Alcohol	Never	33,799 (9.9%)
consumption*	Regular consumption	280,475 (82.2%)
	Excessive	27,102 (7.9%)
Smoking*	Never smoked	138,456 (40.6%)
	Former smoker	147,920 (43.3%)
	Current smoker	55,000 (16.1%)
Chronic	None	207,262 (60.7%)
disease*	At least one	134,114 (39.3%)
Self-rated	Excellent, (very) good	252,118 (73.8%)
health*	Fair, poor	89,258 (26.2%)
Psychological	None or low	207,079 (60.6%)
distress*	Moderate	1198,853 (34.8%)
	High	15,444 (4.6%)
Loneliness*	Not lonely	198,705 (58.2%)
	Somewhat lonely	114,428 (33.5%)
	Severely lonely	18,393 (5.4%)
	Very severely lonely	9,850 (2.9%)
Completing	Paper and pencil	149,630 (43.8%)
survey	Internet	191,249 (56.0%)
	Face-to-face	337 (0.1%)
	Telephone	160 (0.05%)

BMI: body mass index, GP: general practitioner. §Registry data variables *Self-reported variables extracted from Health Survey.

Table 2. Prevalence loneliness across age groups N (%)

	19-40	41-64	65-80	81+
Not lonely	36,383 (65.2%)	71,665 (60.3%)	80,639 (56.3%)	10,018 (42.6%)
Somewhat lonely	15,123 (27.1%)	36,985 (31.1%)	51,611 (36.0%)	10,709 (45.5%)
Severely lonely	2,870 (5.1%)	6,365 (5.4%)	7,228 (5.0%)	1,930 (8.2%)
Very severely lonely	1,441 (2.6%)	3,799 (3.2%)	3,753 (2.6%)	857 (3.6%)

Associations between loneliness and expenditure categories

Table 3 reports the associations of loneliness with different categories of healthcare expenditure. In models 1-4, loneliness is associated with higher expenditures, albeit with smaller (and in specialized care some non-significant) IRRs in models 4, partially confirming hypothesis 4. After controlling for all potential confounders (model 6, Table 3), loneliness was still directly associated with increased mental healthcare expenditure, confirming hypothesis 2a. That is, the IRR for loneliness categories ranged between 1.17 [1.04; 1.33] and 1.31 [1.08; 1.58], indicating higher expenditure in mental healthcare for lonely people compared to non-lonely people. Model 6 also indicates a small direct increase of GP expenditure for individuals reporting higher levels of loneliness (1.08 [1.04; 1.13]), in line with hypothesis 3. However, the association of very severe loneliness with pharmaceutical expenditure was no longer statistically significant (1.00 [0.85; 1.18]) in model 6, rejecting hypothesis 2b. The association between very severe loneliness and specialized care expenditure was negative in model 6 (i.e. IRR of 0.88 [0.80-0.97]).

Marginal expenditure of loneliness

Table 4 reports the point estimate of marginal spending of loneliness (in million €) for the different healthcare categories in 2016, with the corresponding 95% confidence interval, and the percentage of overall annual spending in each category. In the fully adjusted model (model 6), loneliness was associated with higher expenditure for mental and GP care (confirming hypothesis 2a and 3) but not for other expenditure categories. For GP expenditure, loneliness was associated with 5.8 million euros [4.5; 7.1], or 0.8% of the total annual GP spending (Table 4). For mental healthcare, loneliness was associated with 340.2 million euros [314.7; 365.8], or 10.3% of the annual mental healthcare spending. For total healthcare and specialized care expenditure, loneliness was associated with 1.0% (435.4 million euros [-494.8; -376.1]), and 2.0% (449.8 million [-474.3;-425.2]) fewer spending, rejecting hypothesis 4.

Table 3. Associations of loneliness with total healthcare, GP, specialized, pharmaceutical, and mental healthcare expenditure. Results from Poisson and Zero-inflated negative binomial regressions (n = 342,095).

	1. loneliness	2. demographic and loneliness	3. demographic, SES, and loneliness	4. demographic, SES, lifestyle, and loneliness	5. demographic, SES, lifestyle, self-perceived health, and loneliness	6. Total: demographic, SES, lifestyle, self-perceived health, psychological distress, and loneliness
Total expenditure	IRR (95%CI)	IRR 95% (CI)	IRR 95% (CI)	IRR 95% (CI)	IRR 95% (CI)	IRR 95% (CI)
Not lonely	ref	ref	ref	ref	ref	ref
Somewhat lonely	**1.38 (1.33-1.42)**	**1.24 (1.20-1.28)**	**1.17 (1.13-1.20)**	**1.14 (1.10-1.18)**	1.00 (0.97-1.03)	**0.96 (0.93-0.99)**
Severely lonely	**1.81 (1.72-1.92)**	**1.66 (1.57-1.76)**	**1.45 (1.37-1.53)**	**1.38 (1.31-1.46)**	1.04 (0.99-1.10)	0.96 (0.91-1.02)
Very severely lonely	**2.10 (1.95-2.25)**	**1.93 (1.80-2.08)**	**1.58 (1.47-1.70)**	**1.50 (1.39-1.61)**	1.05 (0.99-1.12)	0.94 (0.87-1.01)
GP expenditure						
Not lonely	ref	Ref	Ref	Ref	Ref	Ref
Somewhat lonely	**1.24 (1.22-1.25)**	**1.18 (1.16-1.19)**	**1.12 (1.11-1.14)**	**1.12 (1.10-1.13)**	**1.06 (1.05-1.08)**	**1.02 (1.01-1.04)**
Severely lonely	**1.53 (1.49-1.57)**	**1.45 (1.41-1.49)**	**1.32 (1.28-1.36)**	**1.30 (1.26-1.33)**	**1.16 (1.13-1.20)**	**1.07 (1.04-1.10)**
Very severely lonely	**1.72 (1.66-1.79)**	**1.65 (1.58-1.72)**	**1.43 (1.38-1.50)**	**1.41 (1.35-1.47)**	**1.22 (1.17-1.27)**	**1.08 (1.04-1.13)**
Specialized care expenditure						
Not lonely	ref	Ref	Ref	Ref	Ref	Ref
Somewhat lonely	**1.11 (1.06-1.16)**	1.05 (1.00-1.11)	1.01 (0.96-1.07)	1.01 (0.96-1.06)	**0.93 (0.88-0.98)**	**0.94 (0.90-0.98)**
Severely lonely	**1.24 (1.15-1.34)**	**1.25 (1.14-1.37)**	**1.15 (1.05-1.26)**	**1.12 (1.03-1.22)**	0.93 (0.85-1.00)	0.94 (0.87-1.02)
Very severely lonely	**1.26 (1.14-1.38)**	**1.26 (1.13-1.39)**	**1.12 (1.01-1.24)**	1.09 (0.98-1.20)	**0.87 (0.79-0.95)**	**0.88 (0.80-0.97)**
Not lonely	ref	Ref	Ref	Ref	Ref	Ref
Somewhat lonely	**1.39 (1.30-1.48)**	**1.30 (1.21-1.40)**	**1.21 (1.12-1.30)**	**1.18 (1.10-1.27)**	1.02 (0.97-1.07)	1.02 (0.96-1.07)
Severely lonely	**1.76 (1.58-1.99)**	**1.76 (1.52-2.04)**	**1.52 (1.31-1.76)**	**1.47 (1.26-1.71)**	1.05 (0.94-1.18)	1.04 (0.94-1.16)
Very severely lonely	**1.90 (1.71-2.12)**	**1.77 (1.58-1.99)**	**1.43 (1.28-1.60)**	**1.38 (1.23-1.55)**	1.01 (0.87-1.18)	1.00 (0.85-1.18)

table continues

	1. loneliness	2. demographic and loneliness	3. demographic, SES, and loneliness	4. demographic, SES, lifestyle, and loneliness	5. demographic, SES, lifestyle, self-perceived health, and loneliness	6. Total: demographic, SES, lifestyle, self-perceived health, psychological distress, and loneliness
Mental healthcare expenditure						
Not lonely	ref	Ref	Ref	Ref	Ref	Ref
Somewhat lonely	**1.40 (1.23-1.60)**	**1.35 (1.19-1.53)**	**1.29 (1.14-1.47)**	**1.26 (1.12-1.43)**	**1.21 (1.08-1.37)**	**1.17 (1.04-1.33)**
Severely lonely	**1.50 (1.26-1.79)**	**1.47 (1.25-1.73)**	**1.36 (1.17-1.57)**	**1.29 (1.12-1.48)**	**1.20 (1.04-1.37)**	1.09 (0.95-1.26)
Very severely lonely	**1.85 (1.49-2.29)**	**1.82 (1.44-2.31)**	**1.59 (1.34-1.97)**	**1.62 (1.33-1.97)**	**1.47 (1.22-1.78)**	**1.31 (1.08-1.58)**

Coefficients with p<0.05 are in bold. GP: general practitioner, IRR: incidence rate ratio, CI: confidence interval, SES: socioeconomic status. Inflated part reported in Appendix A1.

Table 4. Average marginal effects of loneliness for healthcare expenditure, extrapolated to entire Dutch 18+ population. Results from Poisson and Zero-inflated negative binomial regressions (n = 342,095).

Million € [95%CI] (% total category spending 2017)

A. model 6: fully adjusted model	Total expenditure	GP expenditure	Specialized care expenditure	Pharmaceutical expenditure	Mental healthcare expenditure
Somewhat lonely	-315.1 [-299.0; -331.2] (-0.7)	3.3 [3.0; 3.5] (0.5)	-314.4 [-289.0; -339.9] (-1.4)	13.7 [-4.4; 31.8] (0.3)	243.4 [235.9; 250.9] (7.4)
Severely lonely	-63.0 [-100.4; -25.6] (-0.1)	1.7 [1.2; 2.3] (0.2)	-69.2 [-97.2; -41.3] (-0.3)	6.0 [-7.7; 19.8] (0.0)	55.2 [48.5; 62.0] (1.7)
Very severely lonely	-57.3 [-95.3; -19.3] (-0.1)	0.9 [0.3; 1.4] (0.1)	-66.2 [-88.2; -44.2] (-0.3)	-1.2 [-14.3; 11.9] (0.1)	41.6 [30.3; 52.8] (1.3)
Total	**-435.4 [-494.7; -376.1] (-1.0)**	**5.8 [4.5; 7.1] (0.8)**	**-449.9. [-474.3; -425.4] (-2.0)**	**18.5 [-26.4; 63.4] (0.4)**	**340.2 [314.7; 365.8] (10.3)**

table continues

B. model 3: basic model + SES	Total expenditure	GP expenditure	Specialized care expenditure	Pharmaceutical expenditure	Mental healthcare expenditure
Somewhat lonely	1,273.2 [1,248.1; 1,298.5] (3.0)	17.8 [19.2; 20.3] (2.8)	200.2 [194.0; 206.4] (0.9)	201.9 [175.1; 228.8] (4.3)	497.1 [455.9; 538.3] (15.1)
Severely lonely	647.6 [578.0; 717.3] (1.5)	9.7 [8.9; 10.4] (1.4)	190.8 [141.1; 240.2] (0.8)	95.6 [66.4; 124.7] (2.1)	212.7 [183.4; 242.1] (6.5)
Very severely lonely	484.5 [416.0; 553.0] (1.1)	7.3 [6.6; 8.1] (1.0)	112.1 [74.6; 149.7] (0.5)	49.8 [38.8; 60.9] (1.1)	179.4 [143.0; 215.8] (5.4)
Total	**2,405.4 [2,242.0; 2,568.8] (5.6)**	**36.7 [34.7 ; 38.7] (5.2)**	**503.1 [422.0; 584.1] (2.2)**	**347.4 [280.3; 414.4] (7.5)**	**889.3 [782.3; 996.2] (27.0)**

C. model 2: basic model	Total expenditure	GP expenditure	Specialized care expenditure	Pharmaceutical expenditure	Mental healthcare expenditure
Somewhat lonely	1,797.0 [1,758.6; 1,835.3] (4.2)	27.6 [26.9; 28.3] (3.9)	450.9 [452.7; 450.1] (2.0)	289.0 [255.3; 322.7] (6.2)	569.1 [521.1; 617.2] (17.3)
Severely lonely	921.7 [837.5; 1,005.8] (2.2)	13.3 [12.5; 14.2] (1.9)	305.7 [247.6; 364.0] (1.4)	138.2 [103.5; 172.9] (3.0)	274.0 [231.2; 316.8] (8.3)
Very severely lonely	744.0 [657.8; 830.2] (1.7)	10.8 [9.8; 11.8] (1.5)	208.8 [164.0; 253.8] (0.9)	85.5 [70.2; 101.0] (1.8)	253.9 [191.8; 316.2] (7.7)
Total	**3,462 [3,253.8; 3,671.4] (8.1)**	**51.8 [49.3; 54.3] (7.3)**	**965.4 [864.3; 1,068.0] (4.3)**	**512.7 [429.0; 596.6] (11.0)**	**1,097.0 [943.9; 1,250.1] (33.3)**

GP: general practitioner, CI: confidence interval, SES: socioeconomic status. A. model 6 is the most extensive model, which includes loneliness, demographic, SES, lifestyle, self-perceived health and psychological distress. B. model 3 includes loneliness, demographic, and SES factors. C. model 2 is the basic model, which includes loneliness and demographic factors.

Subgroup analyses

The interaction effects between age and loneliness were significant for total, pharmaceutical and mental healthcare, indicating a different association between loneliness and expenditure across age groups for these categories. Figure 2 (Appendix) visualizes the spending patterns incurred per expenditure category for non-lonely, somewhat lonely, severely lonely, and very severely lonely individuals in the entire sample as well as in each age group (i.e. 19-40, 41-64, 65-80 and 81+). The corresponding IRR's and CI's of loneliness are reported in the Appendix, Table A2. Figure 2 and Table A1 show that in the fully adjusted model (model 6) expenditure for adults over 40 (total and pharmaceutical) tend to be lower with increasing loneliness. Furthermore, age and loneliness do not have a significant interaction effect for GP expenditure, rejecting hypothesis 3a. Conversely, for the youngest age group (19-40), total expenditure is higher for severely lonely respondents compared to those who do not report loneliness. For mental healthcare, expenditure were even higher with very severe loneliness (IRR of 1.83 [1.34; 2.50]). In percentages, 6.3% of mental healthcare expenditure can be attributed to loneliness for age group 19-40, 3.1% in 41-64 year-olds, 0.7% in 65-80 year-olds, and 0,1% fewer healthcare spending in 81+ year-olds, in fully adjusted models. This represents 61.8%, 30.0%, 6.9%, and 1.3% of the overall contribution of loneliness and increased mental healthcare expenditure, per age group respectively.

Discussion

This study assessed the impact of loneliness on different types of healthcare expenditure, controlling for a range of individual demographic factors, socio-economic, lifestyle, and health indicators. The study is based on a linked, large dataset resulting in a nationally representative sample of the Dutch adult population (n = 341,376). Firstly, our results reveal that loneliness is associated with higher indirect spending in all expenditure categories (i.e. models 1 - 4), in line with hypothesis 1. However, as the model was further adjusted for self-perceived health and psychological distress, the positive association between loneliness and expenditure reversed. The pattern of higher spending for lonely individuals namely only holds for mental healthcare and GP expenditure, confirming hypothesis 2a and 3. Contrarily, the association is non-significant for pharmaceutical and total expenditure (hypotheses 2b and 4) and is even reversed (i.e. lonely individuals incur fewer expenditure) for specialized healthcare expenditure.

The reduction (and in some cases reversing) of the association between loneliness and expenditure across the models suggests that the relationship between loneliness and expenditure might be mediated by self-perceived health and psychological distress.

While this finding is in line with an extensive body of research that relates loneliness to worse physical [6-10] and mental health [3, 10], it complicates determining the total amount of (healthcare related) expenditure associated with loneliness, and hence rejecting or confirming hypothesis 4. As our results indicate, loneliness may be associated with an indirect increase of 3,5 billion Euro (8.1%) of total healthcare expenditure in the simplest estimation, or a direct decrease of 435.4 million Euro (1.0%) of total healthcare expenditure in the fully adjusted model. Lower expenditure associated with more loneliness are particularly apparent in specialized care. This could be explained by avoidance of care by lonely people compared to non-lonely people [16]. Since specialized care represents a large part of total healthcare expenditure, the net results of all hypotheses result in lower total healthcare expenditure (hypothesis 4). Further research, preferably with longitudinal designs, is required to clarify the underlying causal or complex mechanisms of loneliness and increased or decreased expenditure in all categories as well as between potential confounders. Longitudinal study designs could provide insight into effects of chronic loneliness over time on health care consumption. Furthermore, longitudinal designs could unravel underlying reverse causal mechanisms between poor health and loneliness. We hypothesized that loneliness leads to poorer mental and physical health. Alternatively however, poorer health may also lead to increased loneliness [4]. In particular, reversed causality between poor mental health and increased loneliness may arise due to decreasing social support and resources of mentally ill individuals [4]. In contrast, further research might find poorer physical health (i.e. accidents or severe illnesses) associated with less loneliness if treatments and social support are intensified. These potentially alternative pathways cannot be disentangled in a cross-sectional study, warranting further longitudinal research.

Nevertheless, our results do show a robust association between loneliness and higher mental healthcare expenditure. Even in the fully adjusted model, loneliness is associated with 10% (i.e. 340 million Euro) additional mental healthcare expenditure annually (hypothesis 2a). This implies that (new) policies or societal programs targeted at combatting loneliness may have the potential to significantly reduce healthcare expenditure, particularly in mental healthcare. As shown in models 1-6, loneliness may affect healthcare expenditure through different pathways (i.e. via worsened self-perceived health and psychological distress). Both economic and health aspects of loneliness should be considered in the development of new public health policies and societal programs in practice. Policies and programs combatting loneliness may even become more relevant in times of pandemic outbreaks and social restrictions as seen in the recent COVID-19 outbreak.

Secondly, our study is the first to reveal distinct associations of loneliness and healthcare

expenditure across various age groups. While most policies and research associates loneliness with older age [2] and we expected healthcare expenditure to be higher for older age groups, our findings clearly indicate that severe loneliness is associated with relatively higher expenditure in younger adults (i.e. in aged 19 to 40) compared to older age groups, particularly for mental healthcare. This is consistent with researchers reporting that younger generations perceive higher levels of stress in today's more individualistic, high-performance society [32]. Programs to address loneliness should target beyond older aged populations, and potential savings in (mental) healthcare expenditure should be considered in economic evaluations of programs.

Limitations

This study is not without limitations. First, some subgroups of the general population are under-represented in the Health Survey dataset. Examples include people of lower SES, with poorer health [33], or institutionalized citizens. However, survey design has taken this into account by oversampling low SES groups and the data were weighted for underrepresentation to mitigate these effects. Nevertheless, the associations for mental healthcare may still be underestimated as institutionalized citizens were not included. Second, this study produced cost estimates for the hypothesized relationships in the conceptual model. In view of the alternative mechanisms mentioned above, these estimates should only be interpreted very cautiously as an estimate of the healthcare related cost of loneliness. Simultaneously, we hope, the estimates indicate that loneliness not only comes with socioemotional costs, but also with financial costs. Third, more research is needed to further validate the cutoff points suggested by van Tilburg & de Jong Gierveld [23].

Conclusion

Loneliness is associated with higher healthcare expenditure in all types of curative healthcare services independent of demographic-, socioeconomic- and lifestyle factors. For mental healthcare and GP spending, loneliness was associated with higher expenditure independent of demographic-, socioeconomic-, lifestyle factors, self-perceived health, and psychological distress. In the other categories, the association of loneliness and increased expenditure may be indirect (i.e. mediated in particular by self-perceived health and psychological distress). Furthermore, contrary to common perceptions of loneliness as an old-age problem, our results show that it plays a larger role in explaining healthcare expenditure in younger adults than it does in older adults. Societal programs targeting at loneliness thus have the potential to generate significant savings in healthcare expenditure, especially in mental healthcare and for younger people.

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Table A1. Associations of loneliness in zero expenditure for GP, specialized, pharmaceutical, and mental healthcare. Results from Zero-inflated negative binomial regressions (n = 342,095).

Inflated IRR (95%CI)	1. loneliness	2. demographic and loneliness	3. demographic, SES, and loneliness	4. demographic, SES, lifestyle, and loneliness	5. demographic, SES, lifestyle, physical health, and loneliness	6. Total: demographic, SES, lifestyle, physical and psychological distress, and loneliness
GP expenditure						
Not lonely	ref	ref	ref	ref	ref	ref
Somewhat lonely	**0.85 (0.82-0.88)**	**0.86 (0.83-0.89)**	**0.90 (0.87-0.93)**	**0.90 (0.87-0.93)**	**0.96 (0.92-0.99)**	1.00 (0.97-1.04)
Severely lonely	**0.70 (0.66-0.75)**	**0.70 (0.65-0.75)**	**0.78 (0.72-0.83)**	**0.78 (0.72-0.84)**	**0.92 (0.85-0.99)**	1.03 (0.95-1.11)
Very severely lonely	**0.68 (0.61-0.75)**	**0.67 (0.61-0.74)**	**0.78 (0.70-0.86)**	**0.78 (0.70-0.87)**	0.99 (0.89-1.10)	**1.16 (1.04-1.30)**
Specialized care expenditure						
Not lonely	ref	Ref	Ref	Ref	Ref	Ref
Somewhat lonely	**0.78 (0.75-0.80)**	**0.83 (0.81-0.86)**	**0.88 (0.85-0.91)**	**0.89 (0.86-0.92)**	0.98 (0.95-1.02)	1.01 (0.98-1.05)
Severely lonely	**0.66 (0.62-0.71)**	**0.68 (0.63-0.73)**	**0.77 (0.72-0.85)**	**0.78 (0.73-0.84)**	1.03 (0.95-1.11)	**1.09 (1.01-1.18)**
Very severely lonely	**0.54 (0.49-0.59)**	**0.54 (0.49-0.60)**	**0.65 (0.54-0.73)**	**0.66 (0.59-0.73)**	0.97 (0.87-1.09)	1.04 (0.93-1.18)
Pharmaceutical expenditure						
Not lonely	ref	Ref	Ref	Ref	Ref	Ref
Somewhat lonely	**0.77 (0.74-0.80)**	**0.83 (0.80-0.87)**	**0.90 (0.86-0.93)**	**0.90 (0.87-0.94)**	1.00 (0.96-1.04)	1.03 (0.99-1.07)
Severely lonely	**0.62 (0.58-0.68)**	**0.65 (0.60-0.71)**	**0.77 (0.71-0.84)**	**0.79 (0.72-0.86)**	1.04 (0.96-1.13)	**1.13 (1.03-1.23)**
Very severely lonely	**0.49 (0.43-0.56)**	**0.51 (0.45-0.58)**	**0.66 (0.58-0.75)**	**0.67 (0.59-0.76)**	1.03 (0.91-1.17)	**1.17 (1.03-1.32)**
Mental healthcare expenditure						
Not lonely	ref	Ref	Ref	Ref	Ref	Ref
Somewhat lonely	**0.49 (0.45-0.52)**	**0.46 (0.43-0.49)**	**0.51 (0.47-0.54)**	**0.51 (0.48-0.55)**	**0.57 (0.53-0.61)**	**0.76 (0.70-0.82)**
Severely lonely	**0.23 (0.21-0.25)**	**0.23 (0.21-0.26)**	**0.28 (0.26-0.31)**	**0.29 (0.26-0.32)**	**0.37 (0.33-0.41)**	**0.64 (0.57-0.71)**
Very severely lonely	**0.17 (0.16-0.19)**	**0.18 (0.17-0.21)**	**0.24 (0.22-0.27)**	**0.25 (0.22-0.28)**	**0.35 (0.31-0.39)**	**0.69 (0.61-0.79)**

Coefficients with p<0.05 are in bold. GP: general practitioner, IRR: incidence rate ratio, CI: confidence interval, SES: socioeconomic status.

Table A2. Stratified analyses by age for total, specialized, pharmaceutical and mental healthcare expenditure. Results from Poisson and Zero-inflated negative binomial models.

IRR (95%CI)	Loneliness	Age group 19-40 N=55,817	Age group 41-64 N=118,814	Age group 65-80 N=143,231	Age group 81+ N=23,415
Total expenditure	Not lonely	ref	ref	ref	ref
	Somewhat lonely	1.08 (0.99-1.18)	**0.90 (0.85-0.96)**	**0.93 (0.90-0.97)**	1.01 (0.96-1.06)
	Severely lonely	**1.24 (1.06-1.44)**	**0.88 (0.80-0.97)**	**0.86 (0.81-0.91)**	1.08 (0.99-1.16)
	Very severely lonely	1.13 (0.91-1.41)	**0.87 (0.77-0.98)**	**0.89 (0.83-0.97)**	0.92 (0.83-1.02)
Pharmaceutical expenditure	Not lonely	ref	Ref	Ref	ref
	Somewhat lonely	0.95 (0.85-1.07)	1.03 (0.96-1.11)	**0.96 (0.91-1.01)**	**0.95 (0.91-0.99)**
	Severely lonely	1.23 (0.94-1.61)	0.99 (0.89-1.10)	**0.89 (0.82-0.96)**	0.97 (0.90-1.04)
	Very severely lonely	1.18 (0.76-1.84)	0.92 (0.81-1.05)	0.90 (0.81-1.00)	**0.84 (0.78-0.91)**
*Inflated**	Not lonely	Ref	Ref	ref	ref
	Somewhat lonely	1.05 (0.98-1.13)	1.02 (0.97-1.07)	1.02 (0.97-1.08)	0.98 (0.81-1.19)
	Severely lonely	1.14 (0.99-1.32)	1.12 (0.99-1.26)	1.02 (0.88-1.18)	**1.49 (1.05-2.11)**
	Very severely lonely	**1.26 (1.01-1.58)**	1.13 (0.96-1.34)	1.04 (0.85-1.29)	1.57 (0.97-2.56)
Mental healthcare expenditure	Not lonely	Ref	Ref	ref	ref
	Somewhat lonely	**1.34 (1.13-1.59)**	1.05 (0.89-1.24)	1.24 (0.98-1.58)	0.94 (0.58-1.50)
	Severely lonely	**1.26 (1.04-1.53)**	0.98 (0.80-1.19)	1.09 (0.78-1.52)	1.35 (0.76-2.38)
	Very severely lonely	**1.83 (1.34-2.50)**	1.00 (0.81-1.24)	0.91 (0.65-1.28)	0.78 (0.42-1.46)
*Inflated**	Not lonely	ref	ref	ref	ref
	Somewhat lonely	**0.72 (0.64-0.82)**	**0.78 (0.71-0.87)**	**0.89 (0.79-1.00)**	0.74 (0.53-1.02)
	Severely lonely	**0.65 (0.54-0.79)**	**0.64 (0.55-0.74)**	**0.80 (0.66-0.96)**	**0.38 (0.26-0.56)**
	Very severely lonely	**0.89 (0.70-0.89)**	**0.62 (0.52-0.74)**	**0.66 (0.54-0.82)**	**0.39 (0.22-0.68)**

Expenditure categories with significant interaction effects for loneliness and age. Coefficients with p<0.05 are in bold. IRR: incidence rate ratio, CI: confidence interval. * Inflated parts of the model reflect the IRR of incurring zero expenditure (vs any expenditure).

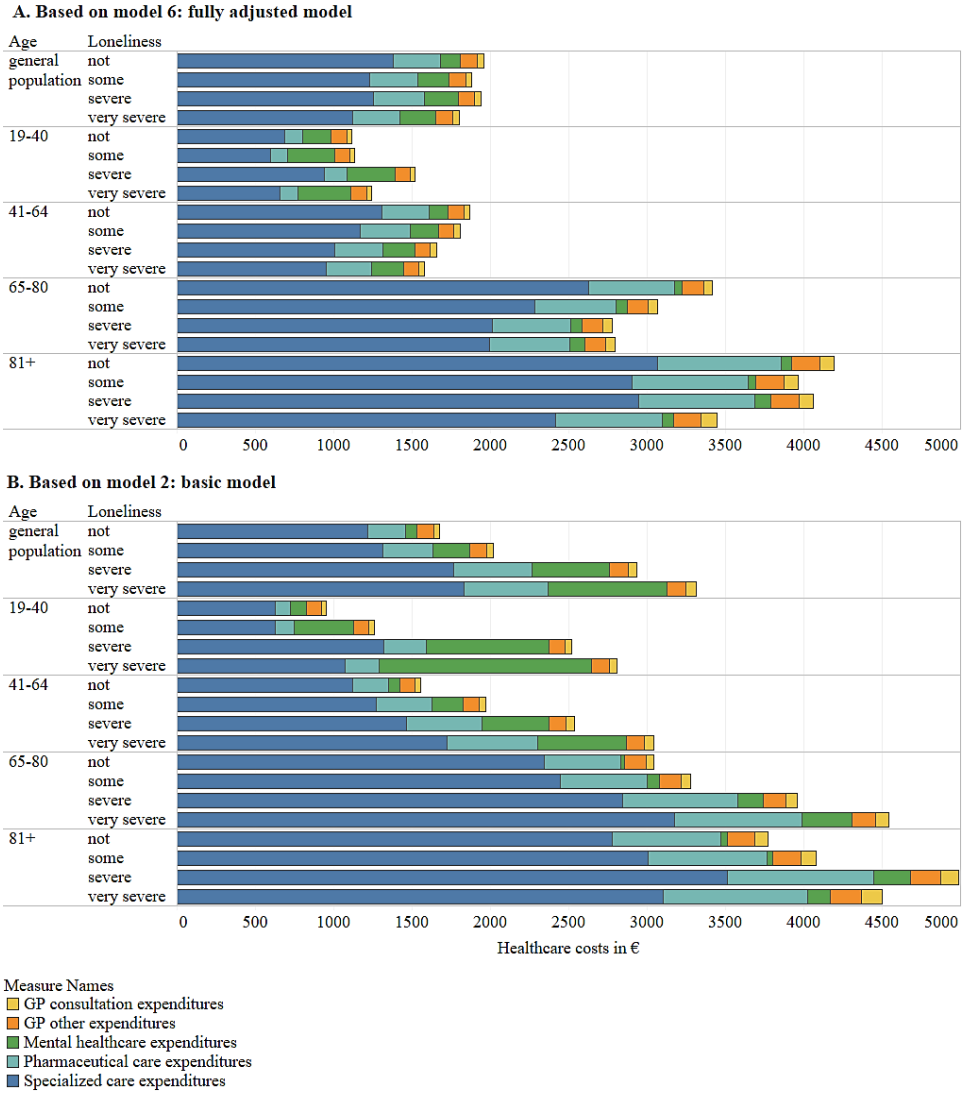

Figure 2. Marginal effects of loneliness on healthcare expenditures based on model 6 (fully adjusted) and 2 (basic), in age categories.

GP: general practitioner.

A. model 6 is the fully adjusted model, which includes loneliness, demographic, SES, lifestyle, self-perceived health, and psychological distress.

B. model 2 is the basic model, which includes loneliness and demographic factors.

Chapter 4

Two sides of the same coin? Absolute income and perceived income inadequacy as social determinants of health

Under review

Chapter 5

Regional differences in health further explained: the contribution of lifestyle, loneliness, and mastery

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Abstract

Like in most Western countries, regional health inequalities are also present in the Netherlands. Explaining these inequalities is necessary for policymakers to target interventions to reduce them. Regional health inequalities are usually attributed to demographic and socio-economic factors, while lifestyle and psychosocial factors are increasingly shown to impact individuals' health. Therefore, this study analyses the role of lifestyle, loneliness, and self-mastery in explaining regional inequalities, in addition to demographic factors and SES, for self-rated health, presence of chronic diseases, and psychological distress. Analyses are performed in the linked dataset from the Dutch Public Health Services, Statistics Netherlands, and the National Institute for Public Health and the Environment for the year 2016 (n= 334,721). The results show that lifestyle, loneliness and self-mastery contribute to the regional health inequalities in self-rated health and presence of chronic diseases. For psychological distress, both loneliness and self-mastery contribute to the regional health inequalities. Addressing lifestyle and psychosocial factors can offer policymakers additional pathways to bridge regional health inequalities. In this study, the region of Zuid-Limburg represents the reference region. Use Compare Regions for Health and Healthcare Costs (*Regiovergelijker gezondheid en zorgkosten*), in order to select all other Dutch regions as reference region.

Introduction

Large socioeconomic health differences are prevalent in the Netherlands, and these differences have barely changed or have even increased in recent decades [1]. There are also regional differences. For example, 78.5% of all adults in the Dutch Public Health Services region of Central Holland (*Hollands Midden*) report a (very) good self-perceived health, compared with 69.5% of those living in South Limburg (*Zuid-Limburg*) [2]. The underlying determinants of health inequalities are very complex. They are often related to socioeconomic status (SES) [3], accumulate over different stages of life, and often lie outside the domain of the health sector [3]. Factors in the areas of housing, well-being, working and living environment, and education are related to health [4]. Moreover, the prevalence of the determinants of health differs greatly per region.

When explaining health differences between regions, the population is usually adjusted for differences in age, gender, income, education level, and migration background. According to studies based on the Health Monitor 2016, 11% of the variation in perceived health can be explained by these factors [5]. The authors suggested that in follow-up research, factors based on well-being and lifestyle should also be included to explain differences in perceived health. There is a large body of evidence for the negative health effects of lifestyle habits, such as smoking, alcohol consumption, and (inadequate) physical activity [6]. Lifestyle determinants alone, however, are not sufficient to explain health differences [3, 7].

In recent years, well-being and psychosocial factors related to health have gained increasing attention. For example, loneliness (the physical experience of a lack of connection with other people [8]) has been directly associated with increased mortality [9], morbidity, poorer mental health [10], and unhealthy habits such as smoking [10, 11], higher body mass index (BMI) [11], and less physical activity [11]. Moreover, in our current participatory society, citizens need better mastery skills to direct their own lives, even when they rely on support or care from others [12]. Although this is important for good (self-rated) health, it is not realistic for everyone [13]. Degrees of loneliness and mastery skills can vary per region and can thus contribute to regional health inequalities. All these factors together complicate efforts to diminish health inequalities. These inequalities represent a complex social issue, which requires a broader view [3]. In addition to demographic factors and SES, more research is needed to determine the contribution of lifestyle, loneliness, and mastery to explaining regional health inequalities.

The aim of this study was to further explain regional health inequalities in self-rated

health, chronic disease, and psychological distress by using a more extensive set of lifestyle factors, loneliness, and mastery, in addition to demographic factors and SES. With the results of this research, we aimed to provide more insight into the factors associated with regional health inequalities in order to provide policymakers with more leads to help diminish health inequalities.

Methods

Data and sampling

This was a cross-sectional study based on data from the Dutch Health Survey (2016) and registry data from Statistics Netherlands. In accordance with the Dutch Public Health Law, Dutch municipalities are obliged to assess local public health issues. For this purpose, the Health Survey is held once every four years. This survey is a collaboration between the Dutch Public Health Services, the Dutch National Institute for Public Health and the Environment (*RIVM*), and Statistics Netherlands. The survey covers various topics regarding the respondent's personal situation, such as lifestyle, mental and physical health, loneliness, household, and mastery. As a result of the sampling method used (complex sample method), weighting factors were calculated based on a number of individual and regional background characteristics to ensure the sample was representative of the entire Dutch population [14]. The sample (*N*= 457,150; response rate: ~40% [14]) included the non-institutionalized population aged 19 years and over. The registry data provided by Statistics Netherlands were based on the Dutch Personal Records Database and data from the Dutch Tax and Customs Administration for the entire Dutch population. All data were linked in a secured environment, which is managed by Statistics Netherlands, and processed anonymously. After data linkage and exclusion of missing data, the sample included 334,721 respondents.

Dependent variables

For this study, three different dependent variables from the Health Survey were used. The variable "self-rated health" was assessed with the question "How would you rate your health in general?", which is answered on a five-point Likert scale. The response categories were dichotomized into good self-rated health ("good" or "very good") and poor self-rated health ("fair", "poor", or "very poor"). The variable "chronic disease" was derived from the question "Do you have one or more long-term diseases (expected duration six months or longer)?", with the answer options "yes" and "no". This question does not differentiate between physical and mental diseases. Psychological distress was derived from the Kessler-10 questionnaire (K10) [15]. The ten questions in this questionnaire are answered on a five-point Likert scale, resulting in a total score ranging from 10 to 50. Scores of 30 and higher were considered as "high risk" (see Appendix Tables A1 and A2 for details).

Independent variables

The independent variables in this study included region, demographic factors, SES, lifestyle, loneliness, and mastery. The variable "region" was based on the 2016 division of the Dutch Public Health Services (resulting in 25 regions). The region of Zuid-Limburg was the reference group as this region scores worst on many health-related factors and outcome measures based on the information published by the RIVM [2]. Zuid-Limburg has the highest percentages of adults with a chronic disease (38.7% vs 33.9% nationwide), adults with (very) poor or fair self-rated health (30.5% vs 24.4%), lonely adults (47.8% vs 43.0%), and adults with insufficient mastery (12.5% vs 9.9%) [2].

Demographic factors included age, gender, migration background, and marital status. SES consisted of the highest attained level of education, the quartile of standardized household income, and income inadequacy. Household income was standardized for the number of persons in the household and then classified into quartiles based on income data of the entire Dutch population. The variable "income inadequacy" was examined with the question "In the past 12 months, have you had any concerns making ends meet with your household income?" Income inadequacy is considered to be a subjective measure of income as part of SES since it is also related to health, in addition to the objective income [16]. Lifestyle variables included BMI category [17] and sufficient physical activity (at least 2.5 hours of moderately intensive exercise or intense training twice a week, as defined by the Health Council [18]) as a proxy for eating and exercise behavior, smoking history, and alcohol consumption ("never", "moderately", or "excessively" (i.e., >14 alcohol beverages a week for women and >21 alcohol beverages a week for men)). The variable "loneliness" was based on the total score on the eleven statements of the De Jong–Gierveld scale [8]. These statements refer to feelings of severe loneliness, problematic situations, companionship, and sociability (e.g., "I experience a general sense of emptiness" or "There are many people I can trust completely"). The answer options are "yes", "more or less" and "no". An individual is considered to be somewhat lonely if their score is in the range of 3 to 8, severely lonely with a score of 9 or 10, and very severely lonely with a score of 11 [19]. The variable "mastery" was assessed with the seven statements of the Pearlin and Schooler Mastery Scale [20]. These statements (e.g., "I have little control over the things that happen to me") are answered on a five-point Likert scale (ranging from "strongly agree" to "strongly disagree"), with a total score of 7–35. The higher the total score, the more control one experiences over their life.

Statistical analyses

The relative risks for the negative health outcomes were modeled using a series of logistic and Poisson regressions. The outcomes "poor self-rated health" and "at least one chronic disease" were modelled with robust Poisson regressions because of the

frequency of these outcomes (prevalence >10%). Odds ratios (ORs) of logistic regressions can substantially overestimate the prevalence ratios (PRs) for this type of outcome variables [21]. For the outcome "psychological distress", logistic regressions were used. For each outcome variable, six regression models were compared. Model 1 was only adjusted for region. This is a categorical variable with 24 dummies and the region of Zuid-Limburg as reference group. In Model 2, region, demographic factors, and SES were accounted for. In Model 3, the outcomes were corrected for region, demographic factors, SES, and a) lifestyle, b) loneliness, or c) mastery, respectively. Finally, in Model 4, all independent variables of this study were accounted for.

Given the number of missing data, all analyses were also performed with multiple imputed data (multivariate imputation by chained equations, 5 imputations, *n*= 452,664) [22]. These results and the original findings were comparable, making the findings robust. All analyses were performed using Stata 16 [23] and applied to the sampling design of the data.

Results

The sample included 334,721 persons, of whom more than half were women (52.4%), with a mean age of 59.2 years (standard deviation (SD): 16.9) (Table 1). The majority of the respondents was Dutch-born (88.0%), 8.4% had a Western migration background, and 3.6% had a non-Western migration background. In addition, 67.0% of the respondents were married or living together, 10.7% had never been married, 6.9% was widowed, and 9.4% was divorced. Furthermore, 74.0% of the respondents experienced a (very) good health, 60.7% had no chronic diseases, and 95.5% had no, a low, or a moderate risk of psychological distress. The mean loneliness score was 2.8 (SD: 3.1) (scores 0–3 indicated "not lonely"). For mastery, the mean score was 26.7 (SD: 5.2) (scale 7–35). The outcomes and factors were also weighted and are described per region (see Appendix Tables A4 and A5). An overview of the missing data can be found in Appendix Table A3.

Table 1. Sample characteristics (n= 334,721)

Variable	Category	*n*	(%)
Gender[§]	Male	159,251	(47.6%)
Migration background[§]	Dutch-born	294,573	(88.0%)
	Western migration background	28,204	(8.4%)
Marital status[*]	Married/living together	224,234	(67.0%)
	Never married	35,899	(10.7%)
	Widowed	23,052	(6.9%)

table continues

Variable	Category	*n*	(%)
Highest attained level of education*	Primary school	19,061	(5.7%)
	Lower vocational education	102,886	(30.7%)
	Middle vocational/secondary	106,341	(31.8%)
Standardized household income quartile§	0-25%	42,250	(12.6%)
	26-50%	84,243	(25.2%)
	51-75%	98,107	(29.3%)
Self-perceived income inadequacy*	Inadequate, major concerns	9,490	(2.8%)
	Inadequate, some concerns	34,273	(10.2%)
	Adequate, minor concerns	115,299	(34.4%)
Physical activity*	Insufficient	94,343	(28.2%)
Body mass index, kg/m²*	Normal (18.5–25)	152,321	(45.5%)
	Overweight (25–30)	128,977	(38.5%)
	Obese (>30)	49,223	(14.7%)
Alcohol consumption*	Never	32,663	(9.8%)
	Moderate	275,392	(82.3%)
Smoking history*	Never smoked	135,642	(40.5%)
	Former smoker	144,994	(43.3%)
Chronic disease*	None	203,330	(60.7%)
Self-rated health*	Very (good)	247,707	(74.0%)
Psychological distress*	No, low or moderate risk	319,533	(95.5%)
		Average	**(SD)**
Age, years§		59.2	(16.9)
Loneliness score*		2.8	(3.1)
Mastery score*		26.7	(5.2)

Based on unweighted, non-imputed data. SD: standard deviation. §Registry data. *Self-reported data

Compared with residents of Zuid-Limburg, all residents of other Dutch regions had a lower risk of poor self-rated health in the uncorrected model, with PRs ranging from 0.72 to 0.93 (Table 2). In other words, if differences between regions remained uncorrected for any population characteristic, residents of Zuid-Limburg had a higher chance of poor self-rated health (8%–39%) than residents of other regions. After adding demographic and SES factors, 23 regions remained significantly different. After adding lifestyle factors, 19 regions remained significantly different, and after adding loneliness, 21 regions remained significantly different. After addition of mastery, 20 regions remained significantly different from Zuid-Limburg (Figure 1 and Appendix Table A6). When using the most extensive model, the regional differences in self-rated health remained significant in 17 of the 24 regions, with PRs ranging from 0.83 to 0.95 (Table 2).

Table 2. Regional differences in uncorrected and fully corrected models

	Self-rated health (very) poor or fair PR(95% CI)		At least one chronic disease PR(95% CI)		High risk for psychological distress OR(95% CI)	
	Model 1: region	Model 4: total*	Model 1: region	Model 4: total*	Model 1: region	Model 4: total*
Zuid-Limburg	1,00 (ref)	1,00 (ref)	1,00 (ref)	1,00 (ref)	1,00 (ref)	1,00 (ref)
Zuid-Holland-Zuid	**0.75 (0.70-0.80)**	**0.83 (0.79-0.88)**	**0.83 (0.78-0.87)**	**0.88 (0.84-0.92)**	**0.66 (0.54-0.79)**	**0.76 (0.60-0.96)**
Zeeland	**0.91 (0.85-0.96)**	1.00 (0.95-1.05)	**0.87 (0.83-0.91)**	**0.89 (0.85-0.93)**	**0.70 (0.58-0.84)**	**0.80 (0.64-0.99)**
Zaanstreek-Waterland	**0.82 (0.78-0.86)**	**0.94 (0.90-0.98)**	**0.93 (0.90-0.97)**	1.01 (0.97-1.05)	**0.82 (0.72-0.94)**	1.09 (0.92-1.30)
West-Brabant	**0.88 (0.84-0.93)**	1.00 (0.95-1.05)	**0.81 (0.77-0.84)**	**0.85 (0.82-0.89)**	**0.75 (0.65-0.88)**	0.96 (0.79-1.16)
Utrecht	**0.73 (0.69-0.76)**	**0.94 (0.90-0.98)**	**0.82 (0.79-0.85)**	**0.95 (0.93-0.98)**	**0.69 (0.61-0.77)**	0.94 (0.81-1.09)
Twente	**0.75 (0.71-0.80)**	**0.88 (0.83-0.93)**	**0.89 (0.85-0.94)**	0.98 (0.94-1.02)	0.96 (0.81-1.14)	**1.49 (1.20-1.84)**
Rotterdam	**0.93 (0.89-0.97)**	**0.93 (0.89-0.96)**	**0.94 (0.91-0.97)**	0.98 (0.95-1.01)	1.07 (0.96-1.19)	0.99 (0.86-1.15)
Noord- en Oost-Gelderland	**0.73 (0.69-0.77)**	**0.89 (0.85-0.93)**	**0.95 (0.92-0.99)**	1.03 (0.99-1.07)	**0.71 (0.62-0.81)**	1.05 (0.89-1.25)
Limburg-Noord	**0.86 (0.82-0.90)**	0.97 (0.93-1.01)	**0.93 (0.89-0.96)**	0.97 (0.94-1.01)	**0.67 (0.59-0.76)**	**0.84 (0.71-0.99)**
Kennemerland	**0.72 (0.68-0.76)**	**0.90 (0.85-0.94)**	**0.84 (0.80-0.88)**	**0.94 (0.90-0.97)**	**0.68 (0.58-0.79)**	1.01 (0.84-1.22)
IJsselland	**0.72 (0.67-0.77)**	**0.91 (0.85-0.97)**	**0.91 (0.87-0.96)**	1.03 (0.98-1.08)	**0.70 (0.58-0.84)**	0.99 (0.79-1.25)
Hollands Noorden	**0.78 (0.74-0.82)**	**0.95 (0.91-0.99)**	**0.87 (0.83-0.91)**	**0.96 (0.92-0.99)**	**0.71 (0.61-0.82)**	0.95 (0.79-1.14)
Hollands Midden	**0.72 (0.68-0.75)**	**0.86 (0.82-0.90)**	**0.93 (0.90-0.97)**	1.02 (0.98-1.05)	**0.82 (0.72-0.92)**	1.11 (0.94-1.30)
Hart voor Brabant	**0.84 (0.80-0.88)**	1.00 (0.96-1.05)	**0.84 (0.80-0.87)**	**0.91 (0.88-0.94)**	**0.76 (0.67-0.86)**	1.05 (0.89-1.24)
Haaglanden	**0.88 (0.84-0.93)**	**0.92 (0.88-0.96)**	0.97 (0.93-1.01)	**1.04 (1.00-1.08)**	**1.27 (1.12-1.44)**	**1.22 (1.03-1.44)**
Groningen	**0.79 (0.74-0.83)**	0.96 (0.92-1.01)	**0.95 (0.91-0.99)**	**1.06 (1.02-1.11)**	**0.66 (0.57-0.78)**	0.84 (0.69-1.03)
Gooi en Vechtstreek	**0.76 (0.70-0.81)**	**0.94 (0.88-0.99)**	**0.85 (0.81-0.90)**	**0.93 (0.89-0.98)**	**0.71 (0.58-0.87)**	1.01 (0.78-1.29)
Gelderland-Zuid	**0.75 (0.71-0.79)**	**0.90 (0.86-0.95)**	**0.86 (0.82-0.90)**	**0.95 (0.91-0.99)**	**0.86 (0.75-0.98)**	1.19 (0.99-1.42)
Gelderland-Midden	**0.76 (0.71-0.81)**	**0.89 (0.84-0.94)**	**0.93 (0.88-0.98)**	1.01 (0.96-1.06)	0.95 (0.78-1.14)	1.19 (0.97-1.46)
Friesland	**0.73 (0.69-0.77)**	**0.86 (0.82-0.91)**	**0.89 (0.86-0.93)**	**0.95 (0.92-0.99)**	**0.66 (0.57-0.77)**	0.95 (0.79-1.14)
Flevoland	**0.81 (0.71-0.92)**	0.96 (0.87-1.07)	0.93 (0.85-1.02)	1.05 (0.96-1.14)	1.01 (0.74-1.37)	1.27 (0.90-1.79)
Drenthe	**0.76 (0.70-0.82)**	**0.88 (0.82-0.94)**	**0.90 (0.84-0.95)**	0.95 (0.90-1.01)	**0.65 (0.52-0.80)**	0.84 (0.63-1.13)
Brabant-Zuidoost	**0.88 (0.84-0.92)**	1.04 (0.99-1.08)	**0.83 (0.80-0.87)**	**0.90 (0.86-0.93)**	**0.83 (0.73-0.94)**	1.04 (0.87-1.24)
Amsterdam	**0.79 (0.74-0.84)**	**0.88 (0.84-0.93)**	**0.83 (0.79-0.87)**	**0.93 (0.89-0.98)**	0.96 (0.84-1.11)	1.03 (0.86-1.23)

Results of robust Poisson and logistic regressions (n= 334,721) based on weighted data. PRs and ORs in bold are significant (P< 0.05). PR: prevalence ratio. OR: odds ratio. CI: confidence interval. *Model 4 was corrected for region, demographic factors, SES, lifestyle, loneliness, and mastery.

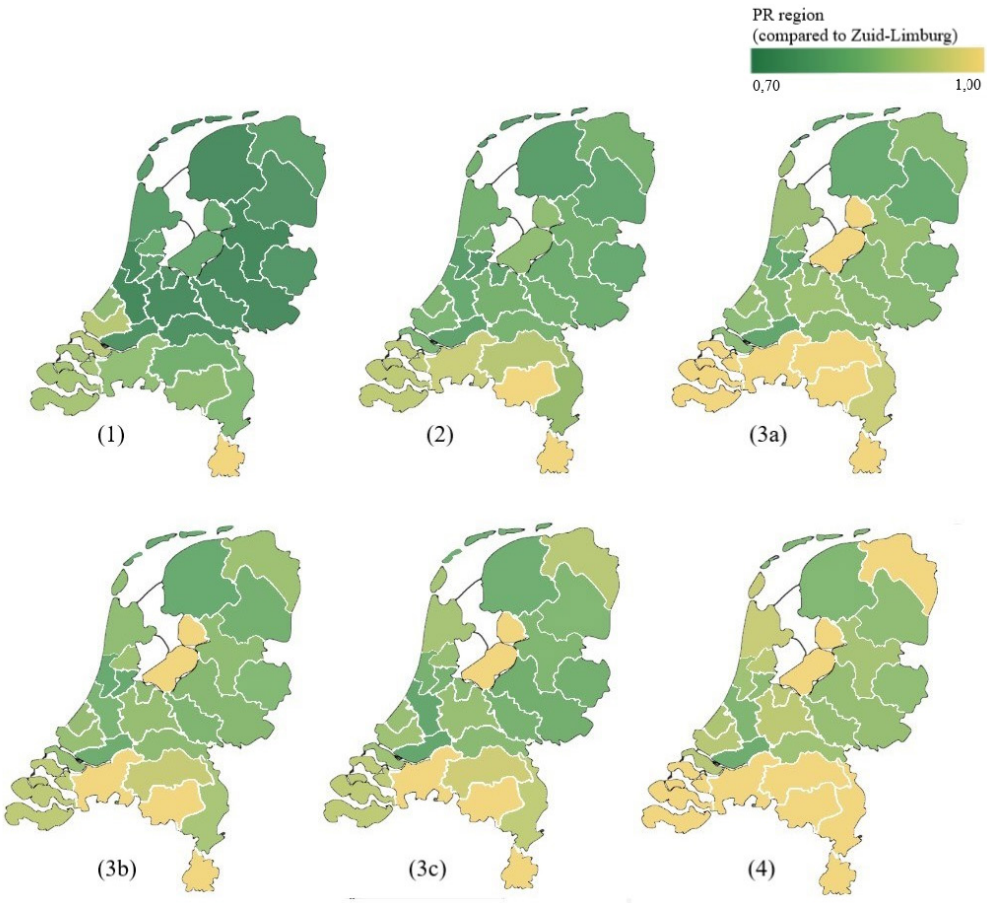

Figure 1. Prevalence ratios of having less than good self-rated health in other Dutch regions compared with Zuid-Limburg

Accounted for (1) region; (2) region, demographic factors, and socioeconomic status (SES); (3a) region, demographic factors, SES, and lifestyle; (3b) region, demographic factors, SES, and loneliness; (3c) region, demographic factors, SES, and mastery; and (4) region, demographic factors, SES, lifestyle, loneliness, and mastery.

The risk of having at least one chronic disease differed significantly between 22 regions and Zuid-Limburg in the uncorrected model; the PRs ranged from 0.81 to 0.95 (Table 2). The regional differences for chronic disease could be partly explained by demographic factors and SES (17 significantly different regions), lifestyle (15 significantly different regions), loneliness (15 significantly different regions), and mastery (14 significantly different regions) (Figure 2 and Appendix Table A7). In the most extensive model, residents of Zuid-Limburg had a higher risk (4%–18%) of having at least one chronic

disease compared with the residents of 12 other regions (significant PRs ranged from 0.85 to 0.96). Residents of the region of Groningen had a higher risk of having at least one chronic disease compared with Zuid-Limburg residents in the most extensive model (PR: 1.06; 95% confidence interval (CI): 1.02–1.11).

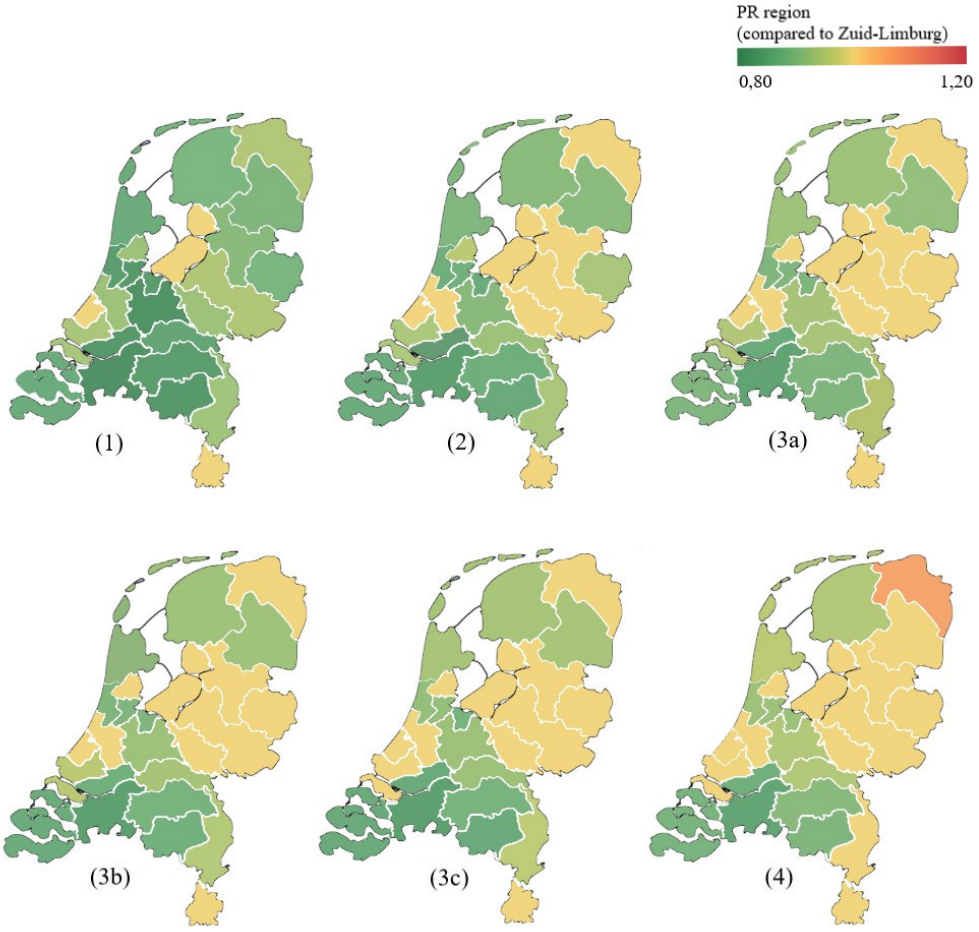

Figure 2. Prevalence ratios of having at least one chronic disease in other Dutch regions compared with Zuid-Limburg

Accounted for (1) region; (2) region, demographic factors, and socioeconomic status (SES); (3a) region, demographic factors, SES, and lifestyle; (3b) region, demographic factors, SES, and loneliness; (3c) region, demographic factors, SES, and mastery; and (4) region, demographic factors, SES, lifestyle, loneliness, and mastery.

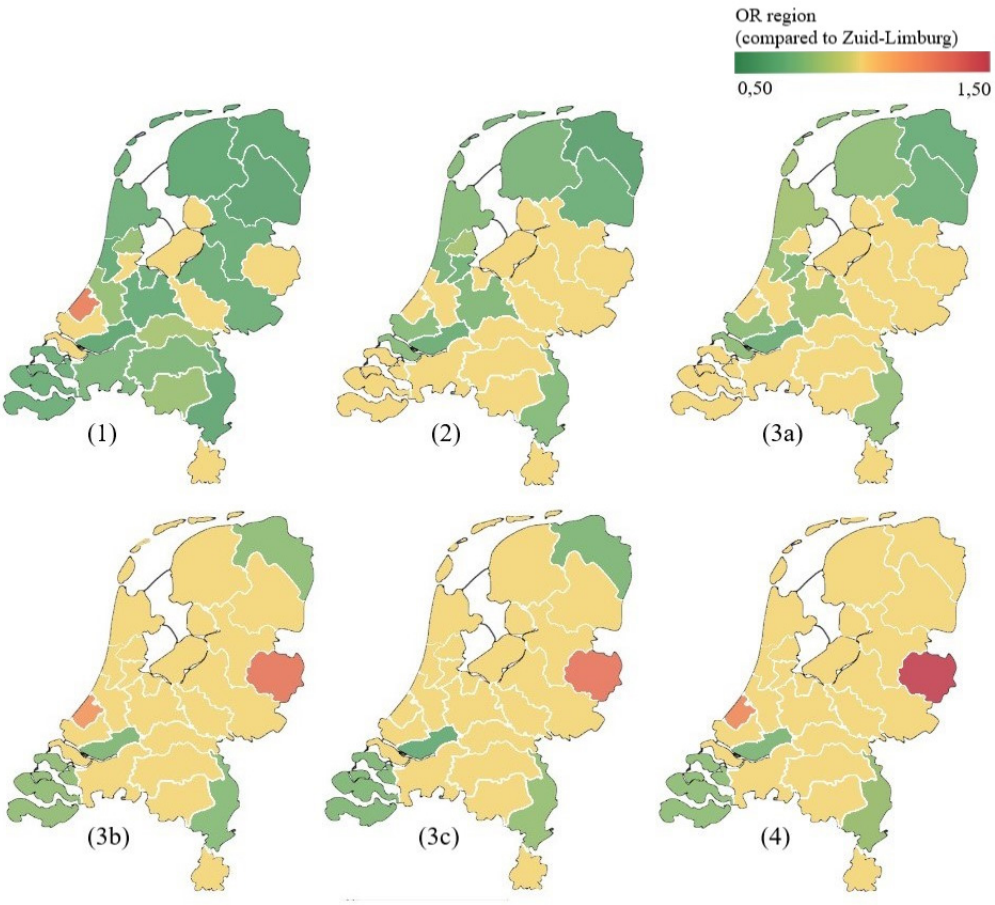

Figure 3. Odds ratios of having high risk of psychological distress in other Dutch regions compared with Zuid-Limburg

Accounted for (1) region; (2) region, demographic factors, and socioeconomic status (SES); (3a) region, demographic factors, SES, and lifestyle; (3b) region, demographic factors, SES, and loneliness; (3c) region, demographic factors, SES, and mastery; and (4) region, demographic factors, SES, lifestyle, loneliness, and mastery.

The risk of psychological distress differed significantly between the 18 other regions and Zuid-Limburg in the uncorrected model; the ORs ranged from 0.65 to 0.86. The regional differences for the risk of psychological distress could be largely explained by demographic factors, SES, loneliness, and mastery (Figure 3 and Appendix Table A8). Of the 19 significantly different regions in Model 1, 12 remained significantly different when demographic factors and SES were added, 10 remained significantly different with the addition of lifestyle, 6 remained significantly different with the addition of

loneliness, and 5 remained significantly different with the addition of mastery. In the most comprehensive model, residents of three other regions had a lower risk of psychological distress compared with residents of Zuid-Limburg. These three regions were *South Holland–South* (Zuid-Holland-Zuid) (OR: 0.76; 95% CI: 0.60–0.96), Zeeland (OR: 0.80; 95% CI: 0.64–0.99), and Northern Limburg (*Limburg-Noord*) (OR: 0.84; 95% CI: 0.71–0.99). The residents of Twente (OR: 1.49; 95% CI: 1.20–1.84) and Haaglanden (OR: 1.22; 95% CI: 1.03–1.44) had a higher risk of psychological distress compared with those living in Zuid-Limburg. After adding demographic factors, SES, lifestyle, loneliness, and mastery, there were no significant differences between the other 19 regions and Zuid-Limburg. The results of the multiple imputed data set were comparable with the results based on the sample of 334,721 respondents.

Discussion

The aim of this study was to explain the regional health differences in self-rated health, chronic disease, and psychological distress based on an extensive set of lifestyle factors, loneliness, and mastery, in addition to demographic factors and SES. When we corrected for all explanatory factors, the number of regions that differed from the region of Zuid-Limburg with respect to self-rated health decreased from 24 to 17. Lifestyle, loneliness, and mastery partly contributed to this difference, with 19, 21, and 20 significant regions, respectively (out of 23 after adjusting for demographic factors and SES). With regard to chronic disease, residents of 12 regions were less likely to have a chronic disease than residents of Zuid-Limburg after accounting for all explanatory factors. Lifestyle and loneliness (number of significantly different regions reduced from 17 to 15 for both) and mastery (from 17 to 14 significant regions) contributed to the differences between regions in self-perceived health and presence of chronic diseases. Of the 19 regions with significant differences in the risk of psychological distress, 14 were no longer significantly different when correcting for the explanatory factors. This could be largely explained by loneliness (from 12 to 6 significant regions) and self-mastery (from 12 to 5 significant regions), in addition to the corrections for demographic characteristics and SES (from 19 to 12 significant regions) and lifestyle (from 12 to 10 significant regions). This study presented regional differences compared with the reference region Zuid-Limburg. In the tool Compare Regions for Health and Healthcare Costs (*Regiovergelijker gezondheid en zorgkosten*), users can select any reference region and display the results of the uncorrected model (Model 1) and the fully corrected model (Model 6) [24].

The correction for demographic factors and SES partly contributed to the explanation of regional differences in self-rated health. This finding is similar to the results of

previous research in the Netherlands, in which municipal differences in self-rated health were partly explained by age, migration background, income, and education level [5]. Similarly, international studies have shown that regional health inequalities can be partially explained by personal characteristics. In the United States, 30% of mortality differences for women are explained by individual characteristics (demographic factors and SES), whereas 53% is attributed to contextual features per state (social cohesion, economic, and socio-political structure) [25]. In England, the north-south divide in cardiovascular diseases can also be partly explained by demographic factors and SES, in this case by smoking behavior, BMI, and blood pressure [26].

After adding all explanatory factors to the model, there were still some regional health inequalities. Which factors can further explain these differences? It is well known that neighborhood characteristics such as social cohesion, facilities, perceived safety, and less nuisance are associated with better health [27, 28]. Statistics Netherlands has published national and regional data on this topic in its Safety Monitor. These data showed that residents of the regions of Amsterdam, Rotterdam, parts of The Hague region, Utrecht city, and Zuid-Limburg feel less safe, experience more nuisance, and are less satisfied with the quality of life in neighborhoods [29]. In addition, the Dutch Opportunity Map (*KansenKaart*), which makes regional differences in upward mobility (i.e., the ability to improve one's social status relative to that of another social group) insightful, has shown that upward mobility in income is less common in people who grew up in the northern provinces of the Netherlands [30]. Upward mobility in education level (higher vocational training or university), on the other hand, is less common in people who grew up in the Dutch Bible Belt and the northern regions. These regional differences could be further investigated, in combination with lifestyle and psychosocial factors.

When explaining poorer health outcomes, cultural and historical aspects are often taken into consideration. For Zuid-Limburg, for example, its mining history is often considered [31]. When the mines closed, not only did many jobs disappear, but the social structures of mine, church, and state also collapsed. These structures provided education, healthcare, social cohesion, and housing in Zuid-Limburg. A possible consequence is that residents of Zuid-Limburg have a more dependent attitude and therefore experience a lower sense of mastery [31]. The disappearance of these structures, and the absence of adequate alternatives [32], has also led to a greater feeling of loneliness and less mastery. Nevertheless, even when we corrected for mastery and loneliness, regional differences remained (5%–20% higher chance of poorer health and 4%–18% higher chance of having a chronic disease). This may indicate the presence of other determinants we did not include or may imply that the used scales insufficiently measure loneliness and mastery. Although these are validated scales, feelings of loneliness and

lower sense of mastery may not have been fully covered by the questions, as people feel politicians and government have abandoned them [32]. Perhaps future (qualitative and) longitudinal research can unravel the mechanisms behind these factors.

Our results offer leads for policymakers to reduce regional health inequalities by tackling unhealthier lifestyles and loneliness and strengthening mastery in the population. For some factors, interventions can be fairly simple by using straightforward programs, such as lifestyle campaigns. To combat loneliness, group interventions are recommended that focus on educational or social activities for specific target groups and not only on home visits or learning how to make friends [33]. In addition, as lifestyle habits, loneliness, and mastery are formed in the broad context of the individual's living environment, the causes of the causes need to be assessed as well [4]. This requires consideration of a broad range of domains beyond healthcare, such as labor, housing, education, and living environment [3, 34]. More qualitative and regional research is needed to determine exactly which problems are prevalent and which interventions are best suited for these problems.

Based on this study, no recommendations on specific interventions can be made, but we have shown that investments in these interventions can reduce regional health inequalities. Prioritization of vulnerable regions and populations is recommended [34], which is also in the interest of a regional approach of making healthcare more sustainable and looking at a broader perspective of prosperity [35, 36]. Regions are taking on a greater role in realizing local partnerships at the border of medical and social care and in bringing coherence in health, income, and well-being [35]. Aside from the possible leads this research offers based on the corrected differences, the uncorrected differences visualize the actual situation in vulnerable regions and indicate that extra attention and investments are needed.

A possible limitation of the study is related to the composition of the sample. It is known that certain groups are less inclined to participate in surveys, for example people with a lower SES and/or worse health, which can lead to selection bias [37]. In addition, people in the lowest income quartile were underrepresented in this dataset (12.6% of the respondents). This was taken into account when sampling and analyzing the data by adding weighting factors. Nevertheless, the weighted data showed that 18.7% of the respondents belonged to the lowest quartile. In addition, institutionalized residents are not included in the sample of the Health Survey. The underrepresentation of this group of citizens may have underestimated the actual regional health inequalities.

A second limitation is the use of cross-sectional data. This made it impossible to draw causal conclusions, and we could only analyze possible associations. For example,

regions with more lonely residents can, as a result, become unhealthier. At the same time, citizens become lonelier as a result of their poorer health.

In conclusion, lifestyle factors, loneliness, and mastery are possible starting points for the explanation of regional health inequalities in the Netherlands. Lifestyle factors contribute to the explanation of regional differences in self-rated health and presence of chronic disease. In addition, loneliness and mastery contribute to explaining regional differences in self-perceived health, chronic disease, and psychological distress.

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Appendix

Table A1. Categories, codes, and sources for dependent and independent variables.

Variable	Category	Code	Sources
Gender§	Male	0	Statistics Netherlands
	Female	1	Statistics Netherlands
Migration background§	Dutch-born	0	Statistics Netherlands
	Western migration background	1	Statistics Netherlands
	Non-western migration background	2	Statistics Netherlands
Marital status*	Married/living together	0	Health Survey
	Never married	1	Health Survey
	Widowed	2	Health Survey
	Divorced	3	Health Survey
Highest attained level of education*	Primary school	3	Health Survey
	Lower vocational education	2	Health Survey
	Middle vocational/secondary	1	Health Survey
	Higher vocational/university	0	Health Survey
Standardized household income quartile§	0-25%	3	Statistics Netherlands
	26-50%	2	Statistics Netherlands
	51-75%	1	Statistics Netherlands
	76-100%	0	Statistics Netherlands
Self-perceived income inadequacy*	Inadequate, major concerns	3	Health Survey
	Inadequate, some concerns	2	Health Survey
	Adequate, minor concerns	1	Health Survey
	Adequate, no concerns	0	Health Survey
Physical activity*	Insufficient	1	Health Survey
	Sufficient	0	Health Survey
BMI*	Underweight (<18.5)	1	Health Survey
	Normal (18.5-25)	0	Health Survey
	Overweight (25-30)	2	Health Survey
	Obese (30>)	3	Health Survey
Alcohol consumption*	Never	0	Health Survey
	Moderate	1	Health Survey
	Excessive	2	Health Survey
Smoking*	Never smoked	0	Health Survey
	Former smoker	1	Health Survey
	Current smoker	2	Health Survey

table continues

Variable	Category	Code	Sources
Loneliness*	Continuous score 0-11[1]	n/a	Health Survey
Mastery*	Continuous score 7-35[2]	n/a	Health Survey
Chronic disease*	None	0	Health Survey
	At least one	1	Health Survey
Self-rated health*	Very (good)	0	Health Survey
	Fair, (very) poor	1	Health Survey
Psychological distress*	No, low or moderate risk (score 10-29)[2]	0	Health Survey
	High (score 30-50)[2]	1	Health Survey

BMI: body mass index. §Registry data *Self-reported data (Health Survey). [1] The variables loneliness and mastery are continuous variables. The 11 statements for loneliness (table A2) are answered "yes", "more or less" or "no" and result in a score between 0 and 11. Respondents scoring 0,1 or 2 are considered not lonely, respondents scoring between 3 up until 8 are somewhat lonely, respondents scoring 9 or 10 are severely lonely and respondents scoring 11 are very severely lonely. The 7 statements for mastery are answered on a 5-point Likert scale (totally agree [lowest score 1], agree, neither agree or disagree, disagree or totally disagree [highest score 5]). This results to a score between 7 and 35, a score of 19 or lower is considered as insufficient mastery. [2] The variable risk for psychological distress is based on the Kessler-10 questionnaire. The 10 questions (table A2) are answered on a 5-point Likert scale (all the time, most of the time, some of the time, a little of the time, and none of the time). The K10 score varies between 10 (no risk) and maximum 50 (high risk).

Table A2. Statements/questions fort he variables loneliness, mastery and psychological distress.

Loneliness (De Jong-Gierveld 1985)[1]	1. There is always someone I can talk to about my day-to-day problems.
	2. I miss having a really close friend.
	3. I experience a general sense of emptiness.
	4. There are plenty of people I can lean on when I have problems.
	5. I miss the pleasure of the company of others.
	6. I find my circle of friends and acquaintances too limited.
	7. There are many people I can trust completely.
	8. There are enough people I feel close to.
	9. I miss having people around me.
	10. I often feel rejected.
	11. I can call on my friends whenever I need them.
Mastery (Pearlin & Schooler 1978)[2]	1. I have little control over the things that happen to me.
	2. No way I can solve some of the problems I have.
	3. There is little I can do to change many of the important things of life.
	4. I often feel helpless in dealing with the problems of life.
	5. Sometimes I feel that I am being pushed around in life.

table continues

	6. What happens in the future mostly depends on me.
	7. I can do just about anything I really set my mind to.
Psychological distress (Kessler 2002) [K10][3]	1. About how often did you feel tired out for no good reason?
	2. About how often did you feel nervous?
	3. About how often did you feel so nervous that nothing could calm you down?
In the past 4 weeks…	4. About how often did you feel hopeless?
	5. About how often did you feel restless or fidgety?
	6. About how often did you feel so restless you could not sit still?
	7. About how often did you feel depressed?
	8. About how often did you feel that everything was an effort?
	9. About how often did you feel so sad that nothing could cheer you up?
	10. About how often did you feel worthless?

[1] The 11 statements by De Jong-Gierveld are answered "yes", "more or less" or "no". [2] The 7 statements by Pearlin & Schooler are answered on a 5-point Likert scale (totally agree, agree, neither agree or disagree, disagree or totally disagree). [3] The K10 questions are answered on a 5-point Likert scale (all the time, most of the time, some of the time, a little of the time, and none of the time).

Table A3. Missing data (n=457,150)

Variable	N	(%)
Region*	0	(0)
Age§	0	(0)
Gender§	0	(0)
Migration background§	0	(0)
Marital state*	11,192	(2.4)
Highest attained level of education *	31,422	(6.9)
Standardized household income quartile§	737	(0.2)
Income inadequacy*	35,643	(7.8)
Physical activity*	33,488	(7.3)
BMI*	21,261	(4.7)
Alcohol consumption*	36,967	(8.1)
Smoking*	32,605	(7.1)
Chronic disease*	8,808	(1.9)
Self-rated health*	5,730	(1.3)
Psychological distress*	20,103	(4.4)
Loneliness*	36,364	(8.0)
Mastery*	36,612	(8.0)

BMI: body mass index. §Registry data *Self-rated data (Health Survey).

Table A4. Descriptive weighted data

Variable	Category	%
Gender§	Male	50.9
Migration background§	Dutch-born	78.8
	Western migration background	4.9
Marital status*	Married/living together	66.1
	Never married	20.3
	Widowed	7.4
Highest attained level of education*	Primary school	6.2
	Lower vocational education	24.4
	Middle vocational/secondary	35.0
Standardized household income quartile§	0-25%	18.7
	26-50%	23.7
	51-75%	27.4
Self perceived income inadequacy*	Inadequate, major concerns	4.7
	Inadequate, some concerns	13.5
	Adequate, minor concerns	35.2
Physical activity*	Insufficient	34.7
Body Mass Index*	Normal (18,5-25)	49.4
	Overweight (25-30)	35.1
	Obese (30>)	13.8
Alcohol consumption*	Never	24.4
	Moderate	75.6
Smoking*	Never smoked	45.8
	Former smoker	33.3
Loneliness*	Somewhat or (very) severely (scores >2)[1]	42.8
Mastery*	Insufficient (score <20)[2]	9.9
Chronic disease*	None	66.0
Self-rated health*	Very (good)	75.6
Psychological distress*	No, low or moderate risk	93.5

BMI: body mass index. §Registry data *Self-rated data (Health Survey). [1]The variables loneliness and mastery are continuous variables. The 11 statements to determine degree of loneliness (table A2) are answered “yes”, “more or less” or “no” and result in a score between 0 and 11. Respondents scoring 0,1 or 2 are considered not lonely, respondents scoring between 3 and 8 are somewhat lonely, respondents scoring 9 or 10 are severely lonely and respondents scoring 11 are very severely lonely. The 7 statements for mastery are answered on a 5-point Likert scale (totally agree [lowest score 1], agree, neither agree or disagree, disagree or totally disagree [highest score 5]). This results to a score between 7 and 35, a score of 19 or lower is considered as insufficient mastery. [2]The variable risk for psychological distress is based on the Kessler-10 questionnaire. The 10 questions (table A2) are answered on a 5-point Likert scale (all the time, most of the time, some of the time, a little of the time, and none of the time). The K10 score varies between 10 (no risk) and maximum 50 (high risk).

Table A5. Percentages per region (n = 334,721)

	BMI		Alcohol consumption	Smoking		Physical activty	Lone-liness	Mastery	Self-rated health	Chronic disease	Psychological distress
%	Overweight	Obese	Excessive	Former smoker	Smoker	In-sufficient	Some-what or (very) severe[1]	In-sufficient[2]	Fair or (very) poor	At least one	High risk
Zuid-Limburg	35,4	16,3	7,4	33,7	22,3	40,6	46,6	11,4	28,0	37,1	7,1
Zuid-Holland-Zuid	36,3	15,1	5,3	32,4	21,1	38,0	41,2	9,5	21,1	30,6	4,9
Zeeland	36,5	13,7	6,2	35,5	17,5	29,9	45,5	10,0	25,6	32,7	5,2
Zaanstreek-Waterland	36,1	14,7	7,3	34,0	21,5	34,0	39,8	9,4	23,0	35,1	5,8
West-Brabant	36,1	13,5	6,5	35,1	17,8	34,8	42,1	9,3	24,6	30,1	5,5
Utrecht	31,2	11,6	7,6	31,4	19,6	33,3	39,5	7,9	20,3	30,6	5,0
Twente	37,4	14,0	8,1	33,1	20,5	29,2	39,3	8,1	21,1	33,4	7,0
Rotterdam	35,4	15,6	6,3	29,7	24,0	39,7	45,6	10,6	26,0	35,0	7,7
Noord- en Oost-Gelderland	37,7	13,8	6,7	36,3	18,5	31,0	36,7	8,5	20,5	35,5	5,3
Limburg-Noord	37,1	13,7	6,5	37,5	18,6	33,7	43,6	8,9	24,1	34,4	4,8
Kennemerland	34,4	12,3	8,0	35,3	19,3	31,6	39,6	7,7	19,9	31,3	4,9
IJsselland	35,5	12,5	7,2	35,5	20,1	31,3	37,8	8,2	20,1	33,9	5,3
Hollands Noorden	34,9	12,9	7,8	36,2	19,6	30,8	39,7	8,3	21,7	32,4	5,1
Hollands Midden	35,4	12,9	7,7	33,3	18,5	31,5	40,1	9,4	20,0	34,8	6,0
Hart voor Brabant	35,4	13,6	7,7	34,8	19,0	33,0	40,0	8,9	23,4	31,1	5,6
Haaglanden	33,9	13,7	6,7	28,2	21,3	34,5	46,6	10,9	24,7	36,2	8,9
Groningen	34,9	13,9	8,0	32,1	24,4	33,8	41,5	8,0	21,9	35,5	4,8
Gooi en Vechtstreek	32,9	9,9	8,6	37,5	17,8	37,5	37,5	7,9	21,1	31,6	5,2
Gelderland-Zuid	34,3	12,8	7,0	31,3	21,6	35,0	40,7	8,5	21,0	31,9	6,1
Gelderland-Midden	32,7	13,8	5,9	33,4	19,4	33,2	41,1	8,9	21,2	34,7	6,9

table continues

	BMI		Alcohol consumption	Smoking		Physical activty	Lone-liness	Mastery	Self-rated health	Chronic disease	Psychological distress
%	Overweight	Obese	Excessive	Former smoker	Smoker	In-sufficient	Some-what or (very) severe[1]	In-sufficient[2]	Fair or (very) poor	At least one	High risk
Friesland	36,2	13,2	7,2	36,2	21,4	32,6	41,9	8,8	20,4	33,3	4,9
Flevoland	37,7	14,5	4,4	32,0	17,5	40,8	42,5	9,6	22,8	34,6	7,0
Drenthe	37,0	15,1	8,2	35,3	22,9	32,5	40,1	8,2	21,2	33,2	4,8
Brabant-Zuidoost	35,0	12,0	7,7	34,5	18,1	31,4	42,0	9,9	24,6	30,9	6,1
Amsterdam	28,6	11,6	9,9	30,7	25,8	31,5	44,5	8,7	22,1	30,8	6,8

BMI: body mass index. Results based on weighted data.[1]Continuous variable, percentage of respondents scoring 3 or higher (of 11) for the De Jong-Gierveld scale. These respondents experience some degree of loneliness (somewhat, severe or very severe). [2]Continuous variable, percentage of respondents scoring 19 or lower (scale 7-35) for mastery, these respondents experience insufficient mastery.

Table A6. Prevalence ratios per region for self-rated health being fair or (very) poor, compared to Zuid-Limburg.

PR (95%CI)	Model 1	Model 2	Model 3a	Model 3b	Model 3c	Model 4
Zuid-Limburg	1,00 (ref)	1,00 (ref)	1,00 (ref)	1,00 (ref)	1,00 (ref)	1,00 (ref)
Zuid-Holland-Zuid	**0,75 (0,70-0,80)**	**0,80 (0,75-0,85)**	**0,81 (0,76-0,86)**	**0,83 (0,78-0,88)**	**0,81 (0,77-0,86)**	**0,83 (0,79-0,88)**
Zeeland	**0,91 (0,85-0,96)**	**0,94 (0,89-1,00)**	**1,02 (0,96-1,07)**	**0,94 (0,89-0,99)**	**0,94 (0,89-1,00)**	1,00 (0,95-1,05)
Zaanstreek-Waterland	**0,82 (0,78-0,86)**	**0,85 (0,81-0,89)**	**0,89 (0,85-0,93)**	**0,90 (0,86-0,95)**	**0,89 (0,85-0,94)**	**0,94 (0,90-0,98)**
West-Brabant	**0,88 (0,84-0,93)**	**0,95 (0,90-1,00)**	**1,00 (0,95-1,05)**	**0,96 (0,91-1,01)**	**0,96 (0,91-1,00)**	1,00 (0,95-1,05)
Utrecht	**0,73 (0,69-0,76)**	**0,85 (0,82-0,89)**	**0,90 (0,86-0,93)**	**0,89 (0,86-0,93)**	**0,89 (0,86-0,93)**	**0,94 (0,90-0,98)**
Twente	**0,75 (0,71-0,80)**	**0,81 (0,77-0,86)**	**0,85 (0,81-0,90)**	**0,86 (0,81-0,90)**	**0,84 (0,80-0,89)**	**0,88 (0,83-0,93)**
Rotterdam	**0,93 (0,89-0,97)**	**0,85 (0,82-0,88)**	**0,87 (0,83-0,90)**	**0,89 (0,86-0,93)**	**0,90 (0,87-0,93)**	**0,93 (0,89-0,96)**
Noord- en Oost-Gelderland	**0,73 (0,69-0,77)**	**0,83 (0,79-0,87)**	**0,87 (0,83-0,92)**	**0,87 (0,83-0,92)**	**0,84 (0,81-0,88)**	**0,89 (0,85-0,93)**
Limburg-Noord	**0,86 (0,82-0,90)**	**0,90 (0,86-0,94)**	**0,95 (0,91-0,99)**	**0,91 (0,87-0,96)**	**0,94 (0,90-0,98)**	0,97 (0,93-1,01)
Kennemerland	**0,72 (0,68-0,76)**	**0,78 (0,74-0,83)**	**0,83 (0,79-0,88)**	**0,82 (0,78-0,87)**	**0,85 (0,81-0,89)**	**0,90 (0,85-0,94)**
IJsselland	**0,72 (0,67-0,77)**	**0,84 (0,78-0,90)**	**0,89 (0,83-0,95)**	**0,88 (0,83-0,95)**	**0,86 (0,80-0,91)**	**0,91 (0,85-0,97)**

table continues

PR (95%CI)	Model 1	Model 2	Model 3a	Model 3b	Model 3c	Model 4
Hollands Noorden	**0,78 (0,74-0,82)**	**0,84 (0,80-0,89)**	**0,90 (0,86-0,95)**	**0,88 (0,84-0,93)**	**0,91 (0,86-0,95)**	**0,95 (0,91-0,99)**
Hollands Midden	**0,72 (0,68-0,75)**	**0,82 (0,78-0,86)**	**0,87 (0,83-0,91)**	**0,85 (0,82-0,89)**	**0,81 (0,77-0,84)**	**0,86 (0,82-0,90)**
Hart voor Brabant	**0,88 (0,84-0,93)**	**0,93 (0,89-0,97)**	**0,98 (0,94-1,02)**	**0,95 (0,91-0,99)**	**0,96 (0,92-1,00)**	**0,92 (0,88-0,96)**
Haaglanden	**0,84 (0,80-0,88)**	**0,86 (0,82-0,90)**	**0,89 (0,85-0,93)**	**0,89 (0,85-0,93)**	**0,89 (0,85-0,93)**	1,00 (0,96-1,05)
Groningen	**0,79 (0,74-0,83)**	**0,85 (0,81-0,90)**	**0,88 (0,84-0,93)**	**0,90 (0,86-0,95)**	**0,93 (0,89-0,98)**	0,96 (0,92-1.01)
Gooi en Vechtstreek	**0,76 (0,70-0,81)**	**0,82 (0,77-0,88)**	**0,88 (0,82-0,94)**	**0,88 (0,83-0,94)**	**0,87 (0,82-0,93)**	**0,94 (0,88-0,99)**
Gelderland-Zuid	**0,75 (0,71-0,79)**	**0,85 (0,80-0,89)**	**0,88 (0,84-0,92)**	**0,88 (0,84-0,92)**	**0,87 (0,83-0,91)**	**0,90 (0,86-0,95)**
Gelderland-Midden	**0,76 (0,71-0,81)**	**0,84 (0,79-0,90)**	**0,88 (0,83-0,94)**	**0,86 (0,81-0,92)**	**0,85 (0,80-0,90)**	**0,89 (0,84-0,94)**
Friesland	**0,73 (0,69-0,77)**	**0,78 (0,74-0,82)**	**0,82 (0,78-0,87)**	**0,82 (0,78-0,86)**	**0,83 (0,79-0,87)**	**0,86 (0,82-0,91)**
Flevoland	**0,81 (0,71-0,92)**	**0,88 (0,78-0,99)**	**0,91 (0,81-1,02)**	**0,91 (0,82-1,02)**	**0,94 (0,84-1,05)**	0,96 (0,87-1,07)
Drenthe	**0,76 (0,70-0,82)**	**0,80 (0,74-0,86)**	**0,82 (0,76-0,88)**	**0,84 (0,78-0,90)**	**0,86 (0,80-0,92)**	**0,88 (0,82-0,94)**
Brabant-Zuidoost	**0,88 (0,84-0,92)**	**0,98 (0,93-1,02)**	**1,05 (1,00-1,09)**	**1,00 (0,95-1,04)**	**0,97 (0,93-1,02)**	1,04 (0,99-1,08)
Amsterdam	**0,79 (0,74-0,84)**	**0,77 (0,73-0,82)**	**0,81 (0,77-0,86)**	**0,82 (0,78-0,87)**	**0,85 (0,80-0,89)**	**0,88 (0,84-0,93)**

PR: prevalence ratio. CI: confidence interval. PR's in bold are significant p<0.05. Model 1: region. Model 2: region, demographic factors, and SES. Model 3a: region, demographic factors, SES, and lifestyle. Model 3b: region, demographic factors, SES, and loneliness. Model 3c: region, demographic factors, SES, and mastery. Model 4: region, demographic factors, SES, lifestyle, loneliness, and mastery. Results from robust Poisson regressions (n = 334,721), based on weighted data.

Table A7. Prevalence ratios per region for at least one chronic disease, compared to Zuid-Limburg.

PR (95% CI)	Model 1	Model 2	Model 3a	Model 3b	Model 3c	Model 4
Zuid-Limburg	1,00 (ref)	1,00 (ref)	1,00 (ref)	1,00 (ref)	1,00 (ref)	1,00 (ref)
Zuid-Holland-Zuid	**0,83 (0,78-0,87)**	**0,86 (0,82-0,91)**	**0,87 (0,82-0,91)**	**0,88 (0,83-0,92)**	**0,87 (0,83-0,91)**	**0,88 (0,84-0,92)**
Zeeland	**0,87 (0,83-0,91)**	**0,87 (0,83-0,91)**	**0,90 (0,86-0,94)**	**0,87 (0,83-0,91)**	**0,87 (0,83-0,91)**	**0,89 (0,85-0,93)**
Zaanstreek-Waterland	**0,93 (0,90-0,97)**	**0,96 (0,93-1,00)**	**0,98 (0,94-1,02)**	**0,99 (0,95-1,03)**	**0,99 (0,95-1,02)**	1,01 (0,97-1,05)
West-Brabant	**0,81 (0,77-0,84)**	**0,84 (0,80-0,87)**	**0,85 (0,82-0,89)**	**0,84 (0,81-0,88)**	**0,84 (0,80-0,87)**	**0,85 (0,82-0,89)**
Utrecht	**0,82 (0,79-0,85)**	**0,91 (0,88-0,94)**	**0,94 (0,91-0,97)**	**0,93 (0,90-0,96)**	**0,93 (0,91-0,96)**	**0,95 (0,93-0,98)**
Twente	**0,89 (0,85-0,94)**	**0,94 (0,90-0,99)**	**0,97 (0,93-1,01)**	**0,97 (0,93-1,01)**	**0,96 (0,92-1,00)**	0,98 (0,94-1,02)

table continues

PR (95% CI)	Model 1	Model 2	Model 3a	Model 3b	Model 3c	Model 4
Rotterdam	**0,94 (0,91-0,97)**	**0,94 (0,91-0,98)**	**0,95 (0,92-0,98)**	**0,96 (0,93-1,00)**	**0,97 (0,94-1,00)**	0,98 (0,95-1,01)
Noord- en Oost-Gelderland	**0,95 (0,92-0,99)**	**1,00 (0,97-1,04)**	**1,02 (0,99-1,06)**	**1,03 (0,99-1,07)**	**1,01 (0,97-1,05)**	1,03 (0,99-1,07)
Limburg-Noord	**0,93 (0,89-0,96)**	**0,94 (0,91-0,98)**	**0,96 (0,93-1,00)**	**0,95 (0,92-0,98)**	**0,96 (0,93-0,99)**	0,97 (0,94-1,01)
Kennemerland	**0,84 (0,80-0,88)**	**0,88 (0,84-0,92)**	**0,90 (0,87-0,94)**	**0,90 (0,87-0,94)**	**0,92 (0,88-0,95)**	**0,94 (0,90-0,97)**
IJsselland	**0,91 (0,87-0,96)**	**1,00 (0,96-1,05)**	**1,03 (0,98-1,08)**	**1,03 (0,98-1,08)**	**1,01 (0,96-1,05)**	1,03 (0,98-1,08)
Hollands Noorden	**0,87 (0,83-0,91)**	**0,90 (0,87-0,94)**	**0,93 (0,90-0,97)**	**0,92 (0,89-0,96)**	**0,94 (0,90-0,98)**	**0,96 (0,92-0,99)**
Hollands Midden	**0,93 (0,90-0,97)**	**1,01 (0,97-1,04)**	**1,03 (1,00-1,07)**	**1,03 (0,99-1,06)**	**0,99 (0,96-1,02)**	1,02 (0,98-1,05)
Hart voor Brabant	**0,84 (0,80-0,87)**	**0,88 (0,85-0,91)**	**0,90 (0,87-0,94)**	**0,89 (0,86-0,93)**	**0,89 (0,86-0,93)**	**0,91 (0,88-0,94)**
Haaglanden	0,97 (0,93-1,01)	**1,00 (0,97-1,04)**	**1,02 (0,99-1,06)**	**1,02 (0,98-1,06)**	**1,02 (0,99-1,06)**	**1,04 (1,00-1,08)**
Groningen	**0,95 (0,91-0,99)**	**1,01 (0,97-1,05)**	**1,03 (0,99-1,07)**	**1,04 (0,99-1,08)**	**1,05 (1,01-1,09)**	**1,06 (1,02-1,11)**
Gooi en Vechtstreek	**0,85 (0,81-0,90)**	**0,87 (0,83-0,92)**	**0,90 (0,86-0,95)**	**0,90 (0,85-0,95)**	**0,90 (0,86-0,95)**	**0,93 (0,89-0,98)**
Gelderland-Zuid	**0,86 (0,82-0,90)**	**0,93 (0,89-0,97)**	**0,94 (0,91-0,98)**	**0,94 (0,91-0,98)**	**0,93 (0,90-0,97)**	**0,95 (0,91-0,99)**
Gelderland-Midden	**0,93 (0,88-0,98)**	**0,99 (0,94-1,04)**	**1,01 (0,96-1,06)**	**1,00 (0,96-1,05)**	**0,99 (0,94-1,04)**	1,01 (0,96-1,06)
Friesland	**0,89 (0,86-0,93)**	**0,91 (0,88-0,95)**	**0,93 (0,90-0,97)**	**0,93 (0,89-0,97)**	**0,94 (0,90-0,97)**	**0,95 (0,92-0,99)**
Flevoland	0,93 (0,85-1,02)	**1,01 (0,92-1,10)**	**1,02 (0,94-1,11)**	**1,03 (0,94-1,12)**	**1,03 (0,95-1,13)**	1,05 (0,96-1,14)
Drenthe	**0,90 (0,84-0,95)**	**0,91 (0,86-0,96)**	**0,92 (0,87-0,97)**	**0,93 (0,88-0,98)**	**0,94 (0,89-1,00)**	0,95 (0,90-1,01)
Brabant-Zuidoost	**0,83 (0,80-0,87)**	**0,87 (0,84-0,91)**	**0,90 (0,87-0,94)**	**0,88 (0,85-0,92)**	**0,87 (0,84-0,91)**	**0,90 (0,86-0,93)**
Amsterdam	**0,83 (0,79-0,87)**	**0,88 (0,84-0,92)**	**0,90 (0,86-0,94)**	**0,90 (0,86-0,94)**	**0,92 (0,88-0,96)**	**0,93 (0,89-0,98)**

PR: prevalence ratio. CI: confidence interval. PR's in bold are significant p<0.05. Model 1: region. Model 2: region, demographic factors, and SES. Model 3a: region, demographic factors, SES, and lifestyle. Model 3b: region, demographic factors, SES, and loneliness. Model 3c: region, demographic factors, SES, and mastery. Model 4: region, demographic factors, SES, lifestyle, loneliness, and mastery. Results from robust Poisson regressions (n = 334,721), based on weighted data.

Table A8. Odds ratios per region for high risk for psychological distress, compared to Zuid-Limburg.

OR (95% CI)	Model 1	Model 2	Model 3a	Model 3b	Model 3c	Model 4
Zuid-Limburg	1,00 (ref)	1,00 (ref)	1,00 (ref)	1,00 (ref)	1,00 (ref)	1,00 (ref)
Zuid-Holland-Zuid	**0,66 (0,54-0,79)**	**0,71 (0,58-0,86)**	**0,72 (0,59-0,88)**	**0,77 (0,63-0,95)**	**0,69 (0,54-0,88)**	**0,76 (0,60-0,96)**
Zeeland	**0,70 (0,58-0,84)**	**0,83 (0,68-1,00)**	**0,91 (0,75-1,11)**	**0,81 (0,66-0,99)**	**0,77 (0,62-0,96)**	**0,80 (0,64-0,99)**
Zaanstreek-Waterland	**0,82 (0,72-0,94)**	**0,86 (0,75-1,00)**	**0,92 (0,80-1,06)**	**1,06 (0,91-1,23)**	**0,97 (0,82-1,15)**	1,09 (0,92-1,30)
West-Brabant	**0,75 (0,65-0,88)**	**0,89 (0,76-1,04)**	**0,95 (0,81-1,12)**	**0,92 (0,78-1,08)**	**0,92 (0,76-1,12)**	0,96 (0,79-1,16)
Utrecht	**0,69 (0,61-0,77)**	**0,77 (0,69-0,87)**	**0,82 (0,73-0,93)**	**0,89 (0,79-1,01)**	**0,87 (0,75-1,00)**	0,94 (0,81-1,09)
Twente	0,96 (0,81-1,14)	**1,08 (0,91-1,28)**	**1,18 (0,98-1,40)**	**1,30 (1,08-1,57)**	**1,31 (1,07-1,60)**	**1,49 (1,20-1,84)**
Rotterdam	1,07 (0,96-1,19)	**0,78 (0,69-0,88)**	**0,80 (0,71-0,90)**	**0,91 (0,80-1,04)**	**0,92 (0,80-1,06)**	0,99 (0,86-1,15)
Noord- en Oost-Gelderland	**0,71 (0,62-0,81)**	**0,94 (0,82-1,08)**	**1,02 (0,88-1,17)**	**1,04 (0,90-1,21)**	**0,97 (0,83-1,14)**	1,05 (0,89-1,25)
Limburg-Noord	**0,67 (0,59-0,76)**	**0,77 (0,67-0,88)**	**0,81 (0,71-0,93)**	**0,78 (0,67-0,90)**	**0,82 (0,70-0,97)**	**0,84 (0,71-0,99)**
Kennemerland	**0,68 (0,58-0,79)**	**0,76 (0,65-0,89)**	**0,82 (0,70-0,96)**	**0,87 (0,74-1,03)**	**0,90 (0,75-1,08)**	1,01 (0,84-1,22)
IJsselland	**0,70 (0,58-0,84)**	**0,86 (0,71-1,05)**	**0,94 (0,77-1,14)**	**1,02 (0,83-1,26)**	**0,86 (0,69-1,08)**	0,99 (0,79-1,25)
Hollands Noorden	**0,71 (0,61-0,82)**	**0,78 (0,67-0,91)**	**0,85 (0,73-0,99)**	**0,90 (0,77-1,06)**	**0,86 (0,72-1,03)**	0,95 (0,79-1,14)
Hollands Midden	**0,82 (0,72-0,92)**	**1,00 (0,88-1,14)**	**1,09 (0,95-1,24)**	**1,15 (1,00-1,32)**	**0,96 (0,82-1,13)**	1,11 (0,94-1,30)
Hart voor Brabant	**0,76 (0,67-0,86)**	**0,91 (0,80-1,04)**	**0,98 (0,86-1,12)**	**0,99 (0,86-1,15)**	**0,99 (0,84-1,17)**	1,05 (0,89-1,24)
Haaglanden	**1,27 (1,12-1,44)**	**1,05 (0,92-1,19)**	**1,10 (0,96-1,26)**	**1,17 (1,02-1,35)**	**1,13 (0,96-1,34)**	**1,22 (1,03-1,44)**
Groningen	**0,66 (0,57-0,78)**	**0,65 (0,55-0,77)**	**0,69 (0,59-0,82)**	**0,80 (0,67-0,95)**	**0,76 (0,62-0,92)**	0,84 (0,69-1,03)
Gooi en Vechtstreek	**0,71 (0,58-0,87)**	**0,82 (0,66-1,02)**	**0,88 (0,71-1,09)**	**0,99 (0,79-1,25)**	**0,88 (0,69-1,13)**	1,01 (0,78-1,29)
Gelderland-Zuid	**0,86 (0,75-0,98)**	**0,98 (0,85-1,13)**	**1,04 (0,90-1,20)**	**1,13 (0,97-1,32)**	**1,09 (0,92-1,29)**	1,19 (0,99-1,42)
Gelderland-Midden	0,95 (0,78-1,14)	**1,10 (0,91-1,32)**	**1,16 (0,97-1,40)**	**1,18 (0,97-1,43)**	**1,10 (0,89-1,35)**	1,19 (0,97-1,46)
Friesland	**0,66 (0,57-0,77)**	**0,75 (0,64-0,88)**	**0,80 (0,68-0,94)**	**0,86 (0,73-1,02)**	**0,86 (0,72-1,03)**	0,95 (0,79-1,14)
Flevoland	1,01 (0,74-1,37)	**0,98 (0,71-1,35)**	**1,03 (0,74-1,43)**	**1,12 (0,80-1,55)**	**1,18 (0,84-1,67)**	1,27 (0,90-1,79)
Drenthe	**0,65 (0,52-0,80)**	**0,70 (0,56-0,88)**	**0,71 (0,57-0,90)**	**0,79 (0,62-1,02)**	**0,80 (0,60-1,07)**	0,84 (0,63-1,13)
Brabant-Zuidoost	**0,83 (0,73-0,94)**	**1,01 (0,88-1,17)**	**1,12 (0,97-1,29)**	**1,08 (0,93-1,25)**	**0,99 (0,84-1,18)**	1,04 (0,87-1,24)
Amsterdam	0,96 (0,84-1,11)	**0,73 (0,62-0,85)**	**0,77 (0,66-0,90)**	**0,90 (0,76-1,06)**	**0,93 (0,78-1,11)**	1,03 (0,86-1,23)

PR: prevalence ratio. CI: confidence interval. PR's in bold are significant p<0.05. Model 1: region. Model 2: region, demographic factors, and SES. Model 3a: region, demographic factors, SES, and lifestyle. Model 3b: region, demographic factors, SES, and loneliness. Model 3c: region, demographic factors, SES, and mastery. Model 4: region, demographic factors, SES, lifestyle, loneliness, and mastery. Results from robust Poisson regressions (n = 334,721), based on weighted data

Chapter 6

Regional differences in healthcare costs further explained: the contribution of health, lifestyle, loneliness, and mastery

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Abstract

Healthcare costs in the Netherlands are rising, and vary considerably among regions. Explaining regional differences in healthcare costs can help policymakers in targeting appropriate interventions in order to restrain costs. Factors usually taken into account when analyzing regional differences in healthcare costs are demographic structure and socioeconomic status (SES). However, health, lifestyle, loneliness and mastery have also been linked to healthcare costs. Therefore, this study analyzes the contribution of health, lifestyle factors (BMI, alcohol consumption, smoking and physical activity), loneliness, and mastery to regional differences in healthcare costs. Analyses are performed in a linked dataset (*n*= 334,721) from the Dutch Public Health Services, Statistics Netherlands, the National Institute for Public Health and the Environment (year 2016), and the healthcare claims database Vektis (year 2017) with Poisson and zero-inflated binomial regressions. Regional differences in general practitioner consult costs remain significant even after taking into account health, lifestyle, loneliness, and mastery. Regional differences in costs for mental, pharmaceutical, and specialized care are less pronounced and can be explained to a large extent. For total healthcare costs, regional differences are mostly explained through the factors included in this study. Hence, addressing lifestyle factors, loneliness and mastery can help policymakers in restraining healthcare costs. In this study, the region of Zuid-Limburg represents the reference region. Use Compare Regions for Health and Healthcare costs (*Regiovergelijker gezondheid en zorgkosten*), in order to select all other Dutch regions as reference region.

Introduction

Healthcare costs in the Netherlands continue to increase annually [1]. Before the coronavirus pandemic, the average annual growth for the coming decades was calculated to be 2.8%, according to the Dutch National Institute for Public Health and the Environment [1]. With rising healthcare costs, the affordability of the Dutch healthcare system is under increasing pressure. In addition, average healthcare costs vary strongly between regions and municipalities in the Netherlands. In 2018, the average healthcare costs, as reimbursed by the basic health insurance plan, averaged €2,625 per insured year (insured years are insured persons weighted for the registration period in the particular municipality; this makes it possible to compare municipalities regardless of births, deaths, or relocations). Between the municipalities with the highest and lowest healthcare costs, however, there was a difference of more than €1,700 (for example, €3,625 in Kerkrade and €1,853 in Urk). Even after adjusting for age and gender, the difference between the municipalities with the highest and lowest healthcare costs was approximately €1,200 (for example, €3,273 for Heerlen and €2,074 for Rozendaal) [2]. The regions with higher healthcare costs are the border regions of Zeeland, Groningen, Drenthe, and South Limburg (*Zuid-Limburg*) in particular. In order to reduce the increase in healthcare costs, explanations for regional differences are needed to provide insight into possible leads.

A study based on relocations in the Netherlands between 2006 and 2013 showed that 70% of regional differences in total healthcare costs are explained by demand factors [3]. Demand factors are all factors that pertain to the individual, such as level of education and health status. In a previous study on population funding, regional differences in specific groups of the chronically ill (people with depression and diabetics) were largely explained by demand factors [4]. In these healthcare cost studies, a part of the Dutch population was assessed, adjusted for age and gender [3, 4], socioeconomic status (SES), and self-reported health [4]. In addition to demographic characteristics, SES, and self-reported health [5], there are other factors that appear to play a role in higher healthcare utilization and, as a result, higher costs, such as an unhealthy lifestyle [6, 7] and loneliness [8, 9]. Lonely citizens visit a doctor more often [8, 9], are more frequently in need of mental healthcare [8] and inpatient care, and are more likely to take antidepressants and anxiolytics [9].

In this national study, we aimed to explain regional variations in healthcare costs based on lifestyle factors, loneliness, and mastery, after adjusting for demographic factors, SES, and general and mental health. In an accompanying article in a special issue of the *Journal for Health Sciences* (*Tijdschrift voor gezondheidswetenschappen*), we also show

that lifestyle, loneliness, and mastery partly explain regional differences in general and mental health (operationalized by means of self-perceived health, chronic illness, and psychological distress) [10].

The research question for the current study was: "Do lifestyle factors, loneliness, and mastery contribute to explaining regional differences in healthcare costs in addition to age, gender, SES, and health status?" The results can direct future preventive interventions and policies to help reduce regional differences in healthcare costs.

Methods

Data and sampling

Data were extracted from a linked dataset provided by the Dutch Public Health Services, Statistics Netherlands, and the healthcare claims–based database Vektis. The Health Survey 2016 provides information about demographic factors, SES, lifestyle, loneliness, mastery, and physical and mental state of health of the respondents [10]. Registry data from Statistics Netherlands (based on the Dutch Personal Records Database and the Dutch Tax and Customs Administration) were linked to the survey data. This linkage provided more information about the migration background of respondents and their household income. Finally, data on national healthcare claims (covered by the basic health insurance under the Healthcare Insurance Act) provided by Vektis were linked for the year 2017. The datasets were linked using pseudonymized RIN numbers provided by Statistics Netherlands in a secured digital environment. After data linkage and exclusion of missing data, the sample consisted of 334,721 persons. To ensure the representativeness of the sample, weighting factors were added to the Health Survey [10].

Dependent variables

The dependent variables were the following five cost categories: total costs (all costs reimbursed by the Healthcare Insurance Act), general practitioner (GP) consultation costs, pharmaceutical costs, specialized care costs (hospital and curative care), and mental healthcare costs (inpatient and outpatient mental healthcare and long-term mental healthcare). For inpatient mental healthcare, costs are covered by the Healthcare Insurance Act for up to three years. After three years, these costs are covered by the Dutch Long-term Care Act. The costs covered by the Long-Term Care Act were not included in the Vektis data.

Independent variables

The independent variables were region, demographic characteristics, SES, general and mental health, lifestyle, loneliness, and mastery. For the variable "region", we used the

regional classification of the Public Health Survey 2016, with the region of Zuid-Limburg as the reference group. Zuid-Limburg was chosen because this is the region with the highest healthcare costs, the highest number of adults with a chronic disease [11], the lowest percentage of adults with a good self-rated health [12], the highest number of lonely adults [13], and the highest number of adults with insufficient mastery [14].

Demographic factors were age, gender, migration background ("Dutch", "Western migration background", or "non-Western migration background"), and marital status ("married/living together", "never married", "widowed", or "divorced"). SES consisted of the highest attained level of education ("primary education", "lower vocational education", "middle vocational or secondary education", or "higher vocational education or university"), standardized household income quartile, and income inadequacy ("inadequate, major concerns", "inadequate, some concerns", "adequate, minor concerns", or "adequate, no concerns") [10]. To assess general health, self-rated health ("(very) good" or "fair, (very) poor") and self-reported chronic disease ("yes, one or more" or "no") were used. The variable "psychological distress" (assessed with the Kessler-10 questionnaire [15]) was used as a proxy for the mental component of health, resulting in a total score ranging from 10 to 50 (a score of 10–29 indicated "no or low risk", and a score 30 indicated "moderate or high risk"). Lifestyle factors included body mass index category (<18.5 kg/m^2 was considered "underweight", 18.5–25 kg/m^2 was "normal", 25–30 kg/m^2 was "overweight", and >30 kg/m^2 was "obese"), smoking history ("never", "former smoker", or "current smoker"), alcohol consumption ("never", "moderate", or "excessive") and (in)sufficient physical activity. Loneliness was assessed with the De Jong-Gierveld scale [16] (continuous score ranging from 0 to 11, whereby a score of 3–8 was considered "moderate", 9–10 was "severe", and 11 was "very severe loneliness"). Mastery was assessed with the Pearlin Mastery Scale (continuous score ranging from 7 to 35, whereby a score ≤19 was considered "insufficient mastery") [17].

Statistical analyses

For total healthcare costs, the incidence rate ratio (IRR) was assessed with Poisson regressions. The IRR represented the change in costs per change of the particular independent variable. For the cost categories of GP consultations, pharmacy, specialist care, and mental healthcare, zero-inflated binomial (ZINB) distributions were used, because most people do not need all these types of healthcare and these cost data therefore contain many zeros (Table 1). The ZINB model is a combination of two separate models. The first part is a logistics model that estimates the probability that a person incurs no costs. The second model is a negative binomial model, which modulates the amount of costs for those who do incur costs. The ZINB model yields two sets of estimates: the odds ratio (OR) for the logistic model and the IRR for the negative binomial model.

For Model 1, only region was included. In Model 2, the demographic characteristics and SES were added to region. Self-perceived health was added in Model 3a, self-reported chronic disease in Model 3b, and psychological distress in Model 3c. In Model 4, the correlation of region with healthcare costs was corrected for demographic factors, SES, self-perceived health, chronic illness, and psychological distress. Lifestyle was added in Model 5a, loneliness in Model 5b, and mastery in Model 5c. In Model 6, all beforementioned factors were included.

Marginal average costs were calculated based on the unadjusted costs (Model 1) and the adjusted costs (Model 6). Marginal costs per region represented the average costs per person in a particular region if the population of this region shared the same demographic factors, SES, general and mental health, lifestyle, loneliness, and mastery as the entire Dutch population. All analyses were performed in Stata 15 [18]. Multiple data imputation to account for missing data was considered. However, in Stata, ZINB models cannot be performed with data imputation, and the analyses were therefore performed with complete data. From previous analyses with this dataset, it appeared that the results of the complete data (complete case analyses) were comparable with the results of the multiple imputed data [10], which indicated that the missing completely at random assumption could be made. Therefore, only the complete case sample was used.

Results

Slightly over half of the sample was female (52.4%), and the mean age was 59.2 years (standard deviation (SD): 16.9) (Appendix Table A1) [10]. The majority of the respondents reported a (very) good health (74.0%) and no chronic disease (60.7%), whereas 4.5% of the respondents reported psychological distress. With regard to healthcare costs in 2017, 17.3% of the respondents incurred no GP consultation costs, 20.1% did not incur any pharmaceutical costs, 26.9% did not incur any specialist care costs, and 96.7% of the respondents incurred no mental healthcare costs (Table 1). The percentages of missing data per variable are shown in Appendix Table A2.

The results for total healthcare costs in the unadjusted model (Model 1) and the most comprehensive model (Model 6) are shown in Table 2. For total healthcare costs, most regional differences with Zuid-Limburg could be explained. Residents of 22 of the other 24 regions incurred significantly lower healthcare costs compared with residents of Zuid-Limburg in the unadjusted model; the IRR varied from 0.77 to 0.90 (Table 2). In the most comprehensive model, residents of Northern Holland (*Hollands Noorden*) (IRR:

0.93) and South Holland–South (*Zuid-Holland-Zuid*) (IRR: 0.92) incurred significantly lower total healthcare costs than residents of Zuid-Limburg. Residents of the region of Amsterdam incurred significantly higher healthcare costs (IRR: 1.14) (Table 2).

Table 1. Descriptive data for healthcare costs based on unweighted data

	Total sample (*N*= 334,721)			Respondents with costs			
Cost category	Median (IQR)	Q1	Q3	*n* (%)	Median (IQR)	Q1	Q3
Total¥	€814.78 (€2,361.94)	€220.17	€2,582.11	334,276 (99.9%)	€817.44 (€2,364.87)	€221.45	€2,586.32
GP consultation¥	€31.55 (€56.30)	€9.07	€65.37	276,873 (82.7%)	€40.80 (€58.00)	€18.62	€76.62
Mental healthcare¥	€0.00 (€0.00)	€0.00	€0.00	10,946 (3.3%)	€1,323.88 (€2,643.87)	€805.69	€3,449.56
Pharmaceutical care¥	€96.65 (€337.69)	€15.27	€352.96	267,385 (79.9%)	€161.87 (€421.20)	€54.08	€475.28
Specialist care¥	€217.86 (€1,155.40)	€0.00	€1155.40	244,774 (63.1%)	€576.23 (€1,725.76)	€144.13	€1,869.89

IQR: interquartile range; Q1: lowest quartile; Q3: highest quartile; GP: general practitioner. ¥Vektis data

Table 2. Incidence rate ratios per region for total healthcare costs compared with Zuid-Limburg based on Poisson regressions (*n*= 334,721)

	IRR (95% CI)	
Region	**Model 1 (region)**	**Model 6 (total)**
Zuid-Limburg	1.00 (ref)	1.00 (ref)
Zuid-Holland-Zuid	**0.78 (0.71-0.85)**	0.92 (0.86-1.00)
Zeeland	**0.91 (0.84-0.99)**	1.02 (0.95-1.09)
Zaanstreek-Waterland	**0.86 (0.80-0.93)**	1.00 (0.93-1.06)
West-Brabant	**0.89 (0.82-0.95)**	1.04 (0.97-1.11)
Utrecht	**0.79 (0.74-0.84)**	1.01 (0.96-1.08)
Twente	**0.89 (0.80-0.99)**	1.08 (0.97-1.20)
Rotterdam-Rijnmond	**0.90 (0.84-0.96)**	1.02 (0.96-1.09)
Noord- en Oost-Gelderland	**0.84 (0.79-0.90)**	0.98 (0.92-1.04)
Limburg-Noord	0.93 (0.86-1.01)	1.03 (0.95-1.11)
Kennemerland	**0.82 (0.76-0.88)**	1.03 (0.96-1.10)
IJsselland	**0.84 (0.77-0.91)**	1.02 (0.95-1.10)
Hollands Noorden	**0.77 (0.72-0.83)**	0.93 (0.87-1.00)
Hollands Midden	**0.80 (0.75-0.86)**	0.95 (0.89-1.01)
Hart voor Brabant	**0.85 (0.76-0.94)**	1.02 (0.92-1.13)
Haaglanden	**0.90 (0.83-0.97)**	1.06 (0.98-1.14)
Groningen	**0.81 (0.75-0.88)**	0.98 (0.91-1.06)

table continues

	IRR (95% CI)	
Region	**Model 1 (region)**	**Model 6 (total)**
Gooi en Vechtstreek	**0.85 (0.77-0.94)**	1.00 (0.91-1.10)
Gelderland-Zuid	**0.87 (0.79-0.96)**	1.06 (0.96-1.17)
Gelderland-Midden	**0.82 (0.76-0.90)**	0.97 (0.90-1.05)
Friesland	**0.85 (0.78-0.91)**	1.00 (0.93-1.07)
Flevoland	**0.78 (0.69-0.87)**	0.96 (0.86-1.06)
Drenthe	**0.85 (0.77-0.95)**	0.99 (0.89-1.09)
Brabant-Zuidoost	**0.87 (0.81-0.93)**	1.02 (0.96-1.09)
Amsterdam	**0.86 (0.79-0.94)**	**1.14 (1.04-1.25)**

IRRs in bold are significant ($P< 0.05$). IRR: incidence rate ratio; CI: confidence interval. Model 1 only takes region into account. In Model 6, the association between region and healthcare costs was corrected for demographic factors, socioeconomic status (SES), general and mental health, lifestyle, loneliness, and mastery. Registry data: age, gender, migration background, and household income. Self-reported data: marital status, education, income inadequacy, general and mental health, lifestyle, loneliness, and mastery.

The results for GP consultation, mental healthcare, pharmaceutical, and specialist care costs are twofold and are shown in Appendix Tables A4–A7. In addition, the marginal costs were calculated based on both parts of the ZINB model. These are visualized in Appendix Figures A1–A4.

By adjusting for demographic factors, SES, and general and mental health, the observed cost differences between regions could be largely explained. The differences that persisted after these corrections could be partly explained by lifestyle, loneliness, and mastery (Appendix Tables A3–A7). Lifestyle (Model 5a) mainly contributed to (small) regional differences in total, GP consultation, pharmaceutical, and specialist care costs. Loneliness (Model 5b) contributed to explaining the (small) regional differences in GP consultation, mental healthcare, and specialist care costs. Mastery (Model 5c) contributed to the (small) differences in mental healthcare and pharmaceutical costs.

The marginal costs for total healthcare are shown in Figure 1, with the greatest (positive) difference seen in Models 1 and 6 for Zuid-Limburg. Here, the average marginal costs decreased significantly from €2,705 per person (based on uncorrected data) to €2,277 per person (based on corrected data). The biggest (negative) difference was observed in the region of Amsterdam, where the average marginal costs rose from €2,327 to €2,595 per person after adjusting for demographic factors, SES, general and mental health, lifestyle, loneliness, and mastery. For the other cost categories, the confidence intervals for Zuid-Limburg did not overlap or only overlapped minimally. The average marginal

costs decreased for GP consultations (from €52 to €48), pharmaceuticals (from €318 to €286), and specialist care (from €1,453 to €,1257) (see Appendix Figures A1–A4).

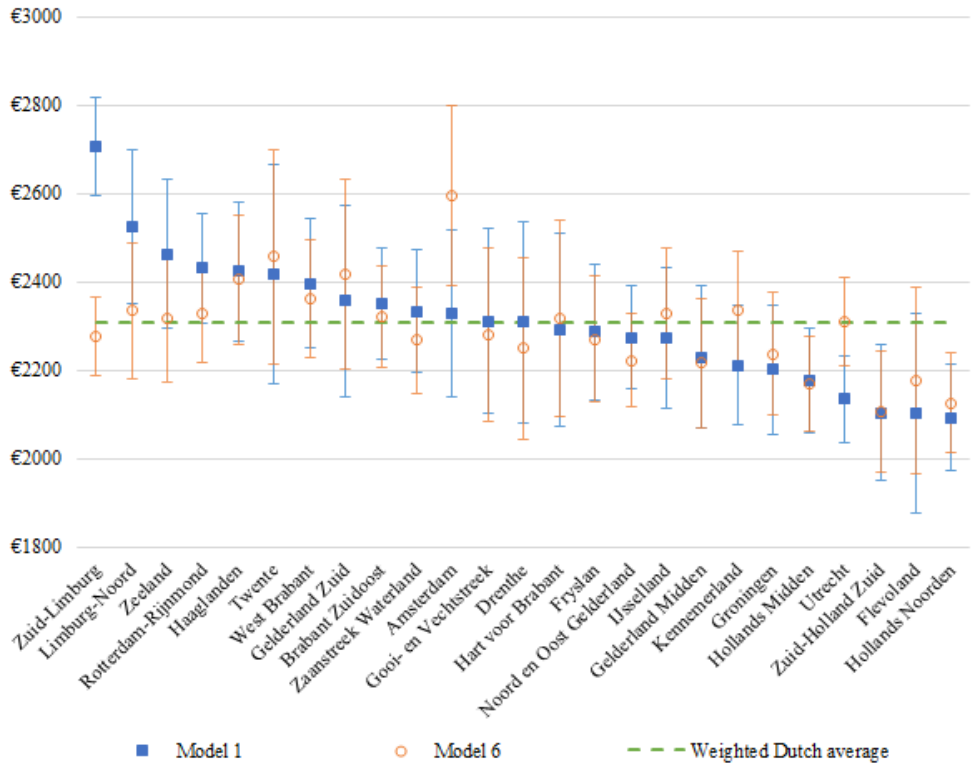

Figure 1. Marginal costs of region for total healthcare costs based on unadjusted costs (Model 1) and fully adjusted costs (Model 6)

Model 1 was only adjusted for region. In Model 6, the association between region and healthcare costs was adjusted for demographic factors, socioeconomic status (SES), general and mental health, lifestyle, loneliness, and mastery. The marginal costs in Model 6 reflect the average costs per person in a specific region if the population of this region shared the same level of demographic factors, SES, general and mental health, lifestyle, loneliness, and mastery as the entire Dutch population. Registry data: age, gender, migration background and household income. Self-reported data: marital status, education, income inadequacy, self-rated health, chronic disease, psychological distress, lifestyle, loneliness, and mastery.

Discussion

We observed large regional differences in healthcare costs in the Netherlands. Based on total healthcare costs, regional differences could be explained. In addition to the most common factors (demographic factors and SES), health status, lifestyle, loneliness, and mastery contributed to these variations in different ways. General and mental health explained a large part of the regional differences in healthcare costs. Lifestyle, loneliness, and mastery contributed directly and to a small extent to the explanation of regional differences in healthcare costs. Our other published study showed that lifestyle, loneliness, and mastery contributed to regional differences in health and thus indirectly to regional differences in healthcare costs as well [10]. This study presented regional differences based on the reference region of Zuid-Limburg. In the Dutch-language tool Compare Regions for Health and Healthcare Costs (*Regiovergelijker gezondheid en zorgkosten*), users can choose their own reference region and compare the results of the uncorrected model (Model 1) and the comprehensive adjusted model (Model 6) [19].

With regard to various healthcare cost categories, a number of findings stand out. First, residents of Zuid-Limburg incurred the highest GP consultation costs, even in the most comprehensive model. In other words, with the same demographic factors, SES, general and mental health, lifestyle, loneliness, and level of mastery, residents of Zuid-Limburg still had more GP consultations. This corresponds with earlier, albeit anecdotal, evidence from research into the health inequalities in Limburg [20]. Even though cost savings for the entire healthcare system are small (in 2017, GP consultation costs represented 1.7% of total healthcare costs), the higher demand for GP care does correspond with the increasing pressure that GPs experience, especially during the coronavirus pandemic [21]. GPs increasingly have to deal with patients with (psycho) social problems, who require other types of care [22, 23]. The results of this study suggest that by intervening in the (causes of) socioeconomic problems, differences in lifestyle, loneliness and mastery, the differences in GP costs—and thus the pressure on GPs—can perhaps be reduced.

Second, regional differences in mental healthcare costs (reimbursed under the Healthcare Insurance Act) were less frequently observed, but they were more persistent than regional differences in other healthcare cost categories. Even when we included all factors in this study, regional differences remained. Further research is needed to determine which factors can further contribute to explaining regional differences in mental healthcare costs. A further breakdown of mental healthcare costs (specialist versus generalist care, inpatient care versus outpatient care versus long-term mental healthcare) possibly provides more insight into regional cost differences. In addition,

combining cost data from the Healthcare Insurance Act and the Long-Term Care Act offers opportunities for improved analyses of long-term, inpatient mental healthcare costs. Moreover, differences between urban and less urban areas within regions or between areas on a smaller geographic scale, such as on a municipal, neighborhood, or neighborhood level, may also contribute to explaining regional differences in healthcare costs in future research.

Our findings help health insurance companies and policymakers justify investments in basic conditions for health, lifestyle, loneliness, and mastery. Although the direct contribution of lifestyle, loneliness, and mastery seems limited, these contributions still result in large variations in healthcare costs between regions. The differences in GP consultation costs, for example, became significantly smaller in 23 regions, and the differences in mental healthcare costs were significantly smaller in three regions. At the population level (difference in marginal costs per person times the average number of residents aged 19 years and over, per region in 2017), we were able to explain €1.6 million in GP consultation costs and €4 million in mental healthcare costs (see Appendix Tables A8 and A9).

In addition to this direct contribution, the three factors also contributed to the explanation of regional health differences [10]. These health differences play a major role in explaining variations in regional healthcare costs. Given these results, the three factors appear to be related to healthcare costs both directly and indirectly. This offers clues for investments in prevention programs and facilities aimed at reducing unhealthy lifestyles and loneliness and improving mastery. In collaboration with partners in social work and informal care, these investments could lead to savings for the medical sector and health insurance companies.

A second implication is extension of the set of individual characteristics in determining healthcare budgets. For example, in order to prevent risk selection and premium differentiation, health insurance companies receive a contribution from the Health Insurance Fund in addition to the premiums collected. This contribution, the risk equalization, is calculated based on, among other things, demographic and socioeconomic characteristics and zip code area [24]. However, certain regions are faced with budget shortages. The results of this research show that factors such as lifestyle, loneliness, mastery, and health contribute to regional differences in healthcare costs. Data on these factors are not available for the entire population and can therefore not be included in the risk equalization calculations for now. As a result, health insurance companies cannot adequately prepare for possible shortages. However, shortages are not unique to health insurance companies, as they also arise in local government

budgets with regard to the Social Support Act, Youth Care Act, and the Participation Act in, for example, Zuid-Limburg [25] and Zeeland [26]. The distribution models for these budgets also do not take into account all individual factors [20] that contribute to health inequalities and healthcare costs.

A potential limitation of this study is the composition of the sample. Selection bias may occur as certain groups of people are less likely to participate in research, such as those with a lower SES and/or poorer health [27]. The sampling method and weighting factors were used to counter this limitation. In addition, the use of the Health Survey sample may have resulted in an underestimation of mental healthcare costs. Even though the size of the group of mental healthcare users in the sample was in line with the national average (approximately 5%), inpatient mental health patients were not included, while they incur (extremely) high costs. This underrepresentation did apply to every region in the Netherlands, making a regional comparison possible, with the assumption that there were no regional differences in policies on institutionalization or inpatient admission in mental healthcare. A second limitation is the use of cross-sectional data. As a result, we could only analyze associations and were unable to draw any causal conclusions. We know that an unhealthy lifestyle and loneliness are related to healthcare costs [6-9]. However, we do not know whether lifestyle and loneliness lead to poor health and thereby to higher healthcare costs, nor whether poor health leads to (more) loneliness and an unhealthy lifestyle. Little is yet known about the relationship between mastery and healthcare costs. Our results show that respondents with sufficient mastery have lower healthcare costs (not tabulated).

The association between mastery and healthcare costs is increasingly important as the role of the citizen (or patient) is becoming more important as society and the healthcare system are increasingly complex [28]. In addition, terms such as “mastery”, “self-management”, and “positive health” are conceptually different, while at the same time they overlap in practice [29]. The Pearlin Mastery Scale specifically relates to individual problem-solving skills. In self-management and positive health, emphasis is placed on an adaptive capacity to deal with challenges, using the individual’s own skills, in combination with their social network and professional support. One of the reason why residents of Zuid-Limburg have the lowest mastery score may be related to the disappearance of the social welfare system that was set up by the Catholic Church and the mining companies in the past [10]. In the measurement of mastery, support by a social network and professionals is not explicitly included. Hypothetically, low mastery may also be related to inadequate social networks and/or professional help. Further research into the association between mastery and self-management and its relation with healthcare costs is required.

In conclusion, the factors included in this study could largely explain regional differences in total healthcare costs. This offers leads for preventive investments aimed at a wide range of individual factors in conjunction. This does not imply an approach that is merely focused on combating an unhealthy lifestyle but also on combating loneliness and improving mastery. This calls for a comprehensive approach and further cooperation between the social and medical sector and *with* education, housing, and public spaces that may affect health skills and self-reliance. In addition, the most vulnerable regions benefit from reconsidering distribution models for risk equalization, since a wider range of individual factors contribute to health, and thus healthcare costs, than the factors that are currently taken into account.

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Appendix

Table A1. Descriptive data (n = 334,721) based on unweighted data.

Sample		N	(%)
Gender[§]	Male	159,251	(47.6%)
	Female	175,470	(52.4%)
Migration background[§]	Dutch-born	294,573	(88.0%)
	Western migration background	28,204	(8.4%)
	Non-western migration background	11,944	(3.6%)
Marital status[*]	Married/living together	224,234	(67.0%)
	Never married	35,899	(10.7%)
	Widowed	23,052	(6.9%)
	Divorced	31,356	(9.4%)
Highest attained level of education*	Primary school	19,061	(5.7%)
	Lower vocational education	102,886	(30.7%)
	Middle vocational/secondary	106,341	(31.8%)
	Higher vocational/university	106,433	(31.8%)
Standardized household income quartile[§]	0-25%	42,250	(12.6%)
	26-50%	84,243	(25.2%)
	51-75%	98,107	(29.3%)
	76-100%	110,121	(32.9%)
Self-perceived income inadequacy*	Inadequate. major concerns	9,490	(2.8%)
	Inadequate. some concerns	34,273	(10.2%)
	Adequate. minor concerns	115,299	(34.4%)
	Adequate. no concerns	175,659	(52.5%)
Chronic disease*	None	203,330	(60.7%)
	At least one	131,391	(39.3%)
Self-rated health*	Very (good)	247,707	(74.0%)
	Fair. (very) poor	87,104	(26.0%)
Psychological distress*	No. low or moderate risk	319,533	(95.5%)
	High	15,188	(4.5%)
Physical activity*	Insufficient	94,343	(28.2%)
	Sufficient	240,378	(71.8%)
BMI*	Underweight (<18.5)	4,200	(1.3%)
	Normal (18.5-25)	152,321	(45.5%)
	Overweight (25-30)	128,977	(38.5%)
	Obese (30>)	49,223	(14.7%)
Alcohol consumption*	Never	32,663	(9.8%)
	Moderate	275,392	(82.3%)
	Excessive	26,666	(8.0%)

table continues

Sample		N	(%)
Smoking*	Never smoked	135,642	(40.5%)
	Former smoker	144,994	(43.3%)
	Current smoker	54,085	(16.2%)
		Mean	**(sd)**
Age§		59.2	(16.9)
Loneliness*		2.8	(3.1)
Mastery*		26.7	(5.2)

§Registry data. *Self-reported data (Health Survey 2016).

Table A2. Missing data (n=457.150)

Variable	N	(%)
Region*	0	(0)
Age§	0	(0)
Gender§	0	(0)
Migration background§	0	(0)
Marital state*	11,192	(2.4)
Highest attained level of education *	31,422	(6.9)
Standardized household income quartile§	737	(0.2)
Income inadequacy*	35,643	(7.8)
Physical activity*	33,488	(7.3)
BMI*	21,261	(4.7)
Alcohol consumption*	36,967	(8.1)
Smoking*	32,605	(7.1)
Chronic disease*	8,808	(1.9)
Self-rated health*	5,730	(1.3)
Psychological distress*	20,103	(4.4)
Loneliness*	36,364	(8.0)
Mastery*	36,612	(8.0)

§Registry data. *Self-reported data (Health Survey 2016).

Table A3. Incidence Rate Ratios per region for total healthcare costs compared to Zuid-Limburg. Results from Poisson regressions (n= 334,721).

IRR (95%CI)	Model 1	Model 2	Model 3a	Model 3b	Model 3c	Model 4	Model 5a	Model 5b	Model 5c	Model 6
Zuid-Limburg	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Zuid-Holland-Zuid	0.78 (0.71-0.85)	0.82 (0.76-0.89)	0.91 (0.84-0.98)	0.89 (0.82-0.96)	0.84 (0.78-0.92)	0.93 (0.86-1.01)	0.93 (0.86-1.01)	0.93 (0.86-1.01)	0.93 (0.86-1.00)	0.92 (0.86-0.99)
Zeeland	0.91 (0.84-0.99)	0.90 (0.83-0.97)	0.94 (0.87-1.01)	0.97 (0.90-1.05)	0.92 (0.85-0.99)	0.99 (0.92-1.07)	1.02 (0.95-1.10)	1.00 (0.93-1.07)	0.99 (0.92-1.06)	1.02 (0.95-1.09)
Zaanstreek-Waterland	0.86 (0.80-0.93)	0.91 (0.85-0.98)	0.98 (0.92-1.05)	0.94 (0.88-1.00)	0.93 (0.87-0.99)	0.98 (0.92-1.05)	1.00 (0.93-1.07)	0.98 (0.92-1.05)	0.99 (0.93-1.06)	1.00 (0.93-1.06)
West-Brabant	0.89 (0.82-0.95)	0.92 (0.86-0.99)	0.96 (0.89-1.03)	1.01 (0.94-1.08)	0.94 (0.87-1.01)	1.03 (0.96-1.10)	1.04 (0.97-1.12)	1.03 (0.96-1.10)	1.02 (0.95-1.10)	1.04 (0.97-1.11)
Utrecht	0.79 (0.74-0.84)	0.92 (0.86-0.97)	0.99 (0.93-1.05)	0.96 (0.91-1.02)	0.94 (0.88-0.99)	1.00 (0.95-1.06)	1.02 (0.96-1.08)	1.00 (0.94-1.06)	1.01 (0.95-1.07)	1.01 (0.96-1.08)
Twente	0.89 (0.80-0.99)	0.96 (0.86-1.07)	1.06 (0.95-1.18)	1.00 (0.90-1.11)	0.97 (0.87-1.08)	1.06 (0.95-1.18)	1.09 (0.98-1.21)	1.06 (0.95-1.17)	1.06 (0.96-1.18)	1.08 (0.97-1.20)
Rotterdam-Rijnmond	0.90 (0.84-0.96)	0.94 (0.88-1.00)	1.01 (0.95-1.08)	0.97 (0.91-1.04)	0.96 (0.90-1.03)	1.02 (0.96-1.08)	1.02 (0.96-1.09)	1.02 (0.95-1.08)	1.02 (0.96-1.09)	1.02 (0.96-1.09)
Noord- en Oost-Gelderland	0.84 (0.79-0.90)	0.90 (0.84-0.95)	0.98 (0.92-1.05)	0.91 (0.85-0.97)	0.91 (0.85-0.97)	0.97 (0.91-1.03)	0.99 (0.93-1.05)	0.96 (0.91-1.03)	0.97 (0.91-1.03)	0.98 (0.92-1.04)
Limburg-Noord	0.93 (0.86-1.01)	0.95 (0.87-1.02)	0.99 (0.92-1.07)	0.98 (0.91-1.06)	0.97 (0.90-1.05)	1.01 (0.93-1.09)	1.02 (0.95-1.11)	1.01 (0.93-1.09)	1.01 (0.94-1.09)	1.03 (0.95-1.11)
Kennemerland	0.82 (0.76-0.88)	0.88 (0.82-0.95)	0.99 (0.92-1.06)	0.95 (0.88-1.01)	0.91 (0.85-.098)	1.01 (0.94-1.08)	1.03 (0.96-1.10)	1.00 (0.94-1.08)	1.02 (0.95-1.09)	1.03 (0.96-1.10)
IJsselland	0.84 (0.77-0.91)	0.95 (0.87-1.03)	1.04 (0.96-1.12)	0.95 (0.88-1.03)	0.97 (0.89-1.05)	1.02 (0.94-1.10)	1.04 (0.96-1.12)	1.01 (0.94-1.09)	1.01 (0.94-1.09)	1.02 (0.95-1.10)
Hollands Noorden	0.77 (0.72-0.83)	0.82 (0.77-0.88)	0.90 (0.84-0.96)	0.87 (0.81-0.93)	0.84 (0.79-0.90)	0.91 (0.85-0.97)	0.93 (0.87-0.99)	0.91 (0.85-0.97)	0.92 (0.86-0.98)	0.93 (0.87-0.99)
Holland-Midden	0.80 (0.75-0.86)	0.89 (0.83-0.95)	0.97 (0.91-1.04)	0.90 (0.84-0.96)	0.90 (0.84-0.96)	0.96 (0.90-1.02)	0.98 (0.92-1.04)	0.95 (0.89-1.02)	0.94 (0.88-1.00)	0.95 (0.89-1.01)

table continues

IRR (95%CI)	Model 1	Model 2	Model 3a	Model 3b	Model 3c	Model 4	Model 5a	Model 5b	Model 5c	Model 6
Hart voor Brabant	0.85 (0.76-0.94)	0.90 (0.81-1.00)	0.95 (0.86-1.05)	0.97 (0.88-1.08)	0.92 (0.83-1.02)	1.00 (0.90-1.11)	1.02 (0.92-1.13)	1.00 (0.90-1.10)	1.00 (0.90-1.11)	1.02 (0.92-1.13)
Haaglanden	0.90 (0.83-0.97)	0.98 (0.91-1.05)	1.05 (0.98-1.13)	0.99 (0.92-1.06)	0.98 (0.91-1.06)	1.04 (0.96-1.12)	1.05 (0.98-1.13)	1.03 (0.96-1.11)	1.05 (0.97-1.13)	1.06 (0.98-1.14)
Groningen	0.81 (0.75-0.88)	0.88 (0.82-0.96)	0.96 (0.89-1.04)	0.89 (0.83-0.96)	0.92 (0.85-0.99)	0.96 (0.89-1.04)	0.98 (0.91-1.05)	0.96 (0.89-1.03)	0.97 (0.90-1.05)	0.98 (0.91-1.06)
Gooi en Vechtstreek	0.85 (0.77-0.94)	0.89 (0.81-0.98)	0.98 (0.89-1.07)	0.96 (0.87-1.05)	0.92 (0.83-1.01)	1.00 (0.91-1.10)	1.00 (0.91-1.10)	1.00 (0.91-1.09)	1.01 (0.92-1.11)	1.00 (0.91-1.10)
Gelderland-Zuid	0.87 (0.79-0.96)	0.97 (0.88-1.07)	1.05 (0.95-1.06)	1.01 (0.92-1.12)	0.98 (0.89-1.08)	1.06 (0.96-1.17)	1.07 (0.97-1.18)	1.06 (0.96-1.16)	1.06 (0.96-1.17)	1.06 (0.96-1.17)
Gelderland-Midden	0.82 (0.76-0.90)	0.90 (0.83-0.97)	0.98 (0.90-1.06)	0.91 (0.84-0.99)	0.91 (0.84-0.98)	0.97 (0.89-1.04)	0.98 (0.91-1.06)	0.96 (0.89-1.03)	0.97 (0.89-1.04)	0.97 (0.90-1.05)
Friesland	0.85 (0.78-0.91)	0.87 (0.80-0.94)	0.98 (0.91-1.06)	0.91 (0.85-0.99)	0.89 (0.83-0.97)	0.99 (0.91-1.06)	1.00 (0.93-1.08)	0.98 (0.91-1.06)	0.99 (0.92-1.06)	1.00 (0.93-1.07)
Flevoland	0.78 (0.69-0.87)	0.89 (0.80-0.99)	0.95 (0.85-1.06)	0.90 (0.81-1.00)	0.90 (0.81-1.01)	0.94 (0.85-1.05)	0.95 (0.85-1.05)	0.94 (0.85-1.04)	0.95 (0.85-1.06)	0.96 (0.86-1.06)
Drenthe	0.85 (0.77-0.95)	0.86 (0.78-0.96)	0.96 (0.87-1.06)	0.92 (0.83-1.02)	0.89 (0.80-0.99)	0.98 (0.89-1.08)	0.99 (0.89-1.09)	0.98 (0.88-1.08)	0.99 (0.89-1.09)	0.99 (0.89-1.09)
Brabant-Zuidoost	0.87 (0.81-0.93)	0.92 (0.86-0.99)	0.95 (0.89-1.02)	1.00 (0.93-1.06)	0.94 (0.88-0.99)	1.01 (0.95-1.17)	1.03 (0.97-1.10)	1.01 (0.94-1.07)	1.00 (0.94-1.07)	1.02 (0.96-1.09)
Amsterdam	0.86 (0.79-0.94)	0.99 (0.91-1.09)	1.10 (1.01-1.21)	1.06 (0.97-1.15)	1.03 (0.94-1.12)	1.12 (1.03-1.22)	1.14 (1.04-1.25)	1.12 (1.02-1.22)	1.13 (1.04-1.24)	1.14 (1.04-1.25)

IRR: Incidence Rate Ratio. CI: confidence interval. Model 1: region. Model 2: region, demographic factors, and SES. Model 3a: region, demographic factors, SES, and self-rated health. Model 3b: region, demographic factors, SES and chronic disease. Model 3c: region, demographic factors, SES and psychological distress. Model 4: region, demographic factors, SES, self-rated health, chronic disease, and psychological distress. Model 5a: region, demographic factors, SES, self-rated health, chronic disease, psychological distress, and lifestyle. Model 5b: region, demographic factors, SES, self-rated health, chronic disease, psychological distress, and loneliness. Model 5c: region, demographic factors, SES, self-rated health, chronic disease, psychological distress, and mastery. Model 6: region, demographic factors, SES, self-rated health, chronic disease, psychological distress, lifestyle, loneliness, and mastery. Registry data: age, gender, migration background and household income. Self-reported data: marital status, education, income inadequacy, self-rated health, chronic disease, psychological distress, lifestyle, loneliness, and mastery.

Table A4. Incidence Rate Ratios per region for GP consultation costs compared to Zuid-Limburg. Results from Zero-inflated negative binomial regressions (n= 334,721).

IRR (95%CI)	Model 1	Model 2		Model 3a	Model 3b		Model 3c					
		Inflated			Inflated			Inflated		Inflated		Inflated
Zuid-Limburg	1.00 (ref)	1.00 (ref)		1.00 (ref)	1.00 (ref)		1.00 (ref)	1.00 (ref)		1.00 (ref)	1.00 (ref)	1.00 (ref)
Zuid-Holland-Zuid	0.82 (0.79-0.86)	1.14 (1.02-1.28)		0.85 (0.82-0.89)	1.13 (1.01-1.27)		0.89 (0.85-0.92)	1.10 (0.98-1.23)		0.87 (0.84-0.91)	1.10 (0.98-1.23)	0.87 (0.83-0.91)	1.12 (1.00-1.25)
Zeeland	0.81 (0.77-0.84)	1.18 (1.07-1.31)		0.81 (0.78-0.84)	1.22 (1.10-1.35)		0.83 (0.80-0.86)	1.21 (1.09-1.35)		0.83 (0.08-0.86)	1.19 (1.07-1.32)	0.82 (0.79-0.85)	1.22 (1.10-1.35)
Zaanstreek-Waterland	0.84 (0.81-0.87)	1.08 (0.99-1.19)		0.86 (0.83-0.89)	1.10 (1.00-1.21)		0.89 (0.86-0.92)	1.08 (0.98-1.18)		0.87 (0.84-0.90)	1.10 (1.00-1.20)	0.87 (0.84-0.90)	1.10 (1.00-1.21)
West-Brabant	0.76 (0.74-0.79)	1.13 (1.02-1.24)		0.80 (0.83-0.89)	1.13 (1.02-1.24)		0.81 (0.78-0.84)	1.12 (1.02-1.24)		0.82 (0.79-0.84)	1.09 (0.99-1.20)	0.80 (0.78-0.83)	1.13 (1.02-1.24)
Utrecht	0.79 (0.77-0.81)	1.29 (1.20-1.39)		0.85 (0.83-0.88)	1.21 (1.12-1.30)		0.87 (0.85-0.90)	1.18 (1.01-1.28)		0.86 (0.84-0.89)	1.19 (1.10-1.28)	0.86 (0.84-0.88)	1.20 (1.12-1.30)
Twente	0.74 (0.71-0.77)	1.50 (1.37-1.65)		0.78 (0.75-0.81)	1.46 (1.33-1.61)		0.81 (0.78-0.84)	1.42 (1.30-1.57)		0.79 (0.76-0.82)	1.45 (1.32-1.60)	0.79 (0.76-0.82)	1.47 (1.34-1.62)
Rotterdam-Rijnmond	0.87 (0.84-0.90)	2.11 (1.97-2.27)		0.87 (0.85-0.90)	2.21 (2.05-2.38)		0.90 (0.87-0.92)	2.18 (2.03-2.35)		0.88 (0.86-0.91)	2.22 (2.06-2.40)	0.88 (0.86-0.91)	2.20 (2.05-2.37)
Noord- en Oost-Gelderland	0.76 (0.74-0.79)	1.25 (1.14-1.36)		0.80 (0.77-0.82)	1.24 (1.14-1.35)		0.82 (0.80-0.85)	1.21 (1.11-1.31)		0.80 (0.77-0.82)	1.24 (1.14-1.36)	0.80 (0.77-0.82)	1.24 (1.14-1.35)
Limburg-Noord	0.88 (0.85-0.91)	1.04 (0.96-1.14)		0.89 (0.87-0.92)	1.05 (0.96-1.15)		0.92 (0.89-0.94)	1.04 (0.95-1.13)		0.91 (0.88-0.93)	1.04 (0.95-1.14)	0.90 (0.88-0.93)	1.05 (0.96-1.15)
Kennemer-land	0.79 (0.76-0.82)	1.08 (0.99-1.18)		0.83 (0.81-0.86)	1.07 (0.98-1.17)		0.87 (0.84-0.90)	1.04 (0.95-1.14)		0.85 (0.82-0.88)	1.05 (0.96-1.15)	0.84 (0.81-0.87)	1.07 (0.97-1.17)
IJsselland	0.74 (0.71-0.78)	1.28 (1.15-1.43)		0.82 (0.78-0.85)	1.20 (1.08-1.34)		0.84 (0.81-0.88)	1.18 (1.06-1.32)		0.82 (0.78-0.85)	1.21 (1.09-1.35)	0.82 (0.79-0.86)	1.20 (1.08-1.34)
Hollands Noorden	0.78 (0.75-0.81)	1.25 (1.14-1.36)		0.80 (0.77-0.83)	1.25 (1.15-1.36)		0.83 (0.80-0.85)	1.22 (1.12-1.33)		0.81 (0.79-0.84)	1.22 (1.12-1.34)	0.81 (0.78-0.84)	1.25 (1.14-1.36)

table continues

IRR (95%CI)	Model 1	Model 2		Model 3a	Model 3b		Model 3c					
			Inflated			Inflated			Inflated			Inflated
Holland-Midden	0.79 (0.77-0.82)	1.22 (1.12-1.32)		0.83 (0.81-0.86)	1.17 (1.08-1.27)		0.91 (0.88-0.94)	1.14 (1.05-1.23)		0.83 (0.81-0.86)	1.18 (1.09-1.28)		0.84 (0.81-0.86)	1.17 (1.08-1.27)
Hart voor Brabant	0.85 (0.82-0.88)	1.10 (1.01-1.19)		0.89 (0.86-0.91)	1.07 (0.98-1.16)		0.88 (0.85-0.91)	1.06 (0.97-1.15)		0.91 (0.88-0.94)	1.04 (0.96-1.13)		0.89 (0.87-0.92)	1.07 (0.98-1.16)
Haaglanden	0.87 (0.83-0.90)	1.11 (1.11-1.13)		0.85 (0.82-0.89)	1.12 (1.11-1.13)		0.90 (0.87-0.93)	1.12 (1.11-1.13)		0.86 (0.83-0.89)	1.12 (1.12-1.13)		0.85 (0.82-0.88)	1.12 (1.11-1.13)
Groningen	0.85 (0.82-0.88)	1.38 (1.26-1.52)		0.88 (0.85-0.92)	1.31 (1.19-1.43)		0.90 (0.86-0.94)	1.28 (1.17-1.40)		0.88 (0.85-0.92)	1.32 (1.20-1.45)		0.90 (0.86-0.93)	1.29 (1.18-1.42)
Gooi en Vechtstreek	0.84 (0.81-0.88)	1.10 (0.97-1.25)		0.88 0.84-0.92)	1.10 (0.97-1.25)		0.84 (0.81-0.88)	1.07 (0.95-1.21)		0.90 (0.86-0.94)	1.07 (0.95-1.21)		0.88 (0.84-0.92)	1.10 (0.97-1.24)
Gelderland-Zuid	0.85 (0.82-0.88)	1.25 (1.14-1.37)		0.89 (0.86-0.92)	1.19 (1.08-1.30)		0.91 (0.88-0.94)	1.16 (1.06-1.27)		0.90 (0.87-0.93)	1.17 (1.07-1.28)		0.89 (0.86-0.92)	1.19 (1.09-1.30)
Gelderland-Midden	0.83 (0.79-0.87)	1.33 (1.191-.48)		0.86 (0.83-0.90)	1.29 (1.16-1.44)		0.88 (0.85-0.92)	1.26 (1.13-1.40)		0.86 (0.83-0.90)	1.29 (1.16-1.44)		0.86 (0.83-0.90)	1.29 (1.16-1.44)
Friesland	0.80 (0.77-0.83)	1.31 (1.20-1.44)		0.81 (0.79-0.84)	1.32 (1.21-1.44)		0.84 (0.82-0.87)	1.28 (1.17-1.40)		0.82 (0.80-0.85)	1.30 (1.19-1.42)		0.82 (0.79-0.85)	1.31 (1.20-1.43)
Flevoland	0.84 (0.78-0.91)	0.98 (0.80-1.19)		0.92 (0.86-0.99)	0.93 (0.76-1.15)		0.95 (0.89-1.02)	0.91 (0.75-1.12)		0.92 (0.86-0.99)	0.93 (0.76-1.15)		0.93 (0.86-0.99)	0.93 (0.76-1.15)
Drenthe	0.83 (0.79-0.87)	1.11 (0.98-1.25)		0.85 (0.81-0.89)	1.14 (1.00-1.29)		0.88 (0.85-0.93)	1.10 (0.97-1.25)		0.87 (0.83-0.91)	1.12 (0.99-1.26)		0.86 (0.82-0.90)	1.13 (1.00-1.28)
Brabant-Zuidoost	0.79 (0.77-0.82)	1.21 (1.11-1.32)		0.82 (0.80-0.85)	1.18 (1.08-1.28)		0.84 (0.82-0.87)	1.18 (1.09-1.29)		0.84 (0.82-0.87)	1.15 (1.06-1.25)		0.83 (0.81-0.86)	1.18 (1.09-1.29)
Amsterdam	0.79 (0.76-0.82)	1.30 (1.18-1.43)		0.83 (0.80-0.86)	1.24 (1.12-1.36)		0.87 (0.84-0.90)	1.19 (1.08-1.32)		0.86 (0.82-0.89)	1.21 (1.10-1.33)		0.85 (0.82-0.88)	1.22 (1.11-1.35)
Zuid-Limburg	1.00 (ref)	1.00 (ref)		1.00 (ref)	1.00 (ref)		1.00 (ref)	1.00 (ref)		1.00 (ref)	1.00 (ref)		1.00 (ref)	1.00 (ref)
Zuid-Holland-Zuid	0.90 (0.86-0.93)	1.08 (0.97-1.21)		0.90 (0.86-0.93)	1.08 (0.97-1.21)		0.90 (0.86-0.94)	1.08 (0.97-1.21)		0.90 (0.86-0.93)	1.08 (0.97-1.21)		0.90 (0.86-0.93)	1.09 (0.97-1.22)

table continues

IRR (95%CI)	Model 1	Model 2		Model 3a	Model 3b		Model 3c					
		Inflated			Inflated			Inflated		Inflated		Inflated
Zeeland	0.84 (0.81-0.87)	1.19 (1.07-1.32)		0.84 (0.81-0.87)	1.19 (1.08-1.33)		0.84 (0.81-0.87)	1.19 (1.07-1.32)		0.83 (0.80-0.86)	1.20 (1.08-1.33)	0.84 (0.80-0.87)	1.20 (1.08-1.33)
Zaanstreek-Waterland	0.89 (0.86-0.92)	1.08 (0.99-1.19)		0.89 (0.87-0.92)	1.09 (0.99-1.19)		0.90 (0.87-0.93)	1.08 (0.99-1.19)		0.89 (0.87-0.92)	1.08 (0.99-1.19)	0.90 (0.87-0.93)	1.09 (0.99-1.19)
West-Brabant	0.82 (0.79-0.85)	1.10 (0.99-1.21)		0.82 (0.79-0.85)	1.10 (1.00-1.21)		0.82 (0.79-0.85)	1.10 (0.99-1.21)		0.82 (0.79-0.85)	1.10 (1.00-1.21)	0.82 (0.79-0.85)	1.10 (1.00-1.21)
Utrecht	0.88 (0.85-0.90)	1.18 (1.09-1.27)		0.88 (0.86-0.90)	1.18 (1.10-1.27)		0.88 (0.86-0.90)	1.18 (1.09-1.27)		0.88 (0.86-0.90)	1.18 (1.09-1.27)	0.88 (0.86-0.91)	1.18 (1.10-1.27)
Twente	0.81 (0.78-0.84)	1.44 (1.31-1.59)		0.81 (0.79-0.84)	1.45 (1.32-1.60)		0.81 (0.78-0.84)	1.44 (1.31-1.59)		0.81 (0.78-0.84)	1.44 (1.31-1.59)	0.81 (0.79-0.84)	1.46 (1.32-1.60)
Rotterdam-Rijnmond	0.90 (0.88-0.93)	2.20 (2.04-2.37)		0.90 (0.88-0.93)	2.21 (2.05-2.38)		0.90 (0.88-0.93)	2.20 (2.04-2.37)		0.90 (0.88-0.93)	2.20 (2.04-2.37)	0.90 (0.88-0.93)	2.21 (2.05-2.39)
Noord- en Oost-Gelderland	0.81 (0.79-0.84)	1.23 (1.13-1.34)		0.82 (0.79-0.84)	1.24 (1.14-1.35)		0.82 (0.79-0.84)	1.23 (1.13-1.34)		0.81 (0.79-0.83)	1.23 (1.13-1.34)	0.81 (0.79-0.84)	1.24 (1.14-1.35)
Limburg-Noord	0.92 (0.90-0.95)	1.03 (0.95-1.13)		0.92 (0.90-0.95)	1.04 (0.95-1.13)		0.92 (0.90-0.95)	1.03 (0.95-1.13)		0.92 (0.90-0.95)	1.03 (0.95-1.13)	0.92 (0.90-0.95)	1.04 (0.95-1.14)
Kennemer-land	0.87 (0.84-0.90)	1.04 (0.95-1.13)		0.87 (0.84-0.90)	1.04 (0.95-1.14)		0.87 (0.85-0.90)	1.04 (0.95-1.13)		0.87 (0.85-0.90)	1.03 (0.95-1.13)	0.88 (0.85-0.90)	1.04 (0.95-1.14)
IJsselland	0.83 (0.80-0.87)	1.20 (1.08-1.34)		0.84 (0.80-0.87)	1.21 (1.09-1.35)		0.84 (0.80-0.87)	1.20 (1.08-1.34)		0.83 (0.80-0.87)	1.20 (1.08-1.34)	0.84 (0.80-0.87)	1.22 (1.09-1.36)
Hollands Noorden	0.83 (0.81-0.86)	1.21 (1.11-1.33)		0.83 (0.81-0.86)	1.22 (1.12-1.33)		0.83 (0.81-0.86)	1.21 (1.11-1.33)		0.84 (0.81-0.86)	1.21 (1.11-1.32)	0.84 (0.81-0.87)	1.22 (1.12-1.33)
Holland-Midden	0.85 (0.83-0.88)	1.16 (1.07-1.26)		0.86 (0.83-0.88)	1.17 (1.08-1.26)		0.85 (0.83-0.88)	1.16 (1.07-1.26)		0.85 (0.82-0.87)	1.16 (1.07-1.26)	0.85 (0.83-0.87)	1.17 (1.08-1.27)
Hart voor Brabant	0.92 (0.89-0.94)	1.04 (0.96-1.13)		0.92 (0.89-0.95)	1.05 (0.96-1.14)		0.92 (0.89-0.95)	1.04 (0.96-1.13)		0.92 (0.89-0.94)	1.04 (0.96-1.13)	0.92 (0.90-0.95)	1.05 (0.97-1.14)
Haaglanden	0.87 (0.84-0.90)	1.12 (0.84-0.90)		0.87 (0.84-0.90)	1.12 (1.12-1.13)		0.87 (0.84-0.91)	1.12 (1.12-1.13)		0.87 (0.84-0.90)	1.12 (1.11-1.13)	0.87 (0.84-0.90)	1.12 (1.12-1.13)

table continues

IRR (95%CI)	Model 1	Model 2		Model 3a	Model 3b		Model 3c					
			Inflated			Inflated		Inflated		Inflated		Inflated
Groningen	0.90 (0.87-0.94)	1.30 (1.18-1.42)		0.90 (0.87-0.94)	1.31 (1.19-1.44)		0.91 (0.87-0.94)	1.30 (1.18-1.42)	0.91 (0.87-0.94)	1.30 (1.18-1.42)	0.91 (0.87-0.94)	1.31 (1.19-1.44)
Gooi en Vechtstreek	0.91 (0.87-0.95)	1.06 (0.94-1.20)		0.91 (0.87-0.95)	1.06 (0.94-1.20)		0.91 (0.87-0.95)	1.06 (0.94-1.20)	0.91 (0.87-0.95)	1.06 (0.93-1.20)	0.92 (0.88-0.96)	1.06 (0.94-1.20)
Gelderland-Zuid	0.91 (0.88-0.94)	1.16 (1.06-1.27)		0.91 (0.88-0.94)	1.16 (1.06-1.27)		0.91 (0.88-0.94)	1.16 (1.06-1.27)	0.91 (0.88-0.94)	1.16 (1.06-1.27)	0.91 (0.88-0.94)	1.17 (1.07-1.27)
Gelderland-Midden	0.88 (0.84-0.91)	1.28 (1.15-1.43)		0.88 (0.85-0.91)	1.29 (1.15-1.44)		0.88 (0.84-0.91)	1.28 (1.15-1.43)	0.87 (0.84-0.91)	1.28 (1.15-1.43)	0.88 (0.84-0.91)	1.29 (1.16-1.44)
Friesland	0.84 (0.82-0.87)	1.28 (1.17-1.40)		0.85 (0.82-0.87)	1.28 (1.18-1.40)		0.85 (0.82-0.87)	1.28 (1.17-1.40)	0.84 (0.82-0.87)	1.28 (1.17-1.40)	0.85 (0.82-0.87)	1.29 (1.18-1.41)
Flevoland	0.95 (0.88-1.01)	0.92 (0.75-1.13)		0.95 (0.88-1.01)	0.92 (0.75-1.14)		0.95 (0.88-1.01)	0.92 (0.75-1.13)	0.95 (0.88-1.01)	0.92 (0.75-1.13)	0.95 (0.89-1.02)	0.93 (0.75-1.14)
Drenthe	0.89 (0.85-0.93)	1.10 (0.97-1.25)		0.89 (0.85-0.93)	1.11 (0.98-1.25)		0.89 (0.86-0.93)	1.10 (0.97-1.25)	0.90 (0.86-0.94)	1.10 (0.97-1.24)	0.90 (0.86-0.93)	1.11 (0.98-1.25)
Brabant-Zuidoost	0.85 (0.82-0.87)	1.16 (1.07-1.27)		0.85 (0.83-0.88)	1.17 (1.07-1.27)		0.85 (0.83-0.88)	1.16 (1.07-1.27)	0.85 (0.82-0.87)	1.17 (1.07-1.27)	0.85 (0.83-0.88)	1.17 (1.07-1.27)
Amsterdam	0.88 (0.85-0.91)	1.19 (1.08-1.31)		0.88 (0.85-0.91)	1.21 (1.10-1.33)		0.88 (0.85-0.92)	1.19 (1.08-1.31)	0.88 (0.85-0.91)	1.19 (1.08-1.31)	0.89 (0.86-0.92)	1.21 (1.10-1.33)

IRR: Incidence Rate Ratio. CI: confidence interval. Model 1: region. Model 2: region, demographic factors, and SES. Model 3a: region, demographic factors, SES, and self-rated health. Model 3b: region, demographic factors, SES and chronic disease. Model 3c: region, demographic factors, SES and psychological distress. Model 4: region, demographic factors, SES, self-rated health, chronic disease, and psychological distress. Model 5a: region, demographic factors, SES, self-rated health, chronic disease, psychological distress, and lifestyle. Model 5b: region, demographic factors, SES, self-rated health, chronic disease, psychological distress, and loneliness. Model 5c: region, demographic factors, SES, self-rated health, chronic disease, psychological distress, and mastery. Model 6: region, demographic factors, SES, self-rated health, chronic disease, psychological distress, lifestyle, loneliness, and mastery. Registry data: age, gender, migration background and household income. Self-reported data: marital status, education, income inadequacy, self-rated health, chronic disease, psychological distress, lifestyle, loneliness, and mastery.

Table A5. Incidence Rate Ratios per region for mental healthcare costs compared to Zuid-Limburg. Results from Zero-inflated negative binomial regressions (n= 334,721).

IRR (95%CI)	Model 1	Model 2		Model 3a	Model 3b		Model 3c					
		Inflated			Inflated		Inflated		Inflated		Inflated	
Zuid-Limburg	1.00 (ref)	1.00 (ref)		1.00 (ref)	1.00 (ref)		1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Zuid-Holland-Zuid	0.47 (0.36-0.62)	1.36 (1.09-1.68)		0.54 (0.41-0.70)	1.22 (0.98-1.53)		0.54 (0.42-0.70)	1.15 (0.92-1.44)	0.57 (0.42-0.76)	1.18 (0.94-1.47)	0.51 (0.40-0.65)	1.14 (0.91-1.42)
Zeeland	0.90 (0.64-1.28)	1.20 (0.98-1.46)		0.92 (0.68-1.26)	1.02 (0.83-1.24)		0.92 (0.68-1.24)	1.01 (0.82-1.24)	0.90 (0.67-1.21)	0.99 (0.81-1.22)	0.85 (0.64-1.13)	1.00 (0.81-1.22)
Zaanstreek-Waterland	0.73 (0.57-0.95)	1.19 (1.02-1.40)		0.75 (0.60-0.94)	1.10 (0.93-1.29)		0.76 (0.61-0.95)	1.04 (0.89-1.23)	0.74 (0.60-0.91)	1.09 (0.93-1.28)	0.71 (0.57-0.89)	1.06 (0.90-1.25)
West-Brabant	1.15 (0.84-1.58)	1.44 (1.20-1.72)		1.12 (0.86-1.45)	1.25 (1.04-1.50)		1.14 (0.87-1.49)	1.25 (1.04-1.50)	1.14 (0.88-1.46)	1.19 (0.99-1.43)	1.05 (0.80-1.39)	1.24 (1.03-1.49)
Utrecht	0.78 (0.64-0.95)	0.99 (0.88-1.12)		0.84 (0.70-1.00)	0.96 (0.84-1.09)		0.84 (0.71-1.00)	0.91 (0.80-1.04)	0.86 (0.72-1.02)	0.93 (0.82-1.06)	0.83 (0.69-1.00)	0.90 (0.79-1.03)
Twente	0.73 (0.55-0.96)	1.24 (1.00-1.54)		0.70 (0.54-0.91)	1.17 (0.94-1.44)		0.71 (0.56-0.89)	1.12 (0.90-1.39)	0.71 (0.56-0.90)	1.17 (0.95-1.45)	0.72 (0.55-0.94)	1.24 (1.01-1.53)
Rotterdam-Rijnmond	0.91 (0.69-1.19)	1.15 (1.01-1.32)		0.89 (0.72-1.11)	1.28 (1.11-1.47)		0.94 (0.75-1.18)	1.23 (1.07-1.42)	0.90 (0.73-1.11)	1.25 (1.08-1.43)	0.90 (0.71-1.15)	1.22 (1.06-1.41)
Noord- en Oost-Gelderland	0.86 (0.66-1.12)	1.49 (1.27-1.74)		0.93 (0.73-1.18)	1.24 (1.06-1.47)		0.91 (0.71-1.15)	1.19 (1.01-1.40)	0.96 (0.75-1.22)	1.28 (1.08-1.51)	0.93 (0.72-1.21)	1.26 (1.06-1.49)
Limburg-Noord	0.90 (0.66-1.22)	1.43 (1.23-1.67)		0.99 (0.74-1.34)	1.23 (1.06-1.44)		1.01 (0.73-1.40)	1.20 (1.02-1.40)	1.03 (0.75-1.42)	1.22 (1.04-1.43)	1.03 (0.74-1.43)	1.17 (0.99-1.37)
Kennemer-land	0.78 (0.55-1.11)	1.09 (0.93-1.28)		0.80 (0.62-1.03)	1.01 (0.86-1.18)		0.80 (0.64-1.01)	0.94 (0.80-1.11)	0.81 (0.64-1.01)	0.97 (0.82-1.14)	0.77 (0.61-0.97)	0.96 (0.81-1.13)
IJsselland	0.76 (0.50-1.14)	1.19 (0.96-1.49)		0.79 (0.54-1.16)	1.06 (0.85-1.33)		0.77 (0.56-1.07)	1.03 (0.83-1.29)	0.78 (0.55-1.09)	1.08 (0.87-1.35)	0.76 (0.55-1.04)	1.05 (0.84-1.31)
Hollands Noorden	0.67 (0.52-0.86)	1.16 (0.99-1.35)		0.71 (0.56-0.90)	1.07 (0.92-1.26)		0.70 (0.56-0.87)	1.04 (0.89-1.22)	0.72 (0.57-0.91)	1.04 (0.88-1.21)	0.68 (0.54-0.86)	1.04 (0.89-1.22)

table continues

IRR (95%CI)	Model 1	Model 2		Model 3a	Model 3b		Model 3c					
		Inflated			Inflated		Inflated		Inflated		Inflated	
Holland-Midden	0.62 (0.50-0.77)	1.13 (0.98-1.30)		0.68 (0.55-0.82)	1.03 (0.89-1.19)		0.68 (0.56-0.81)	0.98 (0.85-1.14)	0.69 (0.57-0.83)	1.05 (0.91-1.22)	0.64 (0.52-0.78)	1.03 (0.89-1.20)
Hart voor Brabant	0.83 (0.58-1.17)	1.39 (1.20-1.61)		0.89 (0.65-1.23)	1.24 (1.07-1.44)		0.91 (0.67-1.25)	1.23 (1.05-1.43)	0.93 (0.68-1.29)	1.21 (1.03-1.41)	0.81 (0.61-1.07)	1.24 (1.06-1.45)
Haaglanden	0.75 (0.59-0.96)	0.86 (0.74-1.00)		0.77 (0.62-0.96)	0.94 (0.81-1.09)		0.82 (0.66-1.02)	0.90 (0.78-1.05)	0.78 (0.63-0.96)	0.95 (0.81-1.10)	0.77 (0.62-0.97)	0.96 (0.82-1.12)
Groningen	0.80 (0.63-1.03)	0.99 (0.84-1.17)		0.83 (0.66-1.03)	1.09 (0.92-1.30)		0.86 (0.68-1.08)	1.04 (0.88-1.24)	0.83 (0.67-1.03)	1.11 (0.93-1.32)	0.83 (0.66-1.05)	0.99 (0.83-1.17)
Gooi en Vechtstreek	0.70 (0.53-0.92)	1.23 (1.01-1.50)		0.74 (0.58-0.93)	1.11 (0.91-1.35)		0.74 (0.59-0.93)	1.06 (0.87-1.30)	0.77 (0.62-0.96)	1.08 (0.88-1.33)	0.70 (0.56-0.89)	1.08 (0.87-1.32)
Gelderland-Zuid	0.94 (0.60-1.46)	1.02 (0.87-1.19)		0.96 (0.67-1.39)	1.00 (0.86-1.17)		0.96 (0.70-1.32)	0.95 (0.81-1.11)	0.95 (0.69-1.31)	0.98 (0.83-1.15)	0.93 (0.68-1.27)	1.00 (0.85-1.18)
Gelderland-Midden	1.04 (0.73-1.48)	1.25 (1.02-1.52)		1.17 (0.78-1.76)	1.19 (0.97-1.45)		1.16 (0.81-1.67)	1.16 (0.94-1.42)	1.14 (0.80-1.64)	1.22 (0.99-1.49)	1.15 (0.72-1.84)	1.25 (1.01-1.55)
Friesland	0.74 (0.58-0.95)	1.29 (1.09-1.52)		0.78 (0.62-0.99)	1.21 (1.02-1.43)		0.79 (0.62-0.99)	1.13 (0.96-1.34)	0.77 (0.62-0.95)	1.19 (1.00-1.41)	0.76 (0.60-0.97)	1.15 (0.97-1.37)
Flevoland	0.71 (0.48-1.04)	1.42 (1.03-1.97)		0.77 (0.54-1.09)	1.40 (1.00-1.98)		0.79 (0.57-1.10)	1.37 (0.96-1.97)	0.78 (0.56-1.10)	1.45 (1.02-2.08)	0.74 (0.53-1.03)	1.46 (1.00-2.11)
Drenthe	0.95 (0.61-1.48)	1.20 (0.94-1.52)		0.93 (0.65-1.32)	1.09 (0.86-1.39)		0.93 (0.67-1.29)	1.03 (0.80-1.31)	0.94 (0.68-1.30)	1.05 (0.82-1.34)	0.90 (0.66-1.24)	1.03 (0.81-1.32)
Brabant-Zuidoost	0.89 (0.71-1.11)	1.44 (1.22-1.70)		0.98 (0.78-1.23)	1.28 (1.08-1.51)		1.03 (0.82-1.29)	1.31 (1.10-1.55)	1.05 (0.84-1.31)	1.24 (1.04-1.47)	0.98 (0.78-1.22)	1.32 (1.11-1.57)
Amsterdam	0.81 (0.64-1.02)	0.71 0.61-0.83)		0.86 (0.70-1.07)	0.86 (0.73-1.00)		0.88 (0.72-1.08)	0.77 (0.65-0.90)	0.91 (0.74-1.11)	0.80 (0.68-0.94)	0.88 (0.71-1.09)	0.78 (0.66-0.92)
Zuid-Limburg	1.00 (ref)	1.00 (ref)		1.00 (ref)	1.00 (ref)		1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Zuid-Holland-Zuid	0.54 (0.42-0.69)	1.10 (0.88-1.38)		0.53 (0.42-0.68)	1.11 (0.88-1.39)		0.54 (0.42-0.68)	1.08 (0.86-1.36)	0.54 (0.42-0.69)	1.11 (0.88-1.40)	0.53 (0.42-0.68)	1.10 (0.88-1.39)

table continues

IRR (95%CI)	Model 1	Model 2		Model 3a	Model 3b		Model 3c					
		Inflated			Inflated			Inflated		Inflated		Inflated
Zeeland	0.86 (0.65-1.14)	0.96 (0.79-1.18)		0.86 (0.65-1.12)	0.96 (0.78-1.18)		0.85 (0.64-1.13)	0.98 (0.80-1.21)	0.85 (0.64-1.13)	0.99 (0.80-1.22)	0.85 (0.64-1.12)	1.00 (0.81-1.24)
Zaanstreek-Waterland	0.73 (0.59-0.90)	1.04 (0.88-1.23)		0.72 (0.58-0.88)	1.05 (0.89-1.24)		0.74 (0.59-0.91)	1.01 (0.85-1.19)	0.73 (0.59-0.90)	1.03 (0.87-1.22)	0.73 (0.59-0.90)	1.02 (0.86-1.21)
West-Brabant	1.09 (0.84-1.43)	1.20 (0.99-1.44)		1.11 (0.85-1.45)	1.19 (0.99-1.44)		1.07 (0.83-1.39)	1.19 (0.99-1.43)	1.10 (0.84-1.44)	1.19 (0.99-1.43)	1.10 (0.85-1.43)	1.19 (0.99-1.43)
Utrecht	0.85 (0.71-1.02)	0.87 (0.76-0.99)		0.85 (0.71-1.01)	0.88 (0.77-1.00)		0.86 (0.72-1.03)	0.85 (0.74-0.97)	0.86 (0.72-1.03)	0.86 (0.75-0.98)	0.86 (0.72-1.03)	0.85 (0.75-0.98)
Twente	0.72 (0.57-0.92)	1.19 (0.96-1.48)		0.73 (0.57-0.93)	1.20 (0.97-1.48)		0.73 (0.57-0.93)	1.15 (0.93-1.43)	0.72 (0.57-0.92)	1.17 (0.94-1.45)	0.73 (0.57-0.94)	1.16 (0.93-1.43)
Rotterdam-Rijnmond	0.93 (0.74-1.17)	1.20 (1.04-1.38)		0.93 (0.74-1.16)	1.20 (1.04-1.39)		0.93 (0.75-1.17)	1.17 (1.01-1.35)	0.94 (0.75-1.18)	1.17 (1.02-1.36)	0.93 (0.75-1.16)	1.16 (1.01-1.34)
Noord- en Oost-Gelderland	0.94 (0.73-1.22)	1.25 (1.05-1.48)		0.95 (0.73-1.24)	1.25 (1.06-1.48)		0.96 (0.74-1.26)	1.22 (1.03-1.45)	0.96 (0.74-1.25)	1.25 (1.05-1.48)	0.97 (0.74-1.28)	1.24 (1.05-1.47)
Limburg-Noord	1.06 (0.75-1.50)	1.16 (0.98-1.36)		1.06 (0.75-1.49)	1.16 (0.98-1.36)		1.06 (0.75-1.48)	1.16 (0.98-1.36)	1.06 (0.76-1.47)	1.15 (0.98-1.35)	1.05 (0.76-1.46)	1.16 (0.98-1.37)
Kennemer-land	0.79 (0.63-0.98)	0.91 (0.77-1.08)		0.78 (0.63-0.96)	0.92 (0.78-1.09)		0.80 (0.64-1.00)	0.89 (0.75-1.05)	0.79 (0.64-0.98)	0.89 (0.75-1.05)	0.79 (0.64-0.97)	0.89 (0.75-1.05)
IJsselland	0.76 (0.57-1.02)	1.04 (0.84-1.30)		0.74 (0.57-0.97)	1.06 (0.85-1.32)		0.78 (0.58-1.05)	1.01 (0.81-1.26)	0.76 (0.56-1.02)	1.06 (0.85-1.33)	0.76 (0.58-0.99)	1.05 (0.84-1.32)
Hollands Noorden	0.69 (0.56-0.86)	1.01 (0.86-1.19)		0.69 (0.55-0.85)	1.02 (0.87-1.20)		0.70 (0.56-0.86)	0.99 (0.84-1.16)	0.70 (0.57-0.88)	1.00 (0.85-1.17)	0.70 (0.56-0.87)	0.99 (0.84-1.17)
Holland-Midden	0.65 (0.54-0.79)	1.02 (0.88-1.19)		0.65 (0.54-0.79)	1.02 (0.88-1.19)		0.66 (0.55-0.80)	1.00 (0.86-1.16)	0.66 (0.55-0.80)	1.05 (0.90-1.22)	0.66 (0.55-0.80)	1.03 (0.89-1.20)
Hart voor Brabant	0.87 (0.65-1.15)	1.19 (1.02-1.39)		0.86 (0.65-1.13)	1.19 (1.02-1.40)		0.88 (0.65-1.19)	1.17 (1.00-1.37)	0.84 (0.64-1.11)	1.18 (1.00-1.38)	0.86 (0.65-1.13)	1.17 (1.00-1.38)
Haaglanden	0.80 (0.64-0.99)	0.94 (0.80-1.10)		0.79 (0.64-0.98)	0.94 (0.80-1.11)		0.79 (0.64-0.98)	0.93 (0.79-1.09)	0.79 (0.64-0.98)	0.93 (0.79-1.09)	0.78 (0.63-0.97)	0.93 (0.79-1.09)

table continues

IRR (95%CI)	Model 1	Model 2		Model 3a	Model 3b		Model 3c					
			Inflated			Inflated		Inflated		Inflated		Inflated
Groningen	0.85 (0.68-1.07)	0.98 (0.83-1.17)		0.85 (0.68-1.07)	0.99 (0.83-1.18)		0.85 (0.68-1.06)	0.95 (0.80-1.13)	0.86 (0.69-1.07)	0.96 (0.80-1.14)	0.85 (0.68-1.07)	0.95 (0.80-1.13)
Gooi en Vechtstreek	0.74 (0.60-0.91)	1.05 (0.85-1.29)		0.74 (0.60-0.92)	1.05 (0.85-1.30)		0.74 (0.60-0.91)	1.01 (0.81-1.24)	0.75 (0.60-0.93)	1.03 (0.83-1.28)	0.75 (0.60-0.92)	1.01 (0.81-1.25)
Gelderland-Zuid	0.94 (0.71-1.25)	0.96 (0.81-1.13)		0.91 (0.72-1.16)	0.96 (0.81-1.14)		0.93 (0.71-1.22)	0.93 (0.79-1.10)	0.95 (0.71-1.27)	0.96 (0.81-1.13)	0.91 (0.72-1.15)	0.95 (0.80-1.12)
Gelderland-Midden	1.13 (0.76-1.70)	1.23 (1.00-1.53)		1.14 (0.75-1.73)	1.25 (1.01-1.55)		1.16 (0.76-1.77)	1.22 (0.98-1.52)	1.14 (0.75-1.74)	1.24 (1.00-1.54)	1.17 (0.75-1.81)	1.25 (1.00-1.55)
Friesland	0.76 (0.61-0.95)	1.11 (0.93-1.32)		0.77 (0.62-0.97)	1.12 (0.94-1.33)		0.76 (0.61-0.95)	1.09 (0.92-1.30)	0.76 (0.61-0.96)	1.09 (0.92-1.30)	0.77 (0.62-0.96)	1.09 (0.92-1.30)
Flevoland	0.78 (0.55-1.09)	1.48 (1.01-2.19)		0.78 (0.55-1.11)	1.48 (1.00-2.18)		0.78 (0.55-1.09)	1.47 (0.99-2.17)	0.79 (0.55-1.13)	1.45 (0.99-2.12)	0.79 (0.55-1.13)	1.44 (0.98-2.12)
Drenthe	0.93 (0.69-1.25)	0.98 (0.77-1.25)		0.91 (0.67-1.24)	0.99 (0.77-1.26)		0.93 (0.68-1.26)	0.96 (0.75-1.23)	0.94 (0.69-1.26)	0.95 (0.74-1.22)	0.92 (0.67-1.26)	0.95 (0.75-1.22)
Brabant-Zuidoost	1.04 (0.83-1.29)	1.28 (1.07-1.52)		1.05 (0.84-1.31)	1.28 (1.07-1.52)		1.05 (0.84-1.31)	1.27 (1.06-1.52)	1.05 (0.85-1.31)	1.29 (1.08-1.54)	1.07 (0.86-1.33)	1.30 (1.08-1.55)
Amsterdam	0.91 (0.75-1.12)	0.71 (0.60-0.85)		0.90 (0.74-1.10)	0.73 (0.62-0.86)		0.93 (0.76-1.14)	0.69 (0.58-0.81)	0.92 (0.76-1.13)	0.69 (0.59-0.82)	0.92 (0.75-1.12)	0.70 (0.59-0.83)

IRR: Incidence Rate Ratio. CI: confidence interval. Model 1: region. Model 2: region, demographic factors, and SES. Model 3a: region, demographic factors, SES, and self-rated health. Model 3b: region, demographic factors, SES and chronic disease. Model 3c: region, demographic factors, SES and psychological distress. Model 4: region, demographic factors, SES, self-rated health, chronic disease, and psychological distress. Model 5a: region, demographic factors, SES, self-rated health, chronic disease, psychological distress, and lifestyle. Model 5b: region, demographic factors, SES, self-rated health, chronic disease, psychological distress, and loneliness. Model 5c: region, demographic factors, SES, self-rated health, chronic disease, psychological distress, and mastery. Model 6: region, demographic factors, SES, self-rated health, chronic disease, psychological distress, lifestyle, loneliness, and mastery. Registry data: age, gender, migration background and household income. Self-reported data: marital status, education, income inadequacy, self-rated health, chronic disease, psychological distress, lifestyle, loneliness, and mastery.

Table A6. Incidence Rate Ratios per region for pharmaceutical costs compared to Zuid-Limburg. Results from Zero-inflated negative binomial regressions (n= 334,721).

IRR (95%CI)	Model 1	Model 2		Model 3a	Model 3b		Model 3c					
			Inflated			Inflated		Inflated		Inflated		Inflated
Zuid-Limburg	1.00 (ref)	1.00 (ref)		1.00 (ref)	1.00 (ref)		1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Zuid-Holland-Zuid	1.12 (0.84-1.50)	1.23 (1.08-1.40)		1.17 (0.90-1.51)	1.19 (1.04-1.35)		1.18 (0.98-1.42)	1.12 (0.99-1.26)	1.19 (1.02-1.38)	1.11 (0.99-1.24)	1.20 (1.04-1.38)	1.09 (0.97-1.22)
Zeeland	1.05 (0.87-1.28)	1.09 (0.97-1.24)		1.11 (0.88-1.40)	1.17 (1.03-1.33)		1.15 (0.87-1.51)	1.16 (1.03-1.31)	1.31 (0.95-1.80)	1.13 (1.00-1.26)	1.30 (0.93-1.83)	1.13 (1.01-1.27)
Zaanstreek-Waterland	0.98 (0.87-1.11)	1.30 (1.18-1.44)		1.17 (0.97-1.40)	1.33 (1.20-1.48)		1.29 (1.03-1.63)	1.29 (1.16-1.42)	1.17 (0.95-1.44)	1.32 (1.20-1.45)	1.22 (0.98-1.51)	1.30 (1.18-1.43)
West-Brabant	1.03 (0.90-1.17)	1.16 (1.04-1.29)		1.21 (0.99-1.48)	1.15 (1.03-1.29)		1.20 (0.97-1.48)	1.14 (1.03-1.27)	1.20 (1.07-1.33)	1.07 (0.96-1.18)	1.18 (1.05-1.34)	1.08 (0.98-1.19)
Utrecht	0.88 (0.79-0.98)	1.63 (1.50-1.77)		1.00 (0.89-1.11)	1.38 (1.27-1.50)		1.04 (0.94-1.16)	1.33 (1.23-1.44)	1.04 (0.96-1.13)	1.33 (1.23-1.44)	1.06 (0.97-1.15)	1.32 (1.22-1.42)
Twente	0.83 (0.75-0.93)	1.35 (1.21-1.50)		0.88 (0.78-1.00)	1.26 (1.12-1.41)		0.95 (0.86-1.06)	1.22 (1.10-1.35)	0.96 (0.88-1.04)	1.25 (1.13-1.39)	0.98 (0.90-1.06)	1.24 (1.12-1.38)
Rotterdam-Rijnmond	1.10 (0.99-1.23)	1.23 (1.12-1.34)		1.23 (1.08-1.41)	1.19 (1.09-1.30)		1.27 (1.12-1.44)	1.15 (1.06-1.25)	1.18 (1.07-1.30)	1.16 (1.07-1.26)	1.20 (1.09-1.32)	1.15 (1.06-1.25)
Noord- en Oost-Gelderland	0.95 (0.84-1.06)	1.35 (1.23-1.49)		1.05 (0.92-1.19)	1.37 (1.24-1.51)		1.15 (1.00-1.32)	1.32 (1.20-1.44)	1.10 (0.94-1.29)	1.39 (1.27-1.52)	1.13 (0.97-1.32)	1.37 (1.25-1.50)
Limburg-Noord	0.94 (0.86-1.02)	1.06 (0.95-1.17)		0.92 (0.83-1.01)	1.09 (0.98-1.21)		0.95 (0.86-1.05)	1.07 (0.97-1.18)	0.98 (0.91-1.05)	1.08 (0.98-1.18)	0.98 (0.91-1.06)	1.07 (0.97-1.17)
Kennemerland	0.85 (0.76-0.94)	1.49 (1.35-1.65)		0.93 (0.82-1.06)	1.44 (1.30-1.59)		1.02 (0.89-1.17)	1.38 (1.25-1.51)	1.05 (0.91-1.21)	1.38 (1.26-1.52)	1.08 (0.94-1.24)	1.37 (1.25-1.50)
IJsselland	0.88 (0.75-1.04)	1.56 (1.39-1.75)		1.03 (0.81-1.29)	1.39 (1.23-1.57)		1.03 (0.89-1.19)	1.35 (1.21-1.51)	1.00 (0.87-1.14)	1.42 (1.27-1.58)	1.00 (0.89-1.12)	1.40 (1.26-1.56)
Hollands Noorden	1.02 (0.88-1.19)	1.70 (1.55-1.87)		1.22 (0.98-1.53)	1.74 (1.58-1.92)		1.14 (0.94-1.39)	1.65 (1.51-1.81)	1.19 (0.92-1.54)	1.64 (1.50-1.80)	1.11 (0.94-1.32)	1.62 (1.48-1.77)

table continues

IRR (95%CI)	Model 1	Model 2		Model 3a	Model 3b		Model 3c					
		Inflated			Inflated			Inflated			Inflated	
Holland-Midden	0.99 (0.82-1.19)	1.45 (1.32-1.59)		1.05 (0.89-1.24)	1.32 (1.21-1.45)		1.06 (0.94-1.21)	1.27 (1.16-1.38)		0.98 (0.89-1.09)	1.34 (1.23-1.46)	0.99 (0.91-1.09)	1.32 (1.22-1.44)
Hart voor Brabant	0.97 (0.84-1.12)	1.34 (1.22-1.47)		1.06 (0.89-1.25)	1.28 (1.16-1.40)		1.03 (0.90-1.18)	1.26 (1.15-1.37)		1.08 (0.97-1.19)	1.22 (1.12-1.33)	1.06 (0.96-1.16)	1.22 (1.12-1.33)
Haaglanden	0.95 (0.85-1.06)	1.26 (1.13-1.39)		1.06 (0.93-1.21)	1.16 (1.04-1.28)		1.13 (0.99-1.28)	1.13 (1.02-1.24)		1.01 (0.93-1.10)	1.16 (1.06-1.28)	1.04 (0.96-1.13)	1.16 (1.05-1.27)
Groningen	0.91 (0.82-1.00)	1.53 (1.38-1.70)		1.00 (0.86-1.16)	1.37 (1.23-1.52)		1.05 (0.93-1.18)	1.32 (1.20-1.46)		0.98 (0.89-1.08)	1.39 (1.26-1.53)	1.00 (0.92-1.10)	1.38 (1.25-1.52)
Gooi en Vechtstreek	1.20 (0.81-1.76)	1.45 (1.26-1.66)		1.41 (0.81-2.47)	1.46 (1.27-1.67)		1.19 (0.88-1.63)	1.36 (1.20-1.53)		1.17 (0.84-1.62)	1.32 (1.17-1.49)	1.12 (0.86-1.45)	1.30 (1.15-1.47)
Gelderland-Zuid	0.99 (0.88-1.11)	1.53 (1.39-1.69)		1.11 (0.96-1.28)	1.38 (1.25-1.53)		1.14 (1.00-1.30)	1.33 (1.20-1.46)		1.07 (0.97-1.18)	1.33 (1.21-1.46)	1.09 (0.99-1.20)	1.32 (1.20-1.45)
Gelderland-Midden	0.97 (0.84-1.11)	1.51 (1.34-1.70)		0.98 (0.87-1.12)	1.39 (1.23-1.57)		1.04 (0.91-1.19)	1.34 (1.19-1.50)		0.97 (0.89-1.06)	1.40 (1.25-1.57)	0.98 (0.89-1.08)	1.38 (1.24-1.55)
Friesland	1.00 (0.86-1.17)	1.38 (1.25-1.53)		1.05 (0.88-1.25)	1.41 (1.27-1.56)		1.10 (0.95-1.27)	1.34 (1.21-1.47)		1.03 (0.92-1.15)	1.35 (1.23-1.48)	1.05 (0.94-1.17)	1.33 1.21-1.46)
Flevoland	0.97 (0.77-1.23)	1.31 (1.05-1.64)		1.14 (0.86-1.51)	1.16 (0.92-1.47)		1.20 (0.85-1.68)	1.14 (0.92-1.41)		1.07 (0.89-1.27)	1.18 (0.95-1.45)	1.08 (0.89-1.32)	1.17 (0.95-1.43)
Drenthe	0.90 (0.75-1.08)	1.21 (1.05-1.39)		0.97 (0.76-1.23)	1.27 (1.09-1.47)		1.03 (0.87-1.22)	1.21 (1.05-1.39)		1.00 (0.87-1.15)	1.23 (1.08-1.40)	1.03 (0.91-1.17)	1.21 (1.06-1.38)
Brabant-Zuidoost	0.90 (0.82-0.98)	1.34 (1.21-1.47)		0.95 (0.85-1.07)	1.28 (1.16-1.41)		0.99 (0.87-1.12)	1.29 (1.17-1.41)		1.02 (0.94-1.12)	1.21 (1.11-1.33)	1.03 (0.92-1.14)	1.24 (1.13-1.35)
Amsterdam	1.26 (1.07-1.48)	1.78 (1.60-1.97)		1.33 (1.12-1.59)	1.44 (1.29-1.60)		1.46 (1.21-1.76)	1.35 (1.22-1.50)		1.24 (1.07-1.44)	1.34 (1.22-1.48)	1.30 (1.12-1.51)	1.32 (1.20-1.46)
Zuid-Limburg	1.00 (ref)	1.00 (ref)		1.00 (ref)	1.00 (ref)		1.00 (ref)	1.00 (ref)		1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Zuid-Holland-Zuid	1.20 (1.04-1.38)	1.09 (0.97-1.22)		1.20 (1.04-1.38)	1.09 (0.97-1.23)		1.20 (1.04-1.38)	1.09 (0.97-1.23)		1.19 (1.04-1.35)	1.09 (0.97-1.22)	1.19 (1.04-1.36)	1.10 (0.98-1.23)

table continues

IRR (95%CI)	Model 1	Model 2		Model 3a	Model 3b		Model 3c					
		Inflated			Inflated			Inflated		Inflated		Inflated
Zeeland	1.30 (0.93-1.83)	1.13 (1.01-1.27)		1.32 (0.94-1.85)	1.12 (1.00-1.26)		1.30 (0.93-1.82)	1.13 (1.01-1.27)		1.29 (0.92-1.81)	1.13 (1.01-1.27)	1.31 (0.93-1.84)	1.12 (1.00-1.26)
Zaanstreek-Waterland	1.22 (0.98-1.51)	1.30 (1.18-1.43)		1.22 (0.99-1.51)	1.30 (1.18-1.43)		1.22 (0.98-1.51)	1.31 (1.19-1.44)		1.22 (0.98-1.53)	1.30 (1.18-1.43)	1.22 (0.98-1.51)	1.31 (1.19-1.44)
West-Brabant	1.18 (1.05-1.34)	1.08 (0.98-1.19)		1.20 (1.06-1.35)	1.08 (0.97-1.19)		1.18 (1.05-1.34)	1.08 (0.98-1.19)		1.18 (1.04-1.33)	1.08 (0.98-1.19)	1.19 (1.05-1.34)	1.08 (0.98-1.19)
Utrecht	1.06 (0.97-1.15)	1.32 (1.22-1.42)		1.07 (0.98-1.16)	1.31 (1.21-1.41)		1.06 (0.97-1.15)	1.32 (1.23-1.43)		1.05 (0.97-1.14)	1.32 (1.22-1.42)	1.06 (0.97-1.15)	1.32 (1.22-1.42)
Twente	0.98 (0.90-1.06)	1.24 (1.12-1.38)		0.99 (0.91-1.07)	1.25 (1.13-1.38)		0.98 (0.90-1.06)	1.25 (1.13-1.39)		0.98 (0.90-1.06)	1.24 (1.12-1.38)	0.98 (0.91-1.06)	1.26 (1.13-1.39)
Rotterdam-Rijnmond	1.20 (1.09-1.32)	1.15 (1.06-1.25)		1.21 (1.09-1.33)	1.16 (1.07-1.26)		1.20 (1.09-1.32)	1.16 (1.06-1.25)		1.20 (1.09-1.32)	1.15 (1.06-1.25)	1.20 (1.09-1.32)	1.16 (1.07-1.26)
Noord- en Oost-Gelderland	1.13 (0.97-1.32)	1.37 (1.25-1.50)		1.14 (0.98-1.33)	1.38 (1.26-1.51)		1.13 (0.97-1.32)	1.38 (1.26-1.51)		1.13 0.97-1.31)	1.37 (1.25-1.50)	1.13 (0.97-1.31)	1.39 (1.27-1.51)
Limburg-Noord	0.98 (0.91-1.06)	1.07 (0.97-1.17)		0.99 (0.92-1.07)	1.07 (0.97-1.17)		0.98 (0.91-1.06)	1.07 (0.97-1.17)		0.98 (0.91-1.06)	1.07 (0.97-1.17)	0.99 (0.91-1.07)	1.06 (0.97-1.17)
Kennemer-land	1.08 (0.94-1.24)	1.37 (1.25-1.50)		1.09 (0.95-1.25)	1.37 (1.24-1.50)		1.08 (0.94-1.24)	1.37 (1.25-1.51)		1.08 (0.94-1.23)	1.37 (1.25-1.50)	1.08 (0.95-1.24)	1.37 (1.25-1.51)
IJsselland	1.00 (0.89-1.12)	1.40 (1.26-1.56)		1.01 (0.90-1.14)	1.41 (1.26-1.57)		1.00 (0.89-1.12)	1.41 (1.26-1.57)		0.99 (0.88-1.12)	1.40 (1.25-1.56)	1.01 (0.89-1.13)	1.42 (1.27-1.59)
Hollands Noorden	1.11 (0.94-1.32)	1.62 (1.48-1.77)		1.12 (0.94-1.34)	1.62 (1.48-1.77)		1.11 (0.94-1.32)	1.63 (1.49-1.78)		1.11 (0.94-1.33)	1.62 (1.48-1.77)	1.12 (0.94-1.34)	1.63 (1.49-1.78)
Holland-Midden	0.99 (0.91-1.09)	1.32 (1.22-1.44)		1.00 (0.92-1.10)	1.33 (1.22-1.44)		0.99 (0.91-1.09)	1.33 (1.22-1.44)		0.98 (0.90-1.07)	1.32 (1.21-1.44)	0.99 (0.90-1.08)	1.33 (1.23-1.45)
Hart voor Brabant	1.06 (0.96-1.16)	1.22 (1.12-1.33)		1.07 (0.97-1.17)	1.22 (1.12-1.32)		1.06 (0.96-1.16)	1.23 (1.13-1.34)		1.05 (0.96-1.16)	1.22 (1.12-1.33)	1.06 (0.97-1.17)	1.22 (1.12-1.33)
Haaglanden	1.04 (0.96-1.13)	1.16 (1.05-1.27)		1.05 (0.96-1.14)	1.15 (1.05-1.27)		1.04 (0.96-1.13)	1.16 (1.05-1.28)		1.04 (0.96-1.14)	1.16 (1.05-1.27)	1.05 (0.96-1.14)	1.16 (1.05-1.27)

table continues

IRR (95%CI)	Model 1	Model 2		Model 3a	Model 3b		Model 3c					
			Inflated			Inflated			Inflated			Inflated
Groningen	1.00 (0.92-1.10)	1.38 (1.25-1.52)		1.00 (0.92-1.10)	1.39 (1.26-1.53)		1.00 (0.92-1.10)	1.38 (1.25-1.52)		1.00 (0.91-1.10)	1.38 (1.25-1.52)		1.00 (0.91-1.09)	1.39 (1.26-1.53)
Gooi en Vechtstreek	1.12 (0.86-1.45)	1.30 (1.15-1.47)		1.14 (0.88-1.47)	1.28 (1.13-1.44)		1.12 (0.87-1.45)	1.31 (1.16-1.48)		1.14 (0.86-1.50)	1.30 (1.15-1.47)		1.15 (0.88-1.50)	1.29 (1.14-1.46)
Gelderland-Zuid	1.09 (0.99-1.20)	1.32 (1.20-1.45)		1.10 (0.99-1.21)	1.31 (1.19-1.44)		1.09 (0.99-1.20)	1.33 (1.21-1.46)		1.08 (0.98-1.19)	1.32 (1.20-1.45)		1.09 (0.99-1.20)	1.32 (1.20-1.45)
Gelderland-Midden	0.98 (0.89-1.08)	1.38 (1.24-1.55)		0.99 (0.90-.09)	1.39 (1.24-1.56)		0.98 (0.89-1.08)	1.39 (1.24-1.56)		0.98 (0.89-1.07)	1.38 (1.23-1.55)		0.98 (0.89-1.08)	1.39 (1.24-1.56)
Friesland	1.05 (0.94-1.17)	1.33 (1.21-1.46)		1.06 (0.95-1.18)	1.33 (1.21-1.46)		1.05 (0.94-1.17)	1.33 (1.21-1.47)		1.05 (0.94-1.17)	1.33 (1.21-1.46)		1.06 (0.94-1.18)	1.33 (1.21-1.47)
Flevoland	1.08 (0.89-1.32)	1.17 (0.95-1.43)		1.09 (0.89-1.33)	1.17 (0.95-1.44)		1.08 (0.89-1.32)	1.17 (0.95-1.44)		1.08 (0.89-1.31)	1.17 (0.95-1.43)		1.08 (0.89-1.32)	1.18 (0.95-1.45)
Drenthe	1.03 (0.91-1.17)	1.21 (1.06-1.38)		1.04 (0.91-1.18)	1.23 (1.08-1.40)		1.03 (0.91-1.17)	1.22 (1.07-1.39)		1.03 (0.91-1.17)	1.21 (1.06-1.38)		1.03 (0.91-1.17)	1.23 (1.08-1.41)
Brabant-Zuidoost	1.03 (0.92-1.14)	1.24 (1.13-1.35)		1.04 (0.94-1.16)	1.22 (1.12-1.34)		1.03 (0.93-1.14)	1.24 (1.13-1.35)		1.02 (0.92-1.14)	1.23 (1.13-1.35)		1.04 (0.93-1.16)	1.23 (1.12-1.34)
Amsterdam	1.30 (1.12-1.51)	1.32 (1.20-1.46)		1.32 (1.13-1.53)	1.33 (1.21-1.47)		1.30 (1.12-1.51)	1.33 (1.20-1.47)		1.30 (1.12-1.50)	1.32 (1.20-1.46)		1.31 (1.13-1.53)	1.34 (1.21-1.48)

IRR: Incidence Rate Ratio. CI: confidence interval. Model 1: region. Model 2: region, demographic factors, and SES. Model 3a: region, demographic factors, SES, and self-rated health. Model 3b: region, demographic factors, SES and chronic disease. Model 3c: region, demographic factors, SES and psychological distress. Model 4: region, demographic factors, SES, self-rated health, chronic disease, and psychological distress. Model 5a: region, demographic factors, SES, self-rated health, chronic disease, psychological distress, and lifestyle. Model 5b: region, demographic factors, SES, self-rated health, chronic disease, psychological distress, and loneliness. Model 5c: region, demographic factors, SES, self-rated health, chronic disease, psychological distress, and mastery. Model 6: region, demographic factors, SES, self-rated health, chronic disease, psychological distress, lifestyle, loneliness, and mastery. Registry data: age, gender, migration background and household income. Self-reported data: marital status, education, income inadequacy, self-rated health, chronic disease, psychological distress, lifestyle, loneliness, and mastery.

Table A7. Incidence Rate Ratios per region for specialized care costs compared to Zuid-Limburg. Results from Zero-inflated negative binomial regressions (n= 334,721).

IRR (95%CI)	Model 1	Model 2		Model 3a	Model 3b		Model 3c					
			Inflated			Inflated		Inflated		Inflated		Inflated
Zuid-Limburg	1.00 (ref)	1.00 (ref)		1.00 (ref)	1.00 (ref)		1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Zuid-Holland-Zuid	0.83 (0.75-0.91)	1.15 (1.04-1.26)		0.83 (0.75-0.91)	1.12 (1.01-1.23)		0.92 (0.84-1.00)	1.07 (0.96-1.18)	0.91 (0.84-1.00)	1.07 (0.97-1.18)	0.84 (0.76-0.93)	1.11 (1.00-1.22)
Zeeland	0.88 (0.80-0.97)	1.01 (0.92-1.10)		0.87 (0.79-0.96)	1.09 (0.98-1.20)		0.92 (0.83-1.01)	1.08 (0.98-1.20)	0.95 (0.86-1.04)	1.04 (0.94-1.15)	0.88 (0.80-0.97)	1.09 (0.98-1.20)
Zaanstreek-Waterland	0.97 (0.88-1.07)	1.08 (1.00-1.17)		1.00 (0.91-1.10)	1.08 (0.99-1.18)		1.03 (0.95-1.12)	1.04 (0.96-1.13)	1.02 (0.94-1.10)	1.08 (0.99-1.17)	1.00 (0.91-1.10)	1.08 (0.99-1.17)
West-Brabant	0.88 (0.81-0.97)	1.02 (0.94-1.11)		0.92 (0.83-1.01)	1.02 (0.93-1.12)		0.93 (0.85-1.02)	1.01 (0.93-1.11)	0.95 (0.87-1.02)	0.95 (0.87-1.04)	0.92 (0.83-1.02)	1.02 (0.93-1.12)
Utrecht	0.90 (0.83-0.98)	1.32 (1.25-1.41)		0.97 (0.89-1.06)	1.16 (1.09-1.24)		1.03 (0.95-1.12)	1.13 (1.05-1.20)	1.02 (0.94-1.10)	1.13 (1.05-1.21)	0.98 (0.90-1.07)	1.16 (1.08-1.24)
Twente	1.02 (0.86-1.20)	1.13 (1.04-1.22)		1.05 (0.89-1.25)	1.05 (0.96-1.15)		1.07 (0.96-1.20)	1.01 (0.92-1.11)	1.03 (0.92-1.17)	1.04 (0.94-1.14)	1.07 (0.90-1.26)	1.06 (0.97-1.16)
Rotterdam-Rijnmond	0.95 (0.87-1.03)	1.10 (1.03-1.17)		1.03 (0.94-1.14)	1.04 (0.97-1.12)		1.09 (1.01-1.19)	1.01 (0.94-1.09)	1.06 (0.98-1.15)	1.03 (0.96-1.11)	1.04 (0.94-1.14)	1.03 (0.96-1.11)
Noord- en Oost-Gelderland	0.94 (0.86-1.02)	1.19 (1.11-1.28)		0.95 (0.87-1.04)	1.22 (1.13-1.31)		1.01 (0.94-1.10)	1.17 (1.09-1.27)	0.96 (0.88-1.03)	1.24 (1.15-1.34)	0.96 (0.87-1.05)	1.22 (1.13-1.32)
Limburg-Noord	0.99 (0.89-1.12)	0.96 (0.89-1.04)		1.03 (0.89-1.20)	1.00 (0.92-1.08)		1.07 (0.90-1.26)	0.97 (0.89-1.05)	1.02 (0.92-1.13)	0.97 (0.89-1.06)	1.04 (0.89-1.21)	0.99 (0.91-1.08)
Kennemer-land	0.92 (0.84-1.02)	1.16 (1.08-1.26)		0.97 (0.87-1.07)	1.13 (1.04-1.23)		1.07 (0.96-1.19)	1.08 (1.00-1.18)	1.03 (0.95-1.12)	1.09 (1.00-1.19)	0.98 (0.88-1.09)	1.13 (1.04-1.22)
IJsselland	1.02 (0.92-1.14)	1.40 (1.28-1.53)		1.08 (0.97-1.20)	1.27 (1.15-1.40)		1.16 (1.05-1.29)	1.24 (1.13-1.37)	1.07 (0.97-1.17)	1.31 (1.18-1.44)	1.09 (0.97-1.21)	1.27 (1.15-1.40)
Hollands Noorden	0.88 (0.80-0.96)	1.31 (1.22-1.41)		0.89 (0.81-0.99)	1.35 (1.24-1.46)		0.92 (0.85-1.01)	1.31 (1.21-1.41)	0.92 (0.84-1.00)	1.31 (1.21-1.42)	0.90 (0.82-1.00)	1.34 (1.24-1.46)

table continues

IRR (95%CI)	Model 1	Model 2		Model 3a	Model 3b		Model 3c					
		Inflated			Inflated			Inflated			Inflated	
Holland-Midden	0.92 (0.84-1.00)	1.23 (1.15-1.32)		0.96 (0.88-1.05)	1.17 (1.08-1.25)		1.00 (0.93-1.09)	1.12 (1.04-1.21)		0.94 (0.87-1.02)	1.19 (1.11-1.29)		0.96 (0.88-1.06)	1.17 (1.09-1.26)
Hart voor Brabant	0.94 (0.80-1.11)	1.07 (1.00-1.15)		1.03 (0.82-1.30)	1.03 (0.96-1.12)		1.13 (0.86-1.49)	1.03 (0.95-1.11)		1.02 (0.88-1.19)	0.99 (0.92-1.07)		1.05 (0.82-1.33)	1.03 (0.96-1.12)
Haaglanden	0.99 (0.89-1.10)	1.05 (0.98-1.14)		1.07 (0.96-1.19)	0.95 (0.88-1.04)		1.15 (1.03-1.29)	0.93 (0.85-1.01)		1.09 (0.99-1.19)	0.97 (0.89-1.05)		1.07 (0.96-1.20)	0.96 (0.88-1.05)
Groningen	0.93 (0.83-1.04)	1.41 (1.31-1.53)		0.98 (0.87-1.11)	1.28 (1.17-1.39)		1.02 (0.91-1.14)	1.24 (1.14-1.35)		0.98 (0.87-1.09)	1.31 (1.20-1.43)		1.00 (0.88-1.13)	1.27 (1.16-1.38)
Gooi en Vechtstreek	0.95 (0.85-1.07)	1.15 (1.04-1.27)		0.97 (0.85-1.10)	1.18 (1.06-1.31)		1.07 (0.94-1.22)	1.13 (1.02-1.26)		0.99 (0.90-1.10)	1.12 (1.01-1.25)		0.98 (0.86-1.10)	1.17 (1.06-1.30)
Gelderland-Zuid	1.02 (0.89-1.17)	1.38 (1.28-1.49)		1.10 (0.93-1.31)	1.28 (1.18-1.39)		1.14 (0.95-1.38)	1.23 (1.14-1.34)		1.06 (0.95-1.19)	1.25 (1.15-1.36)		1.09 (0.94-1.25)	1.28 (1.18-1.39)
Gelderland-Midden	0.88 (0.79-0.97)	1.22 (1.11-1.34)		0.90 (0.81-1.01)	1.15 (1.04-1.27)		0.98 (0.87-1.10)	1.11 (1.01-1.23)		0.94 (0.85-1.04)	1.17 (1.06-1.29)		0.91 (0.81-1.01)	1.16 (1.05-1.28)
Friesland	0.94 (0.84-1.05)	1.33 (1.24-1.44)		0.96 (0.84-1.10)	1.38 (1.27-1.50)		1.05 (0.92-1.21)	1.32 (1.22-1.43)		0.98 (0.89-1.09)	1.35 (1.24-1.47)		0.98 (0.85-1.12)	1.37 (1.27-1.49)
Flevoland	0.86 (0.74-0.99)	1.11 (0.94-1.31)		0.91 (0.79-1.05)	0.97 (0.80-1.18)		0.99 (0.85-1.15)	0.95 (0.78-1.15)		0.92 (0.80-1.06)	0.98 (0.81-1.20)		0.91 (0.79-1.05)	0.97 (0.80-1.18)
Drenthe	0.89 (0.77-1.04)	1.10 (0.99-1.23)		0.89 (0.76-1.03)	1.16 (1.03-1.30)		0.97 (0.86-1.10)	1.11 (0.99-1.24)		0.95 (0.84-1.08)	1.13 (1.00-1.27)		0.90 (0.77-1.05)	1.15 (1.02-1.29)
Brabant-Zuidoost	0.96 (0.88-1.05)	1.09 (1.01-1.17)		0.99 (0.89-1.10)	1.05 (0.97-1.14)		0.98 (0.90-1.06)	1.06 (0.98-1.14)		1.02 (0.94-1.11)	1.01 (0.93-1.09)		0.99 (0.89-1.10)	1.06 (0.98-1.14)
Amsterdam	0.93 (0.81-1.07)	1.33 (1.23-1.44)		1.08 (0.91-1.28)	1.10 (1.01-1.21)		1.10 (0.98-1.23)	1.04 (0.95-1.14)		1.10 (0.96-1.26)	1.05 (0.96-1.15)		1.06 (0.92-1.23)	1.09 (0.99-1.19)
Zuid-Limburg	1.00 (ref)	1.00 (ref)		1.00 (ref)	1.00 (ref)		1.00 (ref)	1.00 (ref)		1.00 (ref)	1.00 (ref)		1.00 (ref)	1.00 (ref)
Zuid-Holland-Zuid	0.95 (0.87-1.03)	1.05 (0.95-1.16)		0.95 (0.87-1.03)	1.05 (0.95-1.17)		0.95 (0.87-1.03)	1.05 (0.95-1.17)		0.95 (0.87-1.03)	1.05 (0.95-1.16)		0.94 (0.87-1.02)	1.06 (0.96-1.17)

table continues

IRR (95%CI)	Model 1	Model 2	Model 3a	Model 3b	Model 3c					
		Inflated		Inflated		Inflated		Inflated		Inflated
Zeeland	0.95 (0.87-1.05)	1.05 (0.95-1.16)	0,97 (0,89-1,07)	1,05 (0,95-1,16)	0,96 (0,87-1,05)	1,05 (0,95-1,16)	0,94 (0,86-1,03)	1,05 (0,95-1,16)	0,96 (0,88-1,06)	1,05 (0,95-1,16)
Zaanstreek-Waterland	1,03 (0,95-1,12)	1,06 (0,97-1,15)	1,04 (0,97-1,13)	1,06 (0,97-1,16)	1,02 (0,95-1,11)	1,07 (0,98-1,16)	1,03 (0,96-1,12)	1,06 (0,97-1,15)	1,03 (0,96-1,11)	1,07 (0,98-1,17)
West-Brabant	0,94 (0,87-1,02)	0,97 (0,88-1,06)	0,95 (0,88-1,03)	0,97 (0,88-1,06)	0,94 (0,87-1,02)	0,97 (0,88-1,06)	0,94 (0,87-1,01)	0,96 (0,88-1,06)	0,94 (0,87-1,01)	0,97 (0,89-1,06)
Utrecht	1,05 (0,96-1,13)	1,12 (1,04-1,20)	1,05 (0,97-1,14)	1,12 (1,05-1,20)	1,04 (0,96-1,13)	1,12 (1,05-1,20)	1,04 (0,96-1,13)	1,12 (1,04-1,20)	1,04 (0,96-1,13)	1,13 (1,05-1,21)
Twente	1,05 (0,95-1,17)	1,02 (0,93-1,12)	1,07 (0,97-1,19)	1,03 (0,94-1,13)	1,05 (0,95-1,17)	1,03 (0,94-1,13)	1,05 (0,95-1,17)	1,02 (0,93-1,12)	1,06 (0,96-1,18)	1,04 (0,94-1,14)
Rotterdam-Rijnmond	1,09 (1,01-1,18)	1,02 (0,94-1,09)	1,10 (1,02-1,19)	1,02 (0,95-1,10)	1,09 (1,01-1,18)	1,02 (0,95-1,10)	1,09 (1,01-1,18)	1,02 (0,94-1,09)	1,09 (1,01-1,18)	1,02 (0,95-1,10)
Noord- en Oost-Gelderland	0,99 (0,92-1,07)	1,22 (1,13-1,32)	1,00 (0,93-1,08)	1,23 (1,13-1,33)	0,98 (0,91-1,06)	1,22 (1,13-1,33)	0,99 (0,92-1,06)	1,22 (1,12-1,32)	0,98 (0,91-1,05)	1,23 (1,14-1,34)
Limburg-Noord	1,05 (0,93-1,18)	0,96 (0,89-1,05)	1,06 (0,94-1,20)	0,97 (0,89-1,05)	1,04 (0,93-1,17)	0,96 (0,89-1,05)	1,04 (0,93-1,18)	0,96 (0,89-1,05)	1,05 (0,93-1,18)	0,97 (0,89-1,05)
Kennemer-land	1,07 (0,98-1,17)	1,07 (0,99-1,17)	1,09 (0,99-1,19)	1,08 (1,00-1,18)	1,07 (0,98-1,17)	1,08 (0,99-1,17)	1,07 (0,98-1,17)	1,07 (0,99-1,17)	1,08 (0,99-1,18)	1,09 (1,00-1,18)
IJsselland	1,12 (1,01-1,23)	1,29 (1,17-1,42)	1,12 (1,02-1,23)	1,30 (1,18-1,44)	1,11 (1,01-1,22)	1,30 (1,17-1,43)	1,11 (1,01-1,22)	1,29 (1,17-1,42)	1,1 (1,01-1,21)	1,31 (1,19-1,45)
Hollands Noorden	0,93 (0,86-1,01)	1,30 (1,20-1,41)	0,95 (0,87-1,03)	1,30 (1,20-1,41)	0,93 (0,86-1,00)	1,30 (1,20-1,41)	0,94 (0,87-1,02)	1,30 (1,20-1,41)	0,95 (0,88-1,03)	1,31 (1,21-1,42)
Holland-Midden	0,98 (0,91-1,05)	1,17 (1,08-1,26)	0,99 (0,92-1,06)	1,18 (1,09-1,27)	0,97 (0,90-1,05)	1,17 (1,09-1,26)	0,97 (0,90-1,04)	1,17 (1,08-1,26)	0,97 (0,90-1,04)	1,18 (1,10-1,27)
Hart voor Brabant	1,07 (0,89-1,30)	1,00 (0,92-1,08)	1,07 (0,90-1,26)	1,00 (0,92-1,08)	1,07 (0,89-1,29)	1,00 (0,93-1,08)	1,08 (0,88-1,32)	1,00 (0,92-1,08)	1,06 (0,89-1,26)	1,00 (0,93-1,08)
Haaglanden	1,13 (1,03-1,24)	0,95 (0,87-1,04)	1,15 (1,04-1,26)	0,96 (0,88-1,04)	1,13 (1,03-1,24)	0,96 (0,88-1,04)	1,13 (1,03-1,24)	0,95 (0,87-1,04)	1,15 (1,04-1,27)	0,96 (0,88-1,05)

table continues

IRR (95%CI)	Model 1	Model 2		Model 3a	Model 3b		Model 3c					
			Inflated			Inflated		Inflated		Inflated		Inflated
Groningen	1,00 (0,90-1,12)	1,29 (1,19-1,41)		1,01 (0,91-1,13)	1,30 (1,20-1,42)		1,00 (0,89-1,11)	1,30 (1,19-1,42)	1,00 (0,90-1,12)	1,29 (1,19-1,41)	1,00 (0,90-1,11)	1,31 (1,20-1,43)
Gooi en Vechtstreek	1,04 (0,94-1,16)	1,11 (1,00-1,23)		1,05 (0,94-1,18)	1,10 (0,99-1,22)		1,03 (0,93-1,15)	1,12 (1,00-1,24)	1,05 (0,94-1,17)	1,11 (1,00-1,23)	1,04 (0,93-1,16)	1,11 (1,00-1,23)
Gelderland-Zuid	1,11 (0,96-1,27)	1,24 (1,14-1,35)		1,12 (0,97-1,30)	1,24 (1,14-1,34)		1,10 (0,96-1,26)	1,24 (1,14-1,35)	1,11 (0,96-1,27)	1,24 (1,14-1,34)	1,11 (0,96-1,30)	1,24 (1,14-1,35)
Gelderland-Midden	0,98 (0,88-1,08)	1,15 (1,04-1,27)		0,99 (0,89-1,09)	1,16 (1,05-1,28)		0,97 (0,88-1,07)	1,16 (1,05-1,28)	0,98 (0,88-1,09)	1,15 (1,04-1,27)	0,98 (0,88-1,08)	1,16 (1,05-1,29)
Friesland	1,03 (0,93-1,15)	1,33 (1,22-1,44)		1,04 (0,94-1,15)	1,33 (1,23-1,45)		1,02 (0,92-1,13)	1,33 (1,23-1,45)	1,03 (0,93-1,14)	1,33 (1,22-1,44)	1,03 (0,93-1,13)	1,34 (1,23-1,45)
Flevoland	0,96 (0,83-1,11)	0,97 (0,79-1,18)		0,97 (0,84-1,11)	0,97 (0,80-1,19)		0,96 (0,83-1,11)	0,97 (0,80-1,19)	0,97 (0,84-1,12)	0,97 (0,79-1,18)	0,97 (0,83-1,12)	0,98 (0,80-1,19)
Drenthe	0,99 (0,88-1,11)	1,11 (0,99-1,25)		1,00 (0,89-1,12)	1,12 (0,99-1,26)		0,99 (0,88-1,11)	1,12 (0,99-1,26)	0,99 (0,88-1,11)	1,11 (0,99-1,25)	0,99 (0,89-1,11)	1,12 (1,00-1,26)
Brabant-Zuidoost	1,01 (0,93-1,09)	1,02 (0,94-1,11)		1,03 (0,95-1,11)	1,02 (0,94-1,11)		1,00 (0,93-1,08)	1,03 (0,95-1,11)	1,00 (0,92-1,08)	1,02 (0,94-1,11)	1,01 (0,93-1,09)	1,02 (0,95-1,11)
Amsterdam	1,12 (1,00-1,25)	1,03 (0,94-1,13)		1,14 (1,01-1,27)	1,04 (0,95-1,14)		1,11 (0,99-1,25)	1,03 (0,94-1,13)	1,12 (1,00-1,25)	1,03 (0,94-1,13)	1,13 (1.00-1,27)	1,05 (0,96-1,15)

IRR: Incidence Rate Ratio. CI: confidence interval. Model 1: region. Model 2: region, demographic factors, and SES. Model 3a: region, demographic factors, SES, and self-rated health. Model 3b: region, demographic factors, SES and chronic disease. Model 3c: region, demographic factors, SES and psychological distress. Model 4: region, demographic factors, SES, self-rated health, chronic disease, and psychological distress. Model 5a: region, demographic factors, SES, self-rated health, chronic disease, psychological distress, and lifestyle. Model 5b: region, demographic factors, SES, self-rated health, chronic disease, psychological distress, and loneliness. Model 5c: region, demographic factors, SES, self-rated health, chronic disease, psychological distress, and mastery. Model 6: region, demographic factors, SES, self-rated health, chronic disease, psychological distress, lifestyle, loneliness, and mastery. Registry data: age, gender, migration background and household income. Self-reported data: marital status, education, income inadequacy, self-rated health, chronic disease, psychological distress, lifestyle, loneliness, and mastery.

Table A8. Explanation of significant regional differences in GP consult costs by adding lifestyle, loneliness and mastery (model 4 compared to model 6).

Region	Model 4		Model 6		Difference between model 4 and 6	Average number of citizens aged 19 or older in 2017*	Increase or decrease regional differences in costs
	Marginal costs	Difference with ref	Marginal costs	Difference with ref			
Zuid-Limburg	47,98	(ref)	€ 47,86	(ref)			
Zuid-Holland-Zuid	€ 42,61	€ 5,37	€ 42,41	€ 5,45	€ 0,08	334.140	€ 26.346,94
Zeeland	€ 39,21	€ 8,77	€ 38,99	€ 8,87	€ 0,10	306.222	€ 30.282,29
Zaanstreek-Waterland	€ 42,61	€ 5,37	€ 42,54	€ 5,32	€ -0,05	264.893	-€ 12.638,05
West-Brabant	€ 38,84	€ 9,14	€ 38,73	€ 9,13	€ -0,01	562.773	-€ 7.203,49
Utrecht	€ 41,16	€ 6,82	€ 41,23	€ 6,63	€ -0,19	666.844	-€ 127.840,66
Twente	€ 36,71	€ 11,27	€ 36,78	€ 11,08	€ -0,19	494.646	-€ 93.859,08
Rotterdam-Rijnmond	€ 37,55	€ 10,43	€ 37,57	€ 10,29	€ -0,14	1.033.491	-€ 148.636,68
Noord- en Oost-Gelderland	€ 37,92	€ 10,06	€ 37,82	€ 10,04	€ -0,02	649.777	-€ 13.002,04
Limburg-Noord	€ 44,02	€ 3,96	€ 43,97	€ 3,89	€ -0,07	421.842	-€ 29.621,75
Kennemerland	€ 41,58	€ 6,40	€ 41,72	€ 6,14	€ -0,26	421.650	-€ 109.430,82
IJsselland	€ 39,04	€ 8,94	€ 38,89	€ 8,97	€ 0,03	403.397	€ 11.258,81
Hollands Noorden	€ 38,80	€ 9,18	€ 39,01	€ 8,85	€ -0,33	518.725	-€ 170.183,30
Holland-Midden	€ 40,03	€ 7,95	€ 39,80	€ 8,06	€ 0,11	551.554	€ 61.277,65
Hart voor Brabant	€ 43,74	€ 4,24	€ 43,88	€ 3,98	€ -0,26	843.239	-€ 219.958,89
Haaglanden	€ 32,89	€ 15,09	€ 32,92	€ 14,94	€ -0,15	860.697	-€ 132.194,45
Groningen	€ 41,70	€ 6,28	€ 41,73	€ 6,13	€ -0,15	475.810	-€ 73.545,95
Gooi en Vechtstreek	€ 43,18	€ 4,80	€ 43,48	€ 4,37	€ -0,43	197.886	-€ 84.410,25
Gelderland-Zuid	€ 42,73	€ 5,25	€ 42,68	€ 5,18	€ -0,07	440.023	-€ 31.611,25
Gelderland-Midden	€ 40,59	€ 7,39	€ 40,45	€ 7,41	€ 0,02	537.356	€ 9.618,67
Friesland	€ 39,12	€ 8,86	€ 39,07	€ 8,78	€ -0,08	511.208	-€ 38.524,63
Flevoland	€ 42,20	€ 5,78	€ 42,25	€ 5,60	€ -0,18	391.288	-€ 69.023,20
Drenthe	€ 39,87	€ 8,11	€ 39,98	€ 7,88	€ -0,23	601.197	-€ 139.736,22
Brabant-Zuidoost	€ 41,20	€ 6,78	€ 41,36	€ 6,50	€ -0,28	847.533	-€ 239.097,53
Total							-€ 1.601.733,89

Model 4: region, demographic factors, SES, self-rated health, chronic disease and psychological distress. Model 6: region, demographic factors, SES, self-rated health, chronic disease, psychological distress, lifestyle, loneliness, and mastery. Registry data: age, gender, migration background and household income. Self-reported data: marital status, education, income inadequacy, self-rated health, chronic disease, psychological distress, lifestyle, loneliness and mastery. * Based on data provided by Statistics Netherlands (opendata.cbs.nl)

Table A9. Explanation of significant regional differences in mental healthcare costs by adding lifestyle, loneliness and mastery (model 4 compared to model 6).

Region	Model 4		Model 6		Difference between model 4 and 6	Average number of citizens aged 19 or older in 2017*	Increase or decrease regional differences in costs
	Marginal costs	Difference with ref	Marginal costs	Difference with ref			
Zuid-Limburg	€ 215,39	(ref)	€ 212,84	(ref)			
Twente	€ 135,08	€ 80,31	€ 138,40	€ 74,44	-€ 5,87	494.646	-€ 2.903.572,02
Hollands Midden	€ 138,53	€ 76,86	€ 137,70	€ 75,14	-€ 1,72	551.554	-€ 948.672,88
Zuid-Holland-Zuid	€ 107,34	€ 108,05	€ 105,40	€ 107,44	-€ 0,61	334.140	-€ 203.825,40
Total							-€ 4.056.070,30

Model 4: region, demographic factors, SES, self-rated health, chronic disease and psychological distress. Model 6: region, demographic factors, SES, self-rated health, chronic disease, psychological distress, lifestyle, loneliness, and mastery. Registry data: age, gender, migration background and household income. Self-reported data: marital status, education, income inadequacy, self-rated health, chronic disease, psychological distress, lifestyle, loneliness and mastery. * Based on data provided by Statistics Netherlands (opendata.cbs.nl)

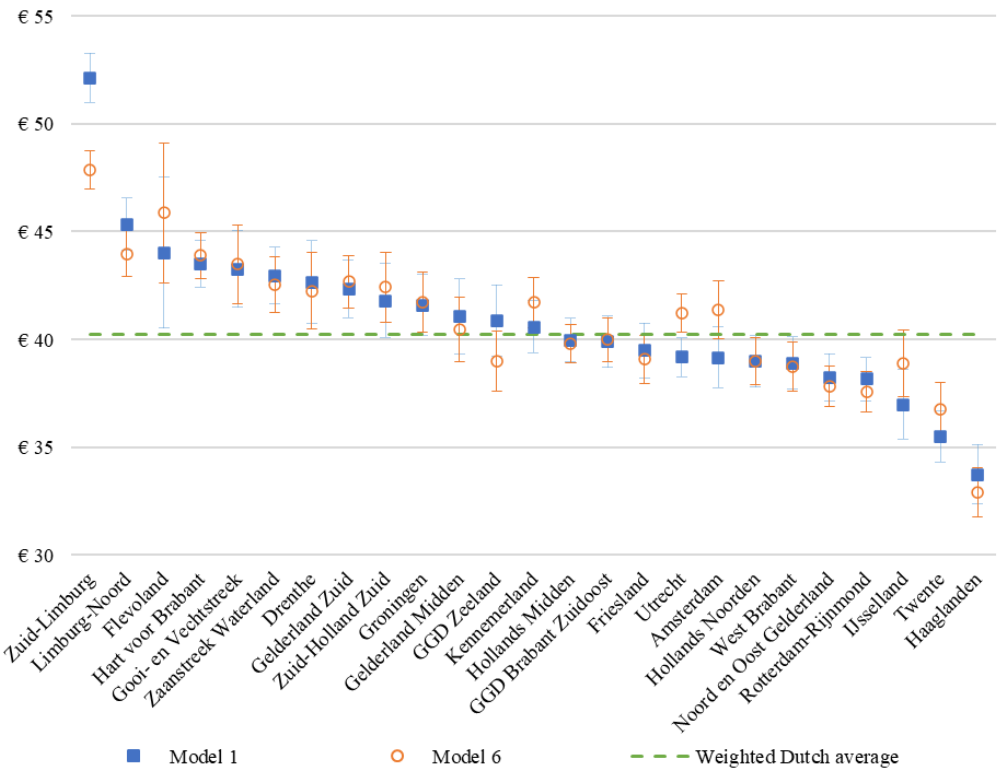

Figure A1. Marginal costs of region for GP consultation costs based on unadjusted (model 1) and fully adjusted costs (model 6).

* Model 1 is adjusted for region only. In model 6, the association of region and healthcare costs is adjusted demographic factors, SES, general and mental health, lifestyle, loneliness and mastery. Registry data: age, gender, migration background and household income. Self-reported data: marital status, education, income inadequacy, self-rated health, chronic disease, psychological distress, lifestyle, loneliness and mastery.

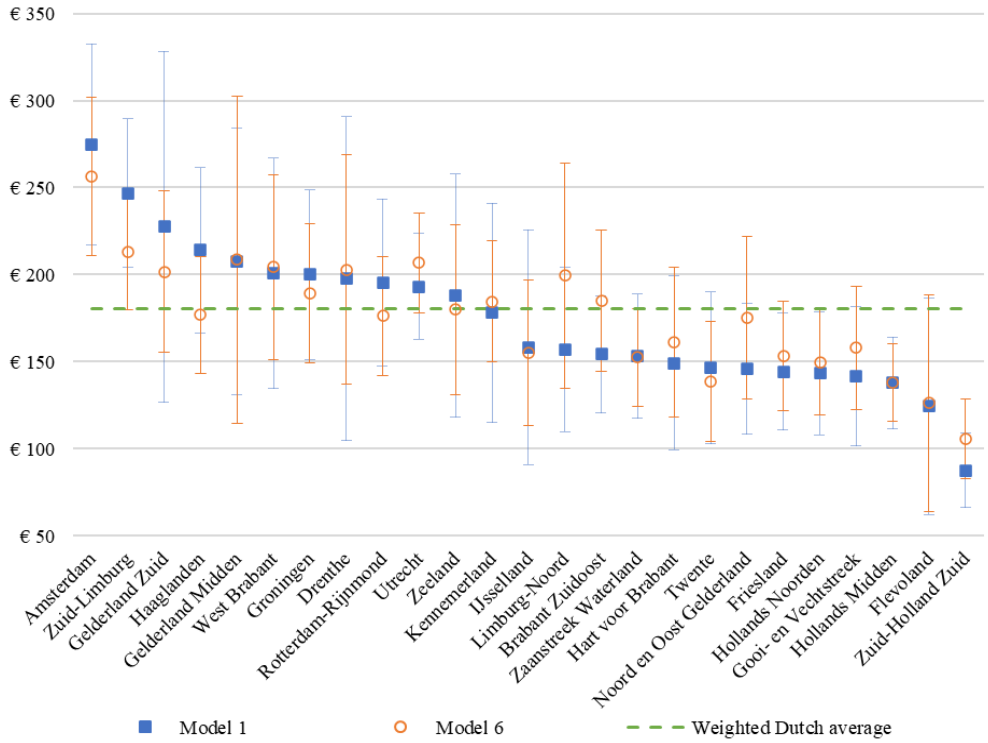

Figure A2. Marginal costs of region for mental healthcare costs based on unadjusted (model 1) and fully adjusted costs (model 6).

* Model 1 is adjusted for region only. In model 6, the association of region and healthcare costs is adjusted demographic factors, SES, general and mental health, lifestyle, loneliness and mastery. Registry data: age, gender, migration background and household income. Self-reported data: marital status, education, income inadequacy, self-rated health, chronic disease, psychological distress, lifestyle, loneliness and mastery.

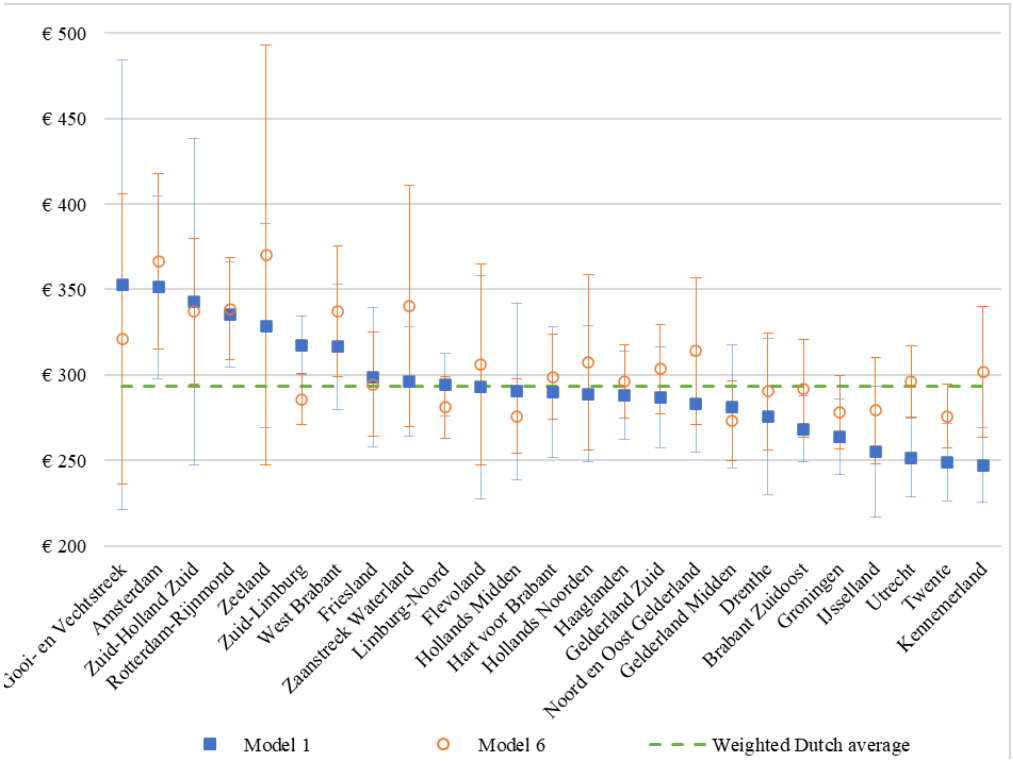

Figure A3. Marginal costs of region for pharmaceutical costs based on unadjusted (model 1) and fully adjusted costs (model 6).

* Model 1 is adjusted for region only. In model 6, the association of region and healthcare costs is adjusted demographic factors, SES, general and mental health, lifestyle, loneliness and mastery. Registry data: age, gender, migration background and household income. Self-reported data: marital status, education, income inadequacy, self-rated health, chronic disease, psychological distress, lifestyle, loneliness and mastery.

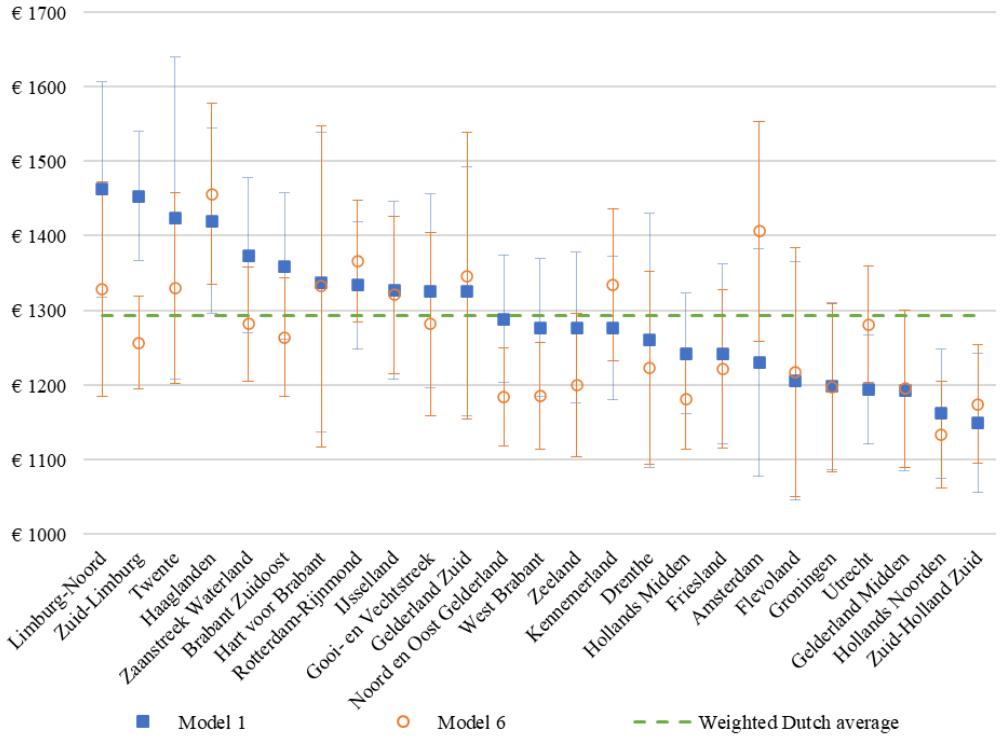

Figure A4. Marginal costs of region for specialized care costs based on unadjusted (model 1) and fully adjusted costs (model 6).

* Model 1 is adjusted for region only. In model 6, the association of region and healthcare costs is adjusted demographic factors, SES, general and mental health, lifestyle, loneliness and mastery. Registry data: age, gender, migration background and household income. Self-reported data: marital status, education, income inadequacy, self-rated health, chronic disease, psychological distress, lifestyle, loneliness and mastery.

Chapter 7

General discussion

While global population health has improved, not everyone has benefitted equally [1-5]. The World Health Organization found that low income populations still face lower healthy life expectancy at birth [1] and The Organization for Economic Cooperation and Development found that the least educated were twice more likely to face poor health compared to people with the highest education across 33 countries [2]. In Europe, overall health has improved, however, great differences exist in health between and within countries and these differences are widening [4, 5]. This is also true for the Netherlands as it is faced with socioeconomic and regional health inequalities [6-10]. Based on two reports commissioned by the Province of Limburg [11, 12], further in-depth analyses were warranted to uncover determinants of health and potential mechanisms underlying health inequalities between Limburg and the rest of the Netherlands.

The aim of this dissertation was to investigate the role of less established social determinants of health in explaining socioeconomic and regional inequalities in health and variations in healthcare expenditures. In addition to established determinants of health, such as demographic factors, socioeconomic status and lifestyle factors, the research in this dissertation studied loneliness, income inadequacy and mastery. Three objectives were formulated for this dissertation, one on a national and one on a regional scale. First, this dissertation aimed to investigate the role of loneliness, income inadequacy and mastery in socioeconomic health inequalities in a national population-based study. Second, these determinants were added to a set of established determinants of health (demographic factors, SES, and lifestyle factors) in attempt to further explain the regional health inequalities in the Netherlands. Third, all of the aforementioned determinants of health were used to further explain regional variations in healthcare expenditures in the Netherlands. These objectives were met by five empirical studies, which have been presented in this dissertation. The empirical studies in Chapters 2, 3 and 4 provide answers for the first objective and the studies in Chapters 5 and 6 provide answers for the second and third objective.

The remainder of this chapter summarizes the main findings of these studies. Subsequently, several theoretical and methodological reflections are described. Finally, implications for policymakers and practitioners are discussed. This chapter concludes with an agenda for future research.

Summary of the main findings

The main findings of the studies in this dissertation are as follows:

1. Loneliness is an important determinant of health as it contributes to the socioeconomic health gap across a range of important health outcomes. The contribution of loneliness is independent of well-established determinants such as

lifestyle and demographic factors. This contribution is particularly pronounced for people between 19 and 40 years old.

2. Loneliness has an independent association with healthcare expenditures. In particular for mental health care costs of people between 19 and 40 years of age. Contrary to common perceptions and expectations of loneliness as an 'old age' problem, loneliness is found to play a larger role in explaining variations in healthcare expenditures in younger adults than it does in older adults.

3. Income inadequacy (i.e. perceived concerns with making ends meet) is associated with poor health outcomes, in particular poor mental health, and independent of absolute income level. Therefore, income inadequacy represents another social determinant of health.

4. An extensive set of social determinants of health underlies but not necessarily fully explains regional variations in health in the Netherlands. Aside from well-established determinants (such as demographic, socioeconomic factors, and lifestyle factors) loneliness and mastery are also associated with regional health differences.

5. Regional variations in healthcare expenditures in the Netherlands can be explained by accounting for demographic, socioeconomic and lifestyle factors, loneliness, mastery and health status. The exception is expenditures for GP consultations as these remain significantly higher in the South of Limburg compared to the rest of the Netherlands.

6. Explanations for high GP consultation expenditures were found both in the demand side and consequent supply-side factors. Due to socioeconomic problems resulting from the historical context in the region, GP's felt the need to expand their responsibilities in order to better fit to population needs. This may also have lowered the barrier for people in the South of Limburg to visit their GP.

The research in this dissertation started with the notion of a 'Limburg-factor'. The 'Limburg-factor' represents multi-faceted causes for reported health inequalities in Limburg. The following domains are considered as contributors to health disadvantages in Limburg: education, labor, mastery, historical burden, cultural environment, trust and societal participation, unhealthy lifestyles, and socioeconomic status [11]. Through the course of the research undertaken for this dissertation, a model was developed in a step-wise manner to include determinants of health simultaneously in explaining regional

health inequalities and regional variations in healthcare expenditures. Loneliness and mastery were also included in the model, in addition to well-established determinants, in order to further explain regional variations in health outcomes. The inclusion of these determinants reduced variations between Limburg and the rest of the Netherlands, in other words, this reduced the 'Limburg-factor'. When accounting for demographic, socioeconomic and lifestyle factors, loneliness and mastery, the remaining 'Limburg-factor' was found to be mainly a 'South-Limburg-factor' as it was primarily the population in South-Limburg that still had worse health outcomes compared to other Dutch regions while the population in the North of Limburg was not different from other regions.

Theoretical reflection

Broad perspective on health inequalities

The research in this dissertation is based on the notion that health inequalities arise in a broad system of factors and layers of determinants. As Barton and Grant [13] visualize in their adaptation of the Dahlgren and Whitehead health map [14], the determinants of health are layered in various levels including the people, their lifestyle and their community, local economy, activities, built and natural environment and the global ecosystem. As a consequence of this broad system of factors and layers, it is imperative to look for the causes of the causes of health inequalities [15]. The research in in this dissertation is focused on determinants linked to the four inner circles of the health map.

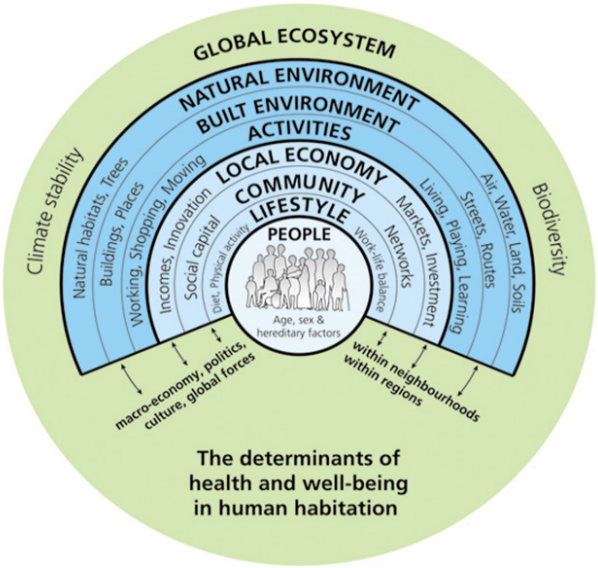

Figure 1. The health map by Barton and Grant 2006 [13], developed from the Dahlgren and Whitehead 1991 model of the determinants of health [14]

From unadjusted to adjusted regional health inequalities and variations in healthcare expenditures

This dissertation focuses on the associations of less established factors such as loneliness, income inadequacy and mastery in health inequalities and variations in healthcare expenditures. In Chapters 5 and 6, various models are presented in a step-wise manner to show the associations of lifestyle factors, loneliness, mastery and health. The very first step in the models however, is a correction for well-known demographic and socioeconomic factors such as age, gender, marital status, migration background, education, and income. These factors help explain regional health inequalities and variations in healthcare expenditures and are well known to confound with other lifestyle and psychosocial factors. When controlling for these demographic and socioeconomic differences (i.e. assuming that distribution of these factors across regions is equal), the gaps between regions narrow. However, regions are still characterized by populations with a certain set of characteristics which means that absolute differences in health and healthcare expenditures will persist as long as underlying population characteristics differ. Various border regions and former industrialized regions such as Twente, the East of Groningen and the South of Limburg, face population decline and aging. These regional differences are not unique to the Netherlands. For example, a North-South divide in UK, where Northern parts of the UK, including Scotland and Wales, also represent (former) industrialized regions that have suffered more from decline in manufacturing and mining employment than Southern regions in the UK [16]. While we can account for these demographic and socioeconomic differences in statistical models, policymakers and practitioners still face the consequences of these demographic and social trends.

The contribution of loneliness and income inadequacy to health inequalities and variations in healthcare expenditures

Chapter 2 shows that loneliness can further explain socioeconomic health inequalities after controlling for age, gender, marital status, migration background, education, absolute income, income inadequacy and lifestyle factors. The findings in Chapter 3 reveal that loneliness also has an independent association with healthcare expenditures. Both studies include a broad range aged group (19 years and older) and find that loneliness plays a larger role in explaining socioeconomic health inequalities and regional variations in mental healthcare expenditures in young adults (19-40 years old) compared to older aged groups. Chapter 4 shows that absolute income and perceived income inadequacy are independently associated with health outcomes and represent different aspects of income. Based on Chapters 2, 3 and 4, the authors recommend that public health policies include loneliness and income inadequacy as determinants of health in tackling health inequalities. Furthermore, policies targeting loneliness should broaden the target

group to include young adults as opposed to policies targeting loneliness mainly in elderly populations [17]. Programs aimed at targeting loneliness could not only benefit from including younger target groups, they could also potentially lead to savings in healthcare expenditures, especially for mental healthcare. Both loneliness and income inadequacy will present even more important determinants of health in light of two recent phenomena. First, as a result of the COVID-19 pandemic, and its subsequent detrimental consequences for loneliness [18] and mental health [19], especially for youth and young adults. Second, as the energy crisis drastically raises cost of living, livelihood concerns become more common in the general population and concerns worsen for already disadvantaged population groups. As a result, financial-related stress and depressive symptoms are also expected to increase [20]. The National Association of General Practitioners already warns for an increase of patients with physical and mental health problems caused by financial problems and related stress [21].

Regional health inequalities, regional variations in healthcare expenditures and the 'South-Limburg factor'

The modifiable determinants included in the models, such as lifestyle, loneliness and mastery, provide directions to regional policymakers where interventions are needed to reduce health inequalities and variations in healthcare expenditures. These modifiable factors also play a part in reducing the 'Limburg factor'. However, even after accounting for these factors, significant differences still remain between South-Limburg and the rest of the Netherlands in terms of higher GP consultation expenditures, poorer self-rated health and higher risk for chronic disease. This means that even with a similar population in terms of age, gender, socioeconomic status, lifestyle, loneliness and mastery, people in the South-Limburg are still more often confronted with poor self-rated health and chronic disease than people in some other Dutch regions and incur higher GP consultation expenditures compared to most other Dutch regions. The findings of this research were able to explain the 'Limburg factor' but not the 'South-Limburg factor'.

In order to find explanations for the remaining 'South-Limburg factor' in GP consultation expenditures, local GP's were interviewed. The results of this qualitative study are not presented in a separate chapter but discussed here to help contextualize the findings from Chapter 6. GP's recognized the findings that people living in the South of Limburg feel less healthy, are more often faced with chronic disease, have unhealthier lifestyles and are more often lonely than other people in the Netherlands. Previous research [11, 22, 23] and the GP interviews point at the direction that these problems have developed from the specific socioeconomic historical context in this region. In the first half of the 20th century, the region of South-Limburg was characterized by three pillars:

the church, the state and the mines [23]. The mines provided employment for many people and social security for their families. The region was one of the most prosperous in the Netherlands. After the closure of the mines in the nineteen seventies, and a lack of proper replacement for other work opportunities, people with the best qualifications left and those with lesser qualifications stayed behind [22]. Unemployment and work disability rose among the remaining population. Along with secularization, and a lack of replacement in social structures the church and the mines once provided, people in the South of Limburg faced socioeconomic problems and less social support. In some neighborhoods and families, unemployment, work disability, unhealthier lives and inadequate social support were passed down through the generations. As Chapter 5 shows, aside from unhealthier lifestyles, people in South-Limburg also experience the most loneliness and the least mastery in the Netherlands. What made this possible? Perhaps it is the sheer societal change that people in South-Limburg faced that was imposed on them from outside, top-down forces that they could not control. Not only did many employment opportunities and social structures disappear in less than a decade, no proper alternatives were implemented in their place [22]. As such, the population in the South of Limburg today is still affected by events set off more than fifty years ago.

GP's in South Limburg recognize this phenomenon and find that even today, they are faced with populations that require more assistance than what the current social structures can provide. GP's describe an overrepresentation of people with low health literacy skills, intellectual disabilities and psychological distress. They argue that as a result of the socioeconomic historical context in the region, GP's in the South of Limburg may have expanded their responsibilities to better fit with local population needs. This in turn may have lowered the barrier for people in the South of Limburg to visit their GP's.

As a result of this socioeconomic historical context, health inequalities observed in the South of Limburg compared to the rest of the Netherlands are partially socioeconomic inequalities that developed over this time. The research in this dissertation adjusted models for socioeconomic status in terms of education, income and income inadequacy. However, these proxies to socio-economic status in 2016 probably fail to completely reflect the socioeconomic history and context the people in South-Limburg were burdened with over last decades.

Methodological reflection

Need for linkage to upstream data

The linked dataset used in the research for this dissertation provided many opportunities in studying socioeconomic and regional health inequalities. However, the microdata in this dataset are based on mostly downstream determinants of health on the individual, community and local economy levels of the health map [13]. There is a need to link upstream data in order to incorporate determinants of health from the built and natural environment of the health map. The differences between downstream and upstream factors are best explained by the classic parable of medical sociologist Irving Zola [24] about a witness at a river current. The witness hears cries for help and responds by helping people out of the water and resuscitating them one after the other. He wonders who is pushing these people in the river, but he is too busy saving people to walk upstream and see. Upstream factors represent underlying, structural determinants of health such as neighborhood characteristics (leisure space, green space, safety, social cohesion, housing quality and nuisance), environmental factors (water, air and soil quality) but also quality of education, labor, income and taxation policies. The sum of all these environmental drivers of health is defined as the exposome (as opposed to the genetic factors defined as the genome)[25]. Exposome research presents opportunities to simultaneously model various factors related to ecosystems, physical and social environments and individual behaviors to various health outcomes [25]. With this approach, it will be possible to include all layers from the Barton and Grant health map [13] and include both upstream and downstream determinants of health.

Linked microdata

The studies presented in this dissertation are based on a linked dataset with so called microdata. In other words, data about individuals. The data were made available by Statistics Netherlands. The researcher linked the various datasets based on pseudonymized identification numbers. Some data are based on what individuals reported themselves in the Public Health Survey and some data are based on registries that are monitored by the municipalities, the Tax authority or Vektis. Vektis collects healthcare claims data that are covered by the basic insurance plan from all insurers in the Netherlands on an annual basis.

The linkage between the Public Health Survey data, Vektis data, and various registry data provide a unique opportunity to study regional variations in 1) various health outcomes, 2) a range of health care expenditure types, 3) with a broad range of determinants of health using data from a substantial number of subjects, allowing for in-depth analyses. The studies in this dissertation operationalized health status with three different outcomes: self-reported health, self-reported chronic disease and psychological

distress (as operationalized by the Kessler Psychological Distress Scale, K10 [26]). In addition, different categories of healthcare expenditures are also studied in relation to social determinants of health. This helped answer questions raised in previous studies for example, the association of loneliness and different types of healthcare costs in a broad-ranged age group [27]. The data linkage provided information on a broad set of determinants of health. These data are broad in the sense that they cover demographic factors (age, gender, marital status and migration background), socioeconomic status (educational level, absolute income and income inadequacy), lifestyle (BMI, alcohol consumption, smoking and physical activity) and psychosocial factors such as loneliness and mastery. This enabled the authors to add less researched determinants of health, such as loneliness and mastery, to well-known determinants of health such as demographic, socioeconomic and lifestyle factors in studying health inequalities. Previous studies showed that these well-known determinants alone could not explain observed health inequalities [28, 29]. For socioeconomic status, it was possible to study associations of both absolute income levels (as registered by the Tax authority) and the perceived level of income inadequacy that people reported themselves in the Public Health Survey. Previous research has shown that these definitions of income are conceptually different and are related to health differently [30, 31]. The research in this dissertation could adjust analyses for both concepts of income. The sample size of roughly 350,000 Dutch adults allowed the researchers to perform in-depth analyses in demographic subgroups such as gender, age and migration groups and sensitivity analyses for robustness of the results.

Challenges to causal inference

The dataset used in this research is limited in the sense that it includes data on health and determinants of health for the year 2016 and healthcare expenditures for the year 2017. While CBS microdata includes time-series of data on, for example, income or health expenditure, public health survey data is cross-sectional and thus inference for this research cannot be causal. The results can only be interpreted in terms of associations between the studied phenomena. For loneliness and health for example, cross-sectional research has related loneliness to poor mental [32, 33] and physical health [33-37], and reversely, poor health to loneliness [38]. In longitudinal research, loneliness was found to both affect [39] and simultaneously be affected by, mental and physical health [40]. This reversed causality cannot be excluded in the studies of this dissertation. Similarly, cross-sectional research has linked unhealthy lifestyles and loneliness to healthcare expenditures [32, 41, 42]. However, the research in this dissertation cannot conclude whether lifestyle and loneliness lead to poor health and therefore high healthcare expenditures, or if poor health leads to (more) loneliness and unhealthier lifestyles. Likewise, various cross-sectional studies have linked

low absolute incomes to poor physical [43] and mental health [44-46] and income inadequacy to poor self-rated [30, 31] physical [31, 47] and mental health [47-49]. Chapter 4 shows that both absolute income and income inadequacy are independently associated with health. However, based on the presented findings we cannot conclude whether low absolute income and perceived income inadequacy lead to poor health, or that poor health in turn leads to less absolute income and therefore (more strongly) perceived income inadequacy. Considering mastery, there is not much known about the relationship between mastery and healthcare expenditures. Chapter 6 points in the direction that people with adequate mastery incur less healthcare expenditures. However, more longitudinal research is needed to build substantial evidence for this relationship. This relationship will become more important over time, especially in the current neoliberal society which emphasizes individuals' own responsibilities and role in participation and patient-centered care together with the ever growing complexity of society and the healthcare system [50].

Implications for policy and practice

Health policies need to transcend domains and include upstream factors

The research is this dissertation shows that multiple determinants of health, both less- and well-established, play a role in explaining socioeconomic health inequalities on a national level and in regional health inequalities. The causes of these determinants are complex, accumulate over the life course and are often found outside the public health domain [51]. Therefore, healthcare and public health policies need to transcend domains, to for example social domain, housing, labor market, spatial planning, education, income and taxation policies, in order to capture more determinants of health that influence socioeconomic health inequalities [52]. The World Health Organization coined this cross-domain cooperation approach Health in All Policies (HiAP) [53]. The HiAP approach systematically considers health implications of decisions across policy domains. The COVID-19 pandemic has highlighted the multiple links between health and other policy domains and demonstrated the need for an integrated governmental approach [54]. The HiAP approach could even go one step further in Health *for* all policies, where health gains are considered beneficial for other domains, such as education and the labor market, and the overall economy [55]. This approach relocates the focus from health promotion (influencing individual lifestyles) to health protection (adjusting the overall environment to a healthy environment) [55].

In addition to health policies crossing domains, they should also incorporate both downstream and upstream approaches. The Zola parable [24] shows that our health system is mostly concerned with (emergency) curative treatments. As Mackenbach states, medical care is needed to treat 'symptoms' and public health is needed for dealing

with 'causes' [56]. However, relatively little attention is paid to the underlying problems and structural determinants of health that lie upstream, the causes of the causes [4]. For example, living wage policies, progressive taxation on income and assets, affordable and sustainable housing, high quality education, neighborhood improvements in terms of green space and social cohesion, and improvements in environmental conditions all provide structural opportunities to help enhance population health and provide larger scaled protection from harmful health effects.

Cross-domain cooperation in practice

Cross-domain cooperation should not only be strived for in policy development, but also in policy implementation. In practice, professionals will also need to look across the borders of their own profession for fruitful cooperation. Local networks of professionals need to be formed around citizens with for example GP's, district nurses, social workers, debt counselors, housing and volunteer associations. These local networks know of opportunities in neighborhoods where people can get easy accessible help before (multiple) problems worsen. An example of this cross-domain cooperation in practice is the intervention 'Social Prescribing' (Welzijn op Recept). This practice enables GP's to refer patients with psychosocial problems to local well-being organizations [57]. It helps people improve their sense of mastery, confidence and social contacts, resulting in overall better health. It is important that networks of local partners provide support during the life course and support starts at the earliest life phase. As shown by the Heckman curve [58], the most impact is generated in the earliest phases of life. In the Netherlands, local consortia currently offer the 'Solid Start' (Kansrijke Start) program which aims to provide every child the best opportunities in the first 1.000 days (during pregnancy and first two years of life) [59]. This program is a collaboration between professionals in the medical domain (GP's, midwives, nurses and health insurers) and social domain (municipality, social support and youth care) to improve and protect health and enhance future opportunities for newborns and their parents.

Budget models in health and social care need improvements

In the Netherlands, every insurer is obliged to accept everyone for health insurance, and insurers are forbidden to charge different premiums based on individual characteristics. In this system, insurers prefer as many healthy, low cost individuals and as few unhealthy, high costs individuals as possible. To minimize this risk selection behavior, insurers are compensated for their population with the risk equalization model [60]. Currently, the model compensates insurers based on personal characteristics such as age, gender, source of income, regional characteristics, socioeconomic status, number of household members and previously incurred healthcare expenditures [61]. This model however, does not properly compensate insurers [61]. For people who report their health as

(very) good the model overcompensates (with €145 per person). Conversely, for people reporting their health as fair or (very) poor the model undercompensates (with €428 per person) [61]. The results of the research in this dissertation should be viewed as a sign of urgency to cooperate with partners in other fields and invest in preventive programs. With the current risk equalization model, predicted losses due to an unhealthy population may incentivize insurers to invest in cross-domain prevention programs in order to improve population health so that said under compensation is lowered. On the other hand, predicted losses may discourage insurers to invest as no budgets remain available for prevention programs. This will also complicate meeting the intentions of the national discussion paper 'Healthcare for the Future' [62] for a more sustainable future health system by encouraging investments in prevention and regional cross-domain collaboration. Currently, the National Health Care Institute [63, 64] and the Dutch Healthcare Authority [64] also advise to improve the risk equalization model. The model could be improved to better predict future necessary regional budgets if the models incorporated a more extensive set of data related to health status, lifestyle, loneliness and mastery.

National budgetary model improvements are not only relevant for healthcare insurers, but also for local government in providing support in the social domain. Since the 2015 transformation of finance and implementation for youth care, social support and participation, many municipalities and regions are faced with budget deficits, for example in the regions of South-Limburg [65] and Zeeland [66]. The models that calculate municipal budgets for youth care, social support and participation do not incorporate factors related to health or healthcare use [11]. Factors related to health and healthcare use need to be researched in relation to social domain support use in order to improve national budgetary models.

Directions for future research

The studies presented in this dissertation show that less researched determinants of health such as loneliness and mastery, should not be overlooked when studying socioeconomic and regional health inequalities. Researchers, policymakers and health insurers should not solely focus on demographic, socioeconomic or lifestyle factors in targeting health inequalities. Instead, a broad view on health and its determinants is needed. The research in this dissertation sought to combine several determinants of health that cover demographic, socioeconomic, lifestyle and psychosocial factors such as loneliness and mastery. In doing so, this research combined factors from the first four layers of the Barton and Grant health map [13] in socioeconomic and regional health inequality research. Several directions for future research emerge from this dissertation. First and foremost, future research should incorporate determinants of health that

include the outer layers of the health map such as the built and natural environment. Mackenbach expands the perspective on health inequalities further in stating that health and mortality improvements for humans have come at the cost of other species and overall planetary health [56]. Future endeavors aimed at improving population health should therefore also fit in 'ecological sustainable boundaries' in order to preserve planetary health and other living species on this planet [56]. The current effects of climate change already become apparent with more extreme weather events, climate migration, food insecurity, air pollution and increased zoonotic diseases (diseases that are transmitted from animals to humans) [54]. Zoonotic diseases, global travel and transport and overcrowded housing all facilitate the speed of disease transmission such as the case of the COVID-19 pandemic [54]. This pandemic increased health inequalities further as the impacts were disproportionally carried by already disadvantaged groups. COVID-19 is therefore coined a synergistic pandemic, a phenomenon where at least two categories of diseases (COVID-19 and a range of non-communicable diseases such as cardiovascular disease and diabetes) are more prevalent in particular social groups that already face all kinds of adversities (medical and social), including of course low socioeconomic status [54, 67]. Within these disadvantaged groups, the health effects of each separate disease are worsened. This in turn widens the gap between already existent health inequalities. This implies that more attention is needed for upstream, structural factors that influence population and planetary health. This requires a multitude of data sources that need to be linked on different levels, such as micro level (the individual), meso level (the neighborhood, employer or school level) and the macro level (national policies and environmental factors).

Second, more longitudinal research is needed to unravel complex causal relationships between demographic, socioeconomic, lifestyle, loneliness, mastery, health and healthcare expenditures. While registry data from Statistics Netherlands and the Tax Authority and healthcare claims data provided by Vektis are available nationwide annually in the period 2012-2020 for the whole Dutch population, the Public Health Survey is run every four years with different samples which hinders longitudinal analyses of the data. Ideally, if the Public Health Survey implemented a cohort study design, this would provide opportunities for longitudinal research into socioeconomic and regional health inequalities in the future. However, the reality shows that the Public Health Survey already faces lower response rates with each new round over the last decade, suggesting that longitudinal cohort design is unfeasible. Existing examples of longitudinal cohort surveys such as the Survey of Health, Ageing and Retirement in Europe (SHARE) shows a complicated sample development after 8 waves, with a decreasing baseline sample and 4 subsequent refreshment samples over time [68]. Low retention rates pose challenges to analyses and may introduce strong selection biases

to the data. On the other hand, modern digital society collects more data than ever in nearly all spheres of life. This offers opportunities for generating new insights and analyzing complex social problems. It requires procedures to ensure individual privacy in line with strict regulations such as the General Data Protection Regulation. The work in this thesis demonstrated the power of safe linkage of existing data repositories in the remote research environment of Statistics Netherlands. Further work with data owners and improving data infrastructure is required to expand the number of available datasets to enable future research.

Third, the research in this dissertation studying underlying determinants of regional inequalities in healthcare expenditures focused on the expenditures in the five biggest cost categories as reimbursed by the basic health insurance package. For specialized care, pharmaceutical and mental healthcare expenditures it may be relevant to pursue in-depth analyses in more detailed cost categories such as specific treatments or pharmaceuticals related to certain (chronic) diseases or specific types of mental healthcare (inpatient or outpatient, short term or long term care).

Fourth, aside from expenditures incurred by health insurers, it is worthwhile to study socio-economic causes of regional health inequalities in other public expenditures such as the social domain, for example youth care, social support or participation. This could help inform and fine-tune budgetary models to actual spending, thus lowering municipal budgetary deficits.

Conclusion

The studies in this dissertation highlight the role of loneliness, income inadequacy and mastery in explaining socioeconomic and regional health inequalities beyond the well-established social determinants including demographic, socio-economic and lifestyle factors. We have been also able to demonstrate that these factors help explain Dutch regional variations in healthcare expenditures. With the addition of these determinants to well established determinants of health we were able to explain the so called 'Limburg-factor': after controlling for these determinants, no differences were observed in health or health expenditure between Limburg and other Dutch regions. However, a 'South-Limburg' factor (i.e. difference in outcomes between South Limburg and other Dutch regions) remained for self-rated health, presence of chronic disease and GP consultation costs. Through qualitative work with local GP's it appeared that further explanations of 'South-Limburg factor' should be sought in the socioeconomic historic context of the South of Limburg and long-term impact on its population.

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Addenda

Summary

While global population health has improved over the years, not everyone has benefitted equally. People with lower incomes and education still face poorer health and lower healthy life expectancy at birth compared to people with higher income and education. Following the global trend, overall health in Europe has also improved, however, great differences exist in health between and within countries and recent research showed that these differences are widening. The Netherlands is no exception as socioeconomic and regional health inequalities are also observed in the Dutch population. Also, the ever increasing costs of healthcare show some regional variation which cannot be explained by demographic factors. In 2017 and 2022, two reports were commissioned by the Province of Limburg in order to see if the inequalities in Limburg had narrowed compared to the rest of the Netherlands. Based on the findings of these reports, further in-depth analyses were warranted to study factors underlying health inequalities between Limburg and the rest of the Netherlands.

The aim of this dissertation is to investigate the role of less established determinants of health in explaining socioeconomic and regional inequalities in health and regional variations in healthcare expenditures. In the context of this dissertation, less established determinants of health represent loneliness, mastery and perceived income inadequacy. The less established determinants of health were added to established determinants of health, which represent demographic, socioeconomic and lifestyle factors. Three objectives were formulated for this dissertation, one on a national and two on a regional scale. What is the role of loneliness and perceived income inadequacy in socioeconomic health inequalities? Second, to what extent can social determinants of health explain regional health inequalities in the Netherlands? Third, to what extent can social determinants of health explain regional variations in healthcare expenditures in the Netherlands?

Chapters 2, 3 and 4 provide answers for the first objective of this dissertation. **Chapter 2** demonstrates that loneliness can further explain the socioeconomic gradient in health across a range of important health outcomes (self-reported health, presence of chronic disease and psychological distress) independently of well-documented determinants such as lifestyle and demographic factors, in particular for (young) adults. As such, loneliness presents a modifiable social determinant of health in tackling health inequalities.

Chapter 3 shows that loneliness is directly and indirectly (i.e. via poor health and psychological distress) associated with higher healthcare expenditures, especially for

mental healthcare. Contrary to common perceptions and expectations of loneliness in old age, loneliness is found to play a larger role in explaining variations in healthcare expenditures in younger adults than it does in older adults.

Chapter 4 reports that income inadequacy is associated with poor health outcomes, in particular poor mental health, independent of absolute income level. It shows that absolute income and perceived income inadequacy represent conceptually different aspects, as some individuals in the highest income group still perceive their incomes as inadequate. This implies that focusing on either absolute income or perceived income inadequacies is not sufficient in health inequality research. Together, Chapters 2,3 and 4 indicate that both loneliness and income inadequacy are determinants of health and should be included in research studying health inequalities and in policy programs targeting health inequalities in a broad aged population.

For the second and third objectives, Chapters 5 and 6 describe studies that include an extensive set of sociodemographic factors in analyzing regional inequalities in health and healthcare costs. Aside from established factors (such as demographic, socioeconomic factors and health status), lifestyle factors, loneliness and mastery are also associated with regional health differences. The studies started with the notion of a Limburg-factor which implies that factors from various domains contribute to health disadvantages in Limburg (education, labor, mastery, historical burden, cultural environment, trust and societal participation, unhealthy lifestyles, and socioeconomic status). Through the course of the research undertaken in chapters 5 and 6, the Limburg-factor was found to be mainly a South-Limburg-factor as the socioeconomic disadvantages and health inequalities were mainly found in the South-Limburg population instead of the population in the North of Limburg.

Chapter 5 explores regional health inequalities in three health outcomes namely, self-reported health, presence of chronic disease and psychological distress. After adjusting for the abovementioned extended set of factors, the differences between the South of Limburg and the rest of the Netherlands were considered explained for psychological distress while differences in self-reported health and presence of chronic disease reduced but remained relevant and statistically significant.

In **Chapter 6,** variations in healthcare expenditures between the South of Limburg and the rest of the Netherlands were explained by demographic, socioeconomic and lifestyle factors, loneliness, master and health status for total healthcare, specialized care, pharmaceutical and mental healthcare expenditures. However, consultation expenditures for General Practitioners (GP's) remained significantly higher in the South

of Limburg than in almost all other regions in the Netherlands.

To provide more explanations for this finding, several interviews with GP's in the South of Limburg were conducted. Based on these interviews, additional explanations were found in the socioeconomic historical context of the region. The mine closures in the nineteen sixties and seventies, and a lack of replacement for alternative work possibilities and social structures, resulted in vast socioeconomic problems for the remaining population in the South of Limburg. GP's report that even today, they are faced with less healthy populations that require more assistance than what the current social structures can provide. GP's describe an overrepresentation of people with low health literacy skills, intellectual disabilities and psychological distress. To better fit population needs, GP's argue they have extended their responsibilities over time, which in turn lowered the barriers for their patients.

Chapter 7 presents the main findings of this dissertation and discusses the theoretical contributions of the work, the methodological strengths and weaknesses, implications for policymakers and practitioners, and outlines directions for future research. Overall, the studies presented in this dissertation show that loneliness, income inadequacy and mastery represent additional determinants of health that are associated with various health outcomes independently of well-documented determinants of health such as demographic, socioeconomic and lifestyle factors. With the inclusion of these determinants, it is possible to explain regional differences in mental health and the majority of healthcare expenditures in the Netherlands. The results of these studies show that public health policy and practice should transcend domains and should combine both upstream and downstream factors in tackling health inequalities.

Samenvatting

Hoewel de gezondheid van de wereldbevolking in de loop der jaren is verbeterd, heeft niet iedereen er in gelijke mate van geprofiteerd. Mensen met een lager inkomen en een lager opleidingsniveau hebben nog steeds te maken met een slechtere gezondheid en een lagere gezonde levensverwachting, in vergelijking met mensen met een hoger inkomen en een hoger opleidingsniveau. Ook in Europa is de algehele gezondheid verbeterd, maar er bestaan grote verschillen in gezondheid tussen en binnen landen. Recent onderzoek heeft aangetoond dat deze verschillen zelfs groter worden. Nederland vormt hierop geen uitzondering, aangezien ook onder de Nederlandse bevolking sociaaleconomische en regionale gezondheidsverschillen worden waargenomen. Ook de steeds stijgende kosten van de gezondheidszorg verschillen regionaal, en deze verschillen kunnen niet worden verklaard door enkel demografische factoren. In 2018 en 2022 zijn in opdracht van de Provincie Limburg twee rapportages opgeleverd om te kijken of de ongelijkheden in Limburg zijn afgenomen ten opzichte van de rest van Nederland. Op basis van de bevindingen uit deze rapporten waren verdere diepgaande analyses nodig om factoren te bestuderen die gezondheidsverschillen tussen Limburg en de rest van Nederland verder kunnen verklaren. Het doel van dit proefschrift is het onderzoeken van de rol van minder bekende determinanten van gezondheid bij het verklaren van sociaaleconomische en regionale ongelijkheden in gezondheid en regionale verschillen in zorgkosten. In de context van dit proefschrift bedoelen we met minder bekende determinanten van gezondheid eenzaamheid, moeite met rondkomen en regie over eigen leven. De minder bekende determinanten van gezondheid worden toegevoegd aan de welbekende determinanten van gezondheid zoals demografische, sociaaleconomische en leefstijlfactoren. Voor dit proefschrift zijn drie doelstellingen geformuleerd, één op landelijk en twee op regionaal niveau. Als eerste, wat is de rol van eenzaamheid en moeite met rondkomen in het verklaren van sociaaleconomische gezondheidsverschillen? Ten tweede, in hoeverre kunnen sociale determinanten van gezondheid regionale gezondheidsverschillen in Nederland verklaren? Ten derde, in hoeverre kunnen sociale determinanten van gezondheid regionale verschillen in zorgkosten in Nederland verklaren?

Hoofdstukken 2, 3 en 4 geven antwoord op de eerste doelstelling van dit proefschrift. **Hoofdstuk 2** laat zien dat eenzaamheid de sociaaleconomische gradiënt in gezondheid verder kan verklaren in een aantal belangrijke gezondheidsuitkomsten (zelf-gerapporteerde gezondheid, aanwezigheid van chronische ziekte(n) en risico op een angststoornis of depressie), onafhankelijk van welbekende determinanten zoals leefstijl en demografische factoren, met name voor (jong-)volwassenen. Dit maakt eenzaamheid een beïnvloedbare sociale determinant van gezondheid en daarmee van belang bij het aanpakken van gezondheidsverschillen.

Hoofdstuk 3 laat zien dat eenzaamheid direct en indirect (d.w.z. via een slechtere fysieke en mentale gezondheid) samenhangt met hogere zorgkosten, met name voor de geestelijke gezondheidszorg. In tegenstelling tot wat algemeen wordt aangenomen en verwacht van eenzaamheid op oudere leeftijd, blijkt eenzaamheid een grotere rol te spelen bij het verklaren van variaties in zorgkosten bij jongere volwassenen dan bij oudere volwassenen.

Hoofdstuk 4 rapporteert dat moeite met rondkomen geassocieerd is met slechtere gezondheidsuitkomsten, in het bijzonder een slechtere mentale gezondheid, onafhankelijk van het absolute inkomensniveau. Het laat zien dat het absolute inkomen en het kunnen rondkomen van het inkomen conceptueel verschillende aspecten vertegenwoordigen, aangezien sommige personen in de hoogste inkomensgroep hun inkomen nog steeds als onvoldoende beschouwen. Dit impliceert dat de focus op ofwel het absolute inkomen ofwel moeite met rondkomen niet voldoende is in onderzoek naar gezondheidsverschillen. Samen geven de hoofdstukken 2, 3 en 4 aan dat zowel eenzaamheid als moeite met rondkomen gezondheidsdeterminanten zijn en moeten worden opgenomen in onderzoek naar gezondheidsverschillen en in beleidsprogramma's gericht op het verkleinen van gezondheidsverschillen in een brede leeftijdsgroep.

Voor de tweede en derde doelstelling beschrijven de hoofdstukken 5 en 6 onderzoeken die een uitgebreide set van sociaal-demografische factoren omvatten bij het analyseren van regionale ongelijkheden in gezondheid en zorgkosten. Naast welbekende factoren (zoals demografische, sociaaleconomische factoren en gezondheidsstatus) hangen ook leefstijlfactoren, eenzaamheid en regie over eigen leven samen met regionale gezondheidsverschillen. De studies zijn gestart vanuit het concept 'de Limburg-factor', wat inhoudt dat factoren uit verschillende domeinen bijdragen aan gezondheidsachterstanden in Limburg (opleiding, arbeid, regie over eigen leven, historische belasting, culturele omgeving, vertrouwen en maatschappelijke participatie, ongezonde leefstijlen en sociaaleconomische status). In de loop van het onderzoek in de hoofdstukken 5 en 6 blijkt de Limburg-factor vooral een Zuid-Limburg factor te zijn, aangezien de sociaaleconomische achterstanden en gezondheidsachterstanden vooral zijn gevonden bij de Zuid-Limburgse bevolking in plaats van bij de bevolking in Noord-Limburg.

Hoofdstuk 5 analyseert regionale gezondheidsverschillen in drie gezondheids-uitkomsten, namelijk zelf-gerapporteerde gezondheid, aanwezigheid van chronische ziekte(n) en het risico op een angststoornis of depressie. Na correctie voor de bovengenoemde uitgebreide set van factoren (demografische, sociaaleconomische, gezondheidsstatus, leefstijl, eenzaamheid en regie over eigen leven), zijn de verschillen

tussen Zuid-Limburg en de rest van Nederland verklaard voor het risico op een angststoornis of depressie, terwijl verschillen in zelf-gerapporteerde gezondheid en aanwezigheid van chronische ziekten kleiner worden maar statistisch significant blijven.

In **hoofdstuk 6** zijn verschillen in zorgkosten tussen Zuid-Limburg en de rest van Nederland verklaard door demografische-, sociaaleconomische- en leefstijlfactoren, gezondheidsstatus, eenzaamheid en regie over eigen leven voor de totale zorgkosten, medisch specialistische, farmaceutische en GGZ-kosten. De huisartsconsultkosten blijven in Zuid-Limburg echter hoger dan in bijna alle andere regio's in Nederland.

Om deze laatste bevinding te kunnen verklaren zijn er interviews gehouden met meerdere huisartsen in Zuid-Limburg. Op basis van deze interviews zijn aanvullende verklaringen gevonden in de sociaaleconomische historische context van de regio. De mijnsluitingen in de jaren zestig en zeventig, en een gebrek aan vervangende werkmogelijkheden en sociale steunstructuren, zorgden voor grote sociaaleconomische problemen voor de overgebleven Zuid-Limburgse bevolking. Huisartsen melden dat ze vandaag de dag nog worden geconfronteerd met minder gezonde bevolkingsgroepen die meer hulp nodig hebben dan wat de huidige sociale steunstructuren kunnen bieden. Huisartsen beschrijven een oververtegenwoordiging van mensen met lage gezondheidsvaardigheden, (licht) verstandelijke beperkingen en psychische klachten. Om beter aan de behoeften van de bevolking te voldoen, geven huisartsen aan dat ze hun verantwoordelijkheden in de loop van de tijd hebben uitgebreid, wat op zijn beurt de drempels voor hun patiënten heeft verlaagd.

Hoofdstuk 7 presenteert de belangrijkste bevindingen van dit proefschrift en bespreekt de theoretische bijdragen van het werk, de methodologische sterke en zwakke punten, implicaties voor beleidsmakers en de praktijk, en schetst richtingen voor toekomstig onderzoek. Over het algemeen laten de studies die in dit proefschrift worden gepresenteerd zien dat eenzaamheid, moeite met rondkomen en regie over eigen leven aanvullende determinanten van gezondheid zijn. Deze determinanten worden geassocieerd met verschillende gezondheidsuitkomsten, onafhankelijk van welbekende gezondheids-determinanten zoals demografische-, sociaaleconomische- en leefstijl-factoren. Met het meenemen van deze determinanten is het mogelijk om regionale verschillen in mentale gezondheid en zorgkosten in Nederland te verklaren. De resultaten van deze studies tonen aan dat het volksgezondheidsbeleid en de uitvoeringspraktijk domeinoverstijgend moeten opereren en factoren zowel stroomopwaarts bij de bron als stroomafwaarts moet combineren om gezondheidsongelijkheden aan te kunnen pakken.

Impact paragraph

As a society, we believe that everyone should have equal chances for good health independent of where you are born or who you are. However, in the Netherlands a person with low education lives 4 years less and lives 14 years in less good health than someone who is higher educated. Likewise, people have poorer health in some regions in the Netherlands compared to people in other regions. For example, people in South-Limburg live on average 2 year less and 6,4 years in less good health than people in the region Hollands-Midden [1, 2]. In addition, average healthcare costs per person differ regionally. Between the municipalities with the highest and lowest healthcare costs, there was a difference of more than €1770,- (€3625,- in Kerkrade and €1853,- in Urk) [3]. Even after adjusting for age and gender, the difference still remained roughly €1200,- (€3273,- in Heerlen and €2074,- in Roosendaal) [3]. In this research we tried to uncover other factors that can also explain these differences and that, importantly, could be acted upon to achieve more equality. If we know this, we can inform policy makers both regionally and nationally on reducing health inequalities. In terms of healthcare costs, identifying factors that underlie regional differences can be a next step for more informed budget allocations.

This chapter describes the practical relevance and implications of the research presented in this dissertation. The knowledge produced by this research has been disseminated through various channels in the past few years. Common scientific channels included publications in peer-reviewed (inter-)national journals and presentations at conferences. In this dissertation, there has been a strong emphasis on more direct societal impact and knowledge dissemination with policymakers and practice. These efforts were made in collaboration with the Living Lab for Public Health and the Living Lab for Sustainable Care. First, the scientific impact will be described and second the societal impact for policymakers and practice.

Scientific impact

The empirical research in this dissertation was guided by the Barton and Grant Health Map [4]. The contribution of this dissertation is based on simultaneously analyzing both well- and less established determinants of health from various circles in the Health Map. Well-established determinants of health represent demographic, socioeconomic and lifestyle factors in this dissertation. Less established determinants consider loneliness, income inadequacy and mastery. The results of this research are presented in two international publications on loneliness and socioeconomic health inequalities, one international publication on income inadequacy and socioeconomic health inequalities and two national publications on explaining regional health inequalities in the

Netherlands. The research on costs of loneliness was also presented at an international scientific conference. The research has led to four major insights relevant for scholars in the field of socioeconomic health inequalities.

First, the results of these publications and contributions expand the knowledge on the role of loneliness in socioeconomic health inequalities beyond the well-established determinants of health. While most research on loneliness is focused on older age groups, the studies in this dissertation include a broad aged population (19 years and older). This helps us to show that the relationships between loneliness, poor health and high healthcare expenditures are prevalent in all age groups and even stronger for young adults compared to older aged groups, especially for mental health and mental healthcare expenditures. These studies contribute to research about mechanisms involving loneliness, mental health (care), and young adults. The need and relevance of this kind of research has grown since the start of the COVID-19 pandemic as youth and young adults are more vulnerable for developing mental health problems during pandemics [5].

Second, the results of one of the publications show that income inadequacy and absolute income represent two different concepts and both relate to health outcomes independently, especially for mental health. Whereas most studies analyzing associations of income on health incorporate measures of either absolute income or income inadequacy, our results suggest that both play an important part in explaining socioeconomic health inequalities and should hence both be recognized and accounted for in empirical work. In light of the recent energy crisis and its impact on cost of living, we also expect income and income inadequacy to become even more important determinants of health in studying socioeconomic health inequalities.

Third, the results presented in the national publications further explain regional inequalities in health and variations in healthcare expenditures in the Netherlands. Aside from the established determinants such as demographic and socioeconomic factors, other determinants such as lifestyle, loneliness and mastery also help to explain why populations in some regions are unhealthier and have higher healthcare expenditures than populations from other regions. For healthcare expenditures, the research provided a novel analysis of healthcare expenditure data with new insights on regional health differences. This advances our understanding of healthcare expenditures, as it is not purely a function of health but also depends on a broad range of social determinants of health.

Fourth, the research in this dissertation has linked various datasets on individual data concerning health, healthcare expenditures, demographics, socioeconomic and lifestyle factors, loneliness and mastery. The sensitive data were pseudo-anonymized by a trusted third party and linked in a secured digital environment. This data linkage proved a valuable basis for answering complex research questions and has the potential to be expanded with more data to answer other questions in the future.

Societal impact

The research presented in this dissertation impacts society in three different ways, first in contributing to regional government policy development, second, in knowledge transfer with local GP's and third, through knowledge dissemination via various national and regional outlets.

Contribution to regional policy development

Research into health inequalities in Limburg was initiated by the 2015 report 'the Limburg-factor' [6]. This report helped the Province of Limburg with developing the policy program 'the Social Agenda'. The Social Agenda aims to close the gap in health inequalities between Limburg and the Netherlands based on five major themes: youth, education, labor, health, and social capital. The Province of Limburg wanted to monitor the Social Agenda which resulted in two grants for two evaluation studies, one in 2018 (baseline) and one in 2022 (first evaluation). These evaluation studies were executed in addition to the studies presented in this dissertation. Both evaluations required a multitude of data sources to reflect on trends over time in the Netherlands and in Limburg for the five themes. To do this, multiple stakeholders were involved such as Statistics Netherlands, the national and regional Public Health Services, Perined (registration of perinatal health data), the Research Centre for Education and the Labour Market, and the Education Monitor Limburg (OnderwijsMonitor Limburg). The subsequent reports for these studies ([7] in 2018 and [8] in 2022) showed that Limburg, more specifically the South of Limburg, faces disadvantages in every theme of the Social Agenda. The results show the urge for more preventive, cross-domain investments on the long-term. The recommendations from these reports are used as input for further policy development in the Province of Limburg for the period 2018-2022 and 2022-2026. The results of the 2018 report received media attention in the daily newspaper The Limburger and have also been used in the development of the regional health agreement for the South of Limburg in 2018 [9] and 2022. Furthermore, the results of the 2018 report contributed to the development of a new public health program in the South of Limburg (Trendbreuk Zuid-Limburg [10]). This prevention program prioritizes the (pre)conception phase, (pre)natal care, (young) children in primary, secondary and vocational schools and parenthood according to the lifecycle approach. In the process

of writing both reports, various presentations were given for the Provincial government, the regional and national Public Health Service and local stakeholders in the field of the labor market, societal participation, education, and public health. As part of the 2022 evaluation, three focus groups were organized with local stakeholders in the field of 1) youth and education, 2) the labor market and societal participation and 3) health and social capital in order to co-create recommendations for further policy development of the Social Agenda as of 2023 [11].

The Council for Public Health and Society (Raad voor Volksgezondheid en Samenleving, RVS) has consulted South Limburg about their regional approach, which has resulted in the advisory report of RVS, titled "A fair chance for a healthy life" [12]. The ministry of Health, Welfare and Sport (VWS) and the ministry of the Interior (Binnenlandse Zaken) visited the region several times to obtain information about health inequalities and to consider making additional investments in the region. This finally resulted, in cooperation with many other partners (housing, labor, welfare, health, education), in the "Region deal for Parkstad", a grant of the national government to increase prosperity.

Knowledge transfer with local GP's

For most health outcomes and healthcare costs categories, regional health inequalities are explained with the addition of a broad range of socioeconomic factors in this dissertation. However, GP consultation expenditures in the South of Limburg remained inexplicably high compared to all other regions in the Netherlands. In order to provide more answers for this phenomenon, interviews were conducted with local GP's. The interviews served two purposes. First, the GP's were informed about the research results underlying the importance of social determinants of health for regional variations in health and healthcare expenditures. Second, the GP's were invited to share other explanations for higher GP consultation expenditures in the South of Limburg in order to inform future policy and research agendas. The interviews helped shed light on upstream socioeconomic and cultural determinants of health that are difficult to address with public health policies. Furthermore, the interviews helped contextualize the findings and (partially) destigmatize the South Limburg population.

Knowledge dissemination via various (inter-)national and regional outlets

Finally, the results presented in this dissertation were shared with society through several channels such as (social) media, websites, newsletters and presentations. A presentation about the costs of loneliness was given for the national program JoinUs in the learning event Stronger Together during the Week against Loneliness in 2021 [13]. JoinUs aims to combat loneliness in young adults [14]. The results of the study were also presented at the international conference Campaign to End Loneliness in

2023. The study on costs of loneliness also received media attention in various national outlets such as NRC, the Telegraaf, Nu.nl and in the regional newspaper The Limburger. Two interviews were given about this study, resulting in an article in the Zorg+Welzijn magazine [15] (magazine for professionals in the social domain) and in the newsletter for the Living Lab for Public Health [16].

The results of the research on regional health inequalities and regional variations in healthcare expenditures were deliberately published in a Dutch peer-reviewed journal in order to increase the research's impact on the national discussion of health inequalities. The two studies became part of the special issue 'socioeconomic health inequalities: radical change in course required'. In addition, English translations for both articles were published for international readers. These results were presented, along with the results from the 2022 report [8], at a public event at the Social Historic Centre for Limburg. These results were also shared in 2019 and 2022 with presentations at the local healthcare network the 'Mijnstreek coalition'. Both reports [7, 8] are published on the Maastricht University website and the Living Lab for Public Health website. For both reports, interviews were given which resulted in news items for the Living Lab for Public Health newsletter. Furthermore, the findings contributed to the goals of the Knowledge and Innovation Agenda Southeast Netherlands 2030 [17]. The agenda was initiated in 2020 with four major goals to improve population health and healthcare in Southeast Netherlands (the region of Southeast Brabant and the province of Limburg) by 2030. One of the four goals focuses on narrowing the gap in socioeconomic health inequalities. The first sub goal is to gain insight in the influence of demographic and socioeconomic trends on health inequalities in this region. The research in this dissertation provides this insight and show that with a broader set of determinants of health, we are able to explain regional health inequalities in mental health, total healthcare costs, specialized care costs, mental healthcare costs and pharmaceutical costs.

The insights on regional health inequalities and variations in healthcare expenditures are also presented in a Dutch web-based tool [18]. This website provides policymakers and health insurers with insights about regional inequalities in health and variations in healthcare expenditures for each region in the Netherlands. An instructional video was developed for this website to help policymakers and health insurers understand and use the research findings in their own day-to-day practice. In addition, the results in Chapter 6 have helped health insurers in updating their regional reports [19].

Finally, based on questions from stakeholders in local government and vocational education, a factsheet was written on health inequalities in student populations in the South of Limburg. The factsheet showed that vocationally trained students (MBO niveau

1, 2, 3 and 4) are at higher risk of facing difficulties in life compared to students in higher tertiary education (HBO) or university (WO). MBO-students are more often raised in single parent families, incur higher healthcare expenditures, are more often unemployed, are more often faced with sexual transmitted diseases and unplanned and/or unwanted pregnancies, and more often report poorer health, unhealthier lifestyles and inadequate incomes compared to HBO- or WO-students. The results were presented at a regional conference and helped legitimize the financing of introducing accessible help and care within vocational school facilities in Zuid-Limburg (MBO Knooppunt [20]) and provided a steppingstone to investigate whether citizenship education can be implemented to reduce these disadvantages (ZonMw grant).

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Invited talks

Wat kost eenzaamheid? Een nationale studie naar eenzaamheid en zorgkosten. Invited oral presentation for the national Stronger Together conference by JoinUS. October 5, 2021

Does loneliness have a cost? A population-wide study of the association between loneliness and healthcare expenditure. Invited oral presentation and panel discussion for the international Campaign to End Loneliness conference. February 2, 2023

Other

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About the author

Rachelle Meisters was born on October 21st 1991 in Heerlen, the Netherlands. After graduating bilingual secondary education *cum laude* at Charlemagne College in Landgraaf, she studied International Business at Maastricht University. During her Bachelor degree, Rachelle completed the MARBLE project for excellent bachelor students and studied for six months at the University of Adelaide, Australia. She obtained her Bachelor of Science in International Business in 2013. During her Masters, Rachelle completed the PREMIUM project for excellent master students. As an extracurricular activity, she was part of the Service Science Factory team which conducted a patient satisfaction study for the Maastricht University Medical Center. Rachelle obtained her Master of Science in International Business with a specialization in Strategic Marketing in 2014. In 2015 she started as a policy maker for participation and labor market policies for the municipality Heerlen.

In 2017 Rachelle started at the Department of Health Services Research as a junior researcher. She worked on the first evaluation of the Social Agenda Limburg. In 2018, her position was extended as a PhD candidate. Her PhD research focused on explaining socioeconomic and regional health inequalities in the Netherlands. She also cooperated with the Department of Rheumatology at Maastricht University Medical Center to publish research on implementation gaps in standards of care for patients with rheumatoid arthritis and rheumatologists across Europe. Rachelle has presented her research at international congresses and in national and regional meetings. For her presentation at the European Alliance of Associations for Rheumatology Congress 2019 she was awarded the Travel Bursary. She served as a tutor for various courses in the Healthcare Policy, Innovation and Management master program and supervised bachelor and master thesis students.

As of November 2022, Rachelle is a researcher at the Department of Social Medicine. Her post-doc research will focus on socioeconomic health inequalities in type 2 diabetes patients.