Assessing multifactorial correlates of health-related quality of life in the general Swiss population

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Abbreviation

SAPALDIA	Swiss Study on Air Pollution and Lung and Heart Diseases
WHO	World Health Organisation
QoL	Quality of Life
HRQoL	Health-related Quality of Life
QALY	Quality Adjusted Life Years
SF-36	The 36-Item Short-Form Health Survey
PCS	Physical Component Score
PF	Physical Functioning
BP	Bodily Pain
RP	Role-Physical
GH	General Health perception
MSC	Mental Component Score
VT	Vitality
SF	Social role Functioning
RE	Role Emotional
MH	Mental Health perception
BMI	Body Mass Index
BIA	Bio-electrical Impedance Analysis
FEV1	Forced Expiratory Volume in 1 second
HbA1C	Glycated hemoglobin
LCA	Latent Class Analysis
LC	Latent Classes

BIC	Bayesian information criterion
AIC	Akaike Information Criterion
CI	Confidence Interval
OR	Odds Ratio
MPA	Moderate physical activity
VPA	Vigorous physical activity
dB	Decibel

Summary

Due to substantial increases in life expectancy, the global proportion of older adults is rapidly growing. Consequently, public health research cannot just focus on mortality and morbidity but it is imperative to consider health-related quality of life outcomes, particularly in older adults. Although, many studies have been conducted over the years to understand factors contributing to health-related quality of life, still much evidentiary information is missing on how these multifactorial health-related contributors are interrelated and affect quality of life in later life stages. There is a consensus in the literature that quality of life is associated with many major life domains covering health conditions, physiological functions, individual and environmental factors as well as social and psychosocial aspects. To contribute towards understanding the holistic multifactorial concept of health-related quality of life, this PhD thesis is aimed at thoroughly elucidating associations of lifestyle, physiological functioning and the environment with health-related quality of life in a Swiss-wide cohort.

The three manuscripts presented in this thesis are based on data from the Swiss Study on Air Pollution and Lung and Heart Diseases (SAPALDIA). This population-based cohort with associated biobank was initiated in 1991 and recently concluded its fourth follow-up (SAPALDIA4 2017/2018). Participants were randomly recruited from eight study areas in Switzerland representing the country's geographic and cultural diversity. The assessments were composed of comprehensive questionnaires capturing broad health and exposure-related information as well as health examinations measuring and collecting biomarkers of physiological importance.

By jointly investigating the association of lifestyle and physiological functioning with health-related quality of life, we established three clusters with significant differences in values of lifestyle and physiological functioning. The cluster with the worst values in these domains (dominated by high cardio-metabolic risk factors) showed substantially lower scores in multiple health-related quality of life components. The analysis on the association of the social and perceived built environment with health-related quality of life resulted in relevant correlations of living alone versus in partnership, pointing towards negative associations of solitary living with health-related

quality of life. Furthermore, high ratings of transportation noise annoyance showed considerable negative associations with health-related quality of life. By diving deeper into the association of noise and health-related quality of life, we found that among the three investigated noise parameter (source-specific transportation noise, noise annoyance and noise sensitivity) noise sensitivity showed strongest and most robust associations with health-related quality of life, attaining a magnitude of potential clinical relevance for some domains.

This PhD thesis adds relevant evidence to the pursuit of understanding the complex notion of health-related quality of life in aging populations. The widespread importance of health-related quality of life research should be acknowledged by decision-makers and translated into policies targeting the maintenance of well-being for older adults. Most importantly, public health interventions should be shaped to reduce the substantial socio-economic gradient in today’s society, as this remains the major predictor of decreased quality of life. Therefore, it is of global relevance and importance to consider frameworks as “Health in All Policies” suggested by the WHO that account for health and aging aiming at improving population health and health equity.

1 INTRODUCTION

1.1 Global burden of demographic aging

Humanity has achieved to increase global life expectancy at birth on average to 72.0 years (74.2 years for females and 69.8 years for males) for most people globally (WHO, 2018) (Figure 1.1). This development is, on the one hand, mostly due to the cure and elimination of infectious diseases at younger ages in low- and middle-income countries. On the other hand, the improvement of diagnostics and treatment methods among older adults with chronic diseases has resulted in a reduction in mortality and expansion in longevity in high-income countries (Bloom, 2011, Christensen et al., 2009).

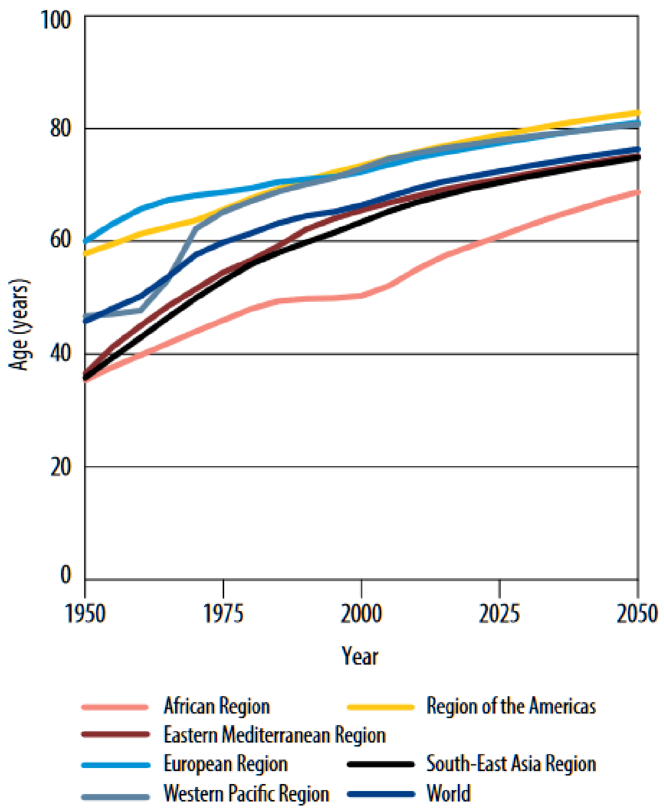

Figure 1.1 Rise in life expectancy from 1950 until forecasts of 2050, divided by WHO region (WHO, 2015)

From 2015 to 2050, the proportion of the global population aged 60 years and older is predicted to increase from 12% to 22%, which well demonstrates the growing "global burden of demographic aging" (Figure 1.2 & Figure 1.3). Particularly in the western world the proportion of people aged 80 years and older is estimated to double by 2080 compared to 2014 (Desa, 2015).

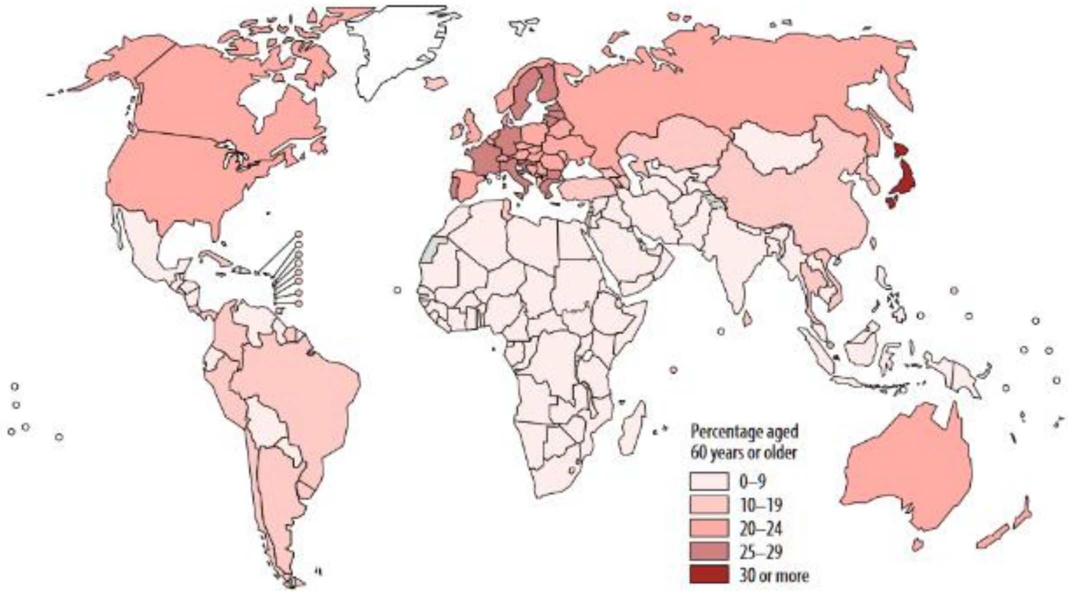

Figure 1.2 People aged 60 years and older, by country in 2015 (WHO, 2015)

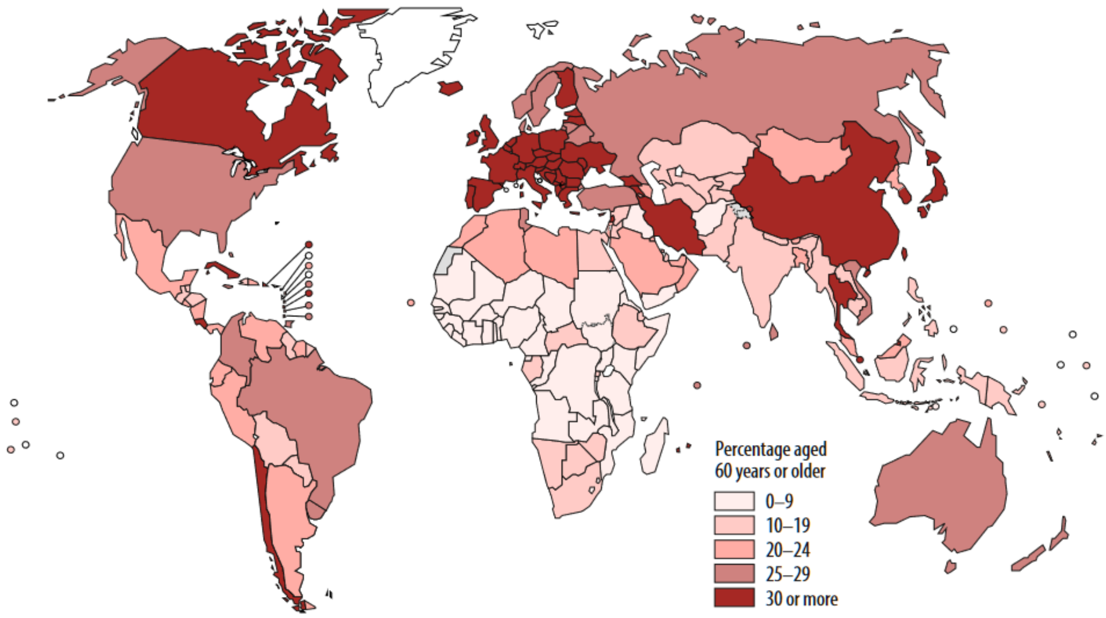

Figure 1.3 People aged 60 years and older, by country projections for 2050 (WHO, 2015)

1.2 Aging

The alterations caused by aging are highly complex (Kirkwood, 2008). Aging can be described as “a procedure that implies a series of alterations in the biological, psychological, and social domains. The multiple profiles that can result from the several combinations occurring among these alterations make aging a multifaceted process, shaped by previous development and, in which the individual has a proactive role, in that, in the interaction with the environment, he can become his own aging’s author” (Wahl et al., 2012). The biology of aging is characterized by steady accumulation of various damages on the molecular- and cellular-level. These intrinsic damages lead over time to gradual decreases in physiological functioning resulting in increased susceptibility to frailty and diseases (Vasto et al., 2010). It is well established that these changes are not consistent and transferrable to every individual. While one older adult may be in good physical and mental condition, another of the exact same age might is dealing with frailty and illness. Partly this may be due to the random mechanisms accompanying aging. Yet, it is well known that aging is heavily influenced by extrinsic factors as an individual’s lifestyle, behavior and environment. Furthermore, these changes are tied to many alterations in social circumstances, such as the loss of close relationships, the end of active occupation and shifts in social positions (Baltes et al., 2005). Hence, multiple intrinsic and extrinsic factors and especially the combination of those determine how we age (Figure 1.4). Thus, it is essential not only to focus on the amelioration of the biological losses linked to aging but also to consider the individual, environmental and social adaptations that are associated with aging (Huber et al., 2011). From a public health perspective these influencing factors must be considered in combination to generate adequate responses and solutions to conquer this global challenge (WHO, 2015).

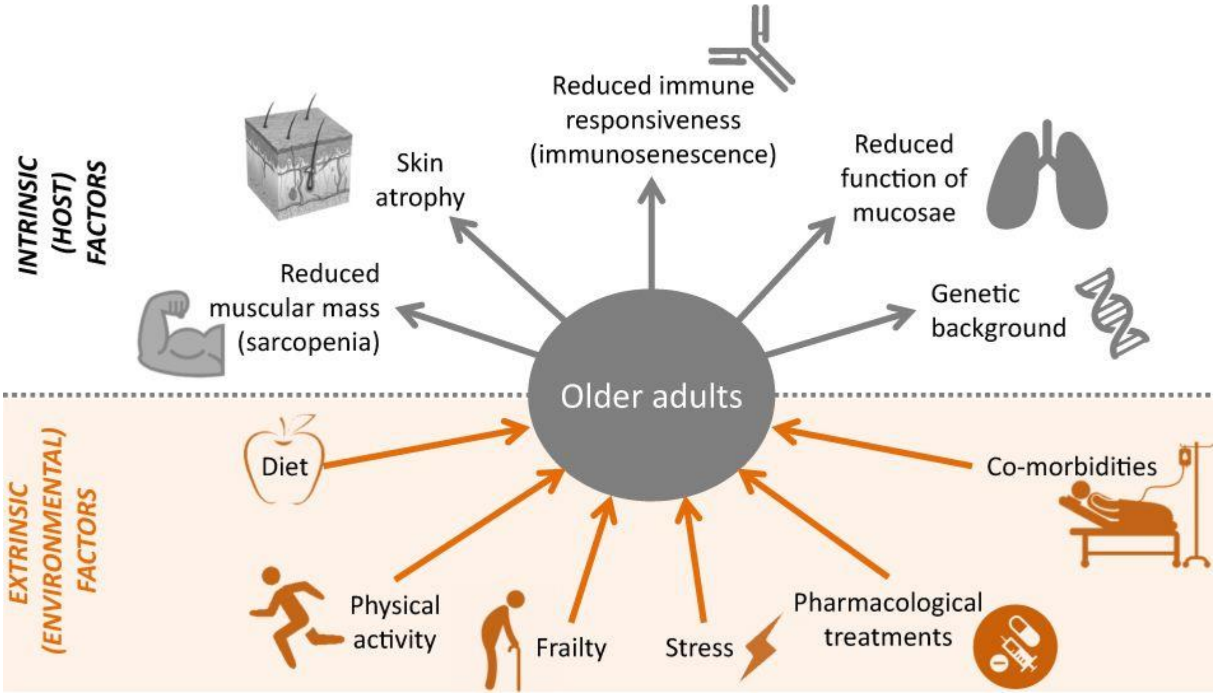

Figure 1.4 Intrinsic and extrinsic factors leading to aging (Del Giudice et al., 2017)

1.3 Quality of life and well-being in the context of aging

As improvements in drug and medical treatment were able to extend life expectancy and improve quality of life (QoL), simple morbidity and mortality measures were no longer adequate for assessing variations in health states. Hence, measurements of QoL and well-being - often used as antonyms in the literature (Meiselman, 2016) - became prominent (Karimi and Brazier, 2016). In the context of disability prevention and aging, it is already a priority to understand the factors contributing to QoL. In fact, reduced QoL has been strongly associated with older age (Corica et al., 2015, Leadley et al., 2014).

The concept of QoL and well-being comprises a broad range of positive feelings as well as personal life assessments. It contains information regarding a comprehensive variety of human behavior and personal health. QoL includes physical and mental health, social relationships, leisure, individual conditions, emotions and mental engagement (Bartels, 2015).

Several definitions and interpretations of the term well-being exist. The World Happiness Report sees happiness as major component of well-being. The OECD report (2013) on subjective well-being created a definition, which is not restricted to measuring only happiness but covers a broader variety of notions, which are included in the term. They define subjective well-being as “good mental states, including all of the various evaluations, positive and negative, that people make of their lives and the affective reactions of people to their experiences.”

In several research areas, the topic of QoL plays a pivotal role. Its strong added value, which is contemplated in many major life domains, reflects the increasing recognition. Numerous studies have been conducted, varying in study designs, datasets and measurement methods, which show that QoL is significantly associated with socio-demographic dimensions like age, gender, marital and family status, education, occupational status, income and social support (Dolan et al., 2008).

In addition to the above-mentioned socio-demographic dimensions, a broad variety of impact factors, such as genetics, the individual emotional history, lifestyle habits and several circumstances of living determine QoL outcomes in later life stages. The same factors play a crucial role in the development of age-related diseases or mental health issues (Probst-Hensch, 2017). Nonetheless, health is shown to be the most crucial correlate of QoL. Indeed, the deterioration of personal health state caused by physical and/or mental diseases, which regularly disrupt daily functioning, display a clear decline in QoL (Angner et al., 2013). Well-being data, which were collected in the German Socio-Economic Panel (SOEP) and British Household Panel Study (BHPS), both large-scale studies with national coverage, are already used in conjunction with economic data to guide public policy.

Moreover, the evidence that high QoL is associated with reduced mortality and age-related diseases, is largely increasing (Chida and Steptoe, 2008). It is moreover seen as one major predictor of longevity in healthy populations (Steptoe and Wardle, 2012).

1.4 The notion of health-related quality of life

In the last decades, the notion of health-related quality of life (HRQoL) has emerged and is on the individual level an expression of physical and mental health perceptions (Dey et al., 2013). It can be defined as “how well a person functions in their life and his or her perceived well-being in physical, mental, and social domains of health” (Killewo et al., 2010).

The concept of HRQoL is used in many scientific disciplines, ranging from observational studies to clinical trials and cost-effectiveness analysis of health technologies and medical treatments, which are gaining more and more significance for healthcare providers. The values, which can be derived from HRQoL measures are utilized as scores defining different states of well-being. Furthermore, these scores are used in the calculation of quality adjusted life years (QALY). QALY are displayed on a scale from zero to one, where zero equals death and one equals full health. Hence, if a score less than one is attained a loss of QoL is expected (Gold et al., 1997).

The most common HRQoL measures are the SF-36, Nottingham Health Profile and Sickness Impact Profile as well as the preference-based measures EQ-5D and SF-6D, which are commonly used for the calculation of QALYs (Coons et al., 2000, Németh, 2006). Understanding the determinants of HRQoL is critical in the present world because it is a prerequisite for improving public health strategies promoting healthy aging (Stocks et al., 2019). This fact will be underlined and discussed multiple times throughout the thesis, as it is of tremendous public health relevance.

1.5 Individual and environmental correlates of health-related quality of life

1.5.1 Lifestyle and physiological functioning

Next to the environment, lifestyle defines the most central risk factor influencing aging as well as HRQoL (Stocks et al., 2019). It plays a key role as modifier in the aging-induced adverse changes of organ systems and is therefore partly responsible for the lasting alterations of physiological functioning. It is well documented that people living an unhealthy lifestyle and showing poor levels of physiological functioning are more likely to become disabled (Beavers et al., 2012, Batsis et al., 2016). Particularly, components of the metabolic syndrome (illustrated in figure 1.5) have shown to be early predictors of increased risk to common chronic diseases and severe disability.

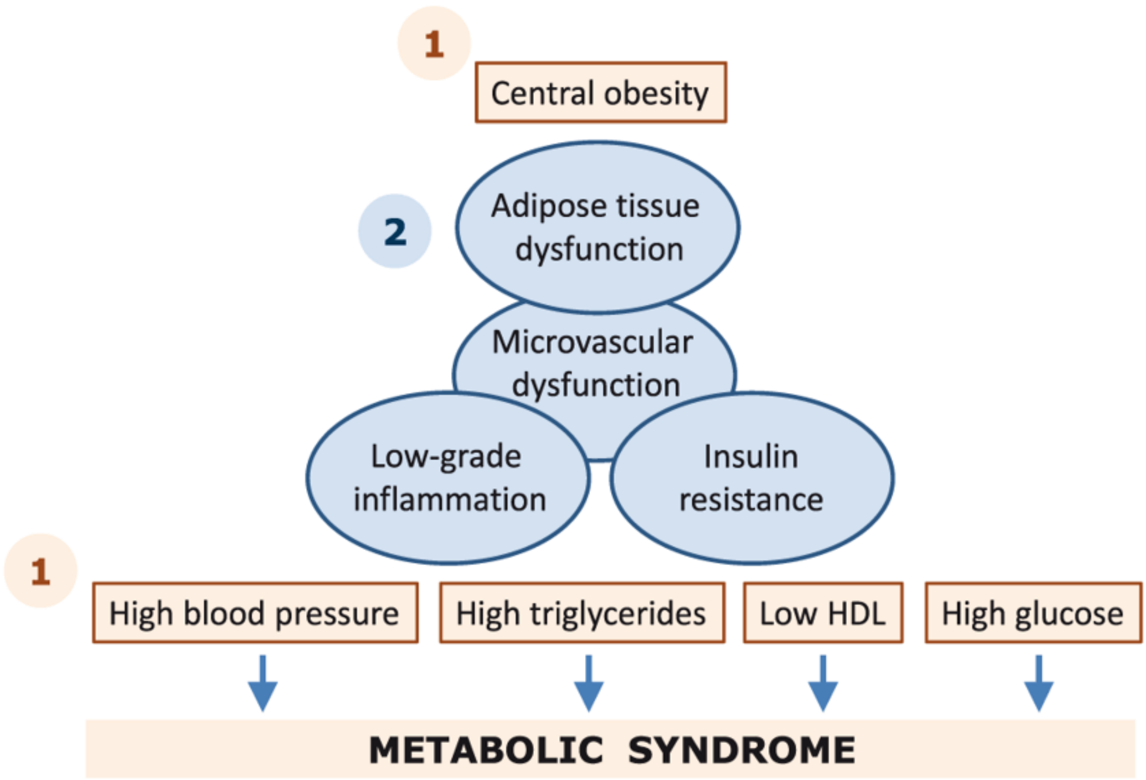

Figure 1.5 Components defining the metabolic syndrome (van Greevenbroek et al., 2016)

Certainly, some causal elements of the metabolic syndrome cannot be prevented, yet many are changeable. These are mostly lifestyle-related elements that can well be tackled by individual changes or environmental (physical and social) adaptations – even though not yet proven as causal (Saklayen, 2018). This point justifies also to further investigate into lifestyle and environmental risk or protective factors, as these factors feed into primary prevention and therefore keep the citizen healthy, compared to interventions on adversities of physiological functioning (secondary prevention), where a disease-onset already occurred and a poor health state is expected (Said et al., 2016).

With modern day advances in medical technology, these risk factors are easily detectable and can be used for research to guide targeted interventions in older adults (Carriere et al., 2013). Most research in these domains usually considers singular effects of risk factors either from poor lifestyle or physiological functioning. Yet, as the example of the metabolic syndrome shows, we must argue if this is not over-simplifying the relationship of these individual parameters also with HRQoL. Identifying behavioral lifestyle patterns and their joint effects with physiological functioning simultaneously, seems inevitable. Many of today's well-known risk behaviors are highly interrelated and do therefore define population subgroups at high risk of poor health. Elucidating these linked patterns of lifestyle and physiological alterations bear enormous potential for the improvement and understanding of public health relevant pathways resulting in adverse health and QoL outcomes, particularly in an era of demographic aging (Laska et al., 2009).

1.5.2 Built environment

It is well recognized that in order to move towards understanding the complete healthy aging phenotype the environment must be considered (Franco et al., 2009). The International Classification of Functioning, Disability and Health (ICF) (WHO, 2001) created a framework to conceptualize the interplay of environmental factors and personal factors, which Clarke and Nieuwenhuijsen (2009) illustrated in a figure (Figure 1.6). The so-called biopsychosocial context established by the ICF describe that environmental factors may facilitate or hinder physical functioning as part of daily activities or participation of older adults taking into account personal factors. These associations can then be modified by adverse health conditions.

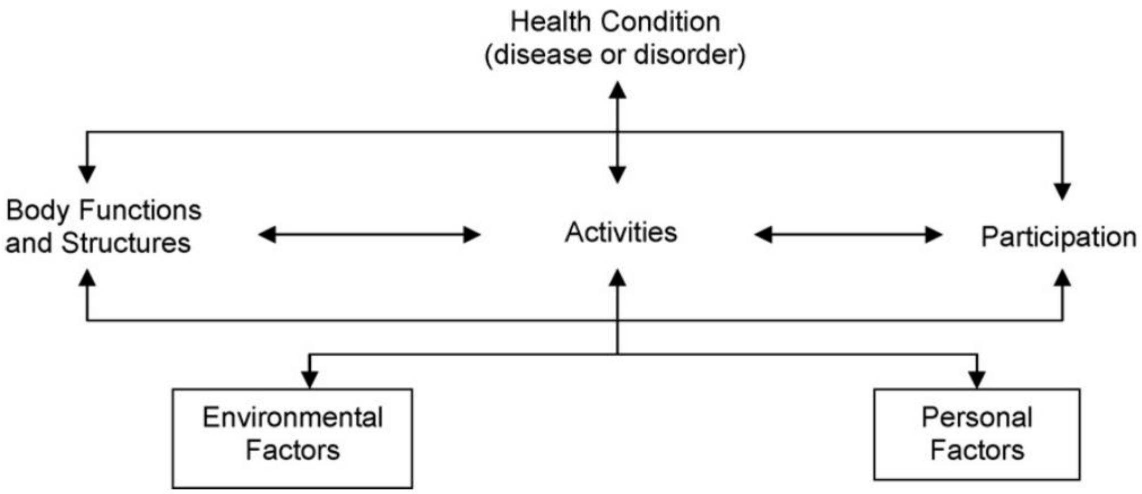

Figure 1.6 Framework illustrating the interplay between environmental-, physical-. personal- factor and health conditions (Clarke and Nieuwenhuijsen, 2009)

By establishing a model of effects of the neighbourhood on aging, it was shown that particularly the urban environment can either be salutogenic or deleterious for healthy aging (Glass et al., 2003, Lambert et al., 2015). There are several explanations why especially the urban environment is expected to affect health. The load of toxic exposures from various well-studied sources (e.g. air pollution, noise exposure) is very different to natural environments and have been proven to significantly affect health in many domains (Landrigan et al., 2018, Münzel and Daiber, 2018, van den Bosch and Ode Sang, 2017). On the psychological level, a central difference compared to natural environments is the restorative value. Research on restoration possibilities showed that natural environments provide a better basis for stress recovery compared to urban environments. This is explained, due to the absence of information processing and reduced physiological arousal (Weber and Trojan, 2018). However, cities can have restorative potential too (green spaces, cafés and recreational amenities), which have proven to reduce stress by moderation of environmental health hazards, as for example noise exposure (Claßen and Bunz, 2018). Moreover, recent research points towards a protective effect of living in urban environments on the above-mentioned stressors by increasing resilience - "urban resilience" (Nunes et al., 2019a, Nunes et al., 2019b).

Older adults desire more and more to "age in place". Which means having the possibility to live and preserve continuity in the same location from retirement onwards. Many challenges have to be tackled in communities, such as ways of transportation and access to groceries or health facilities. Hence, decisions concerning these environmental assets and amenities - as a city's aesthetical appearance, its parks, shops, cafes, cultural opportunities and its public transportation network - have to be made considering a widespread of areas as promotion of physical activity, social interaction or on-wards education (Lui et al., 2009).

The perception of the built environment can be defined by the overall satisfaction with the living situation and the environment, as well as the proximity to areas characterizing the neighborhood such as green spaces, access to public transportation or access to public places (Stathi et al., 2012). Evidence points in the direction that positive perceptions of the built environment are associated with higher scores in mental health components of HRQoL. On the contrary, low accessibility to public transportation, green spaces or low perceptions of attractiveness of the neighborhood may adversely affect HRQoL (Lavin et al., 2006, Croucher et al., 2007).

Furthermore, the built environment is assumed to provide residents with opportunities of improving their social capital and diminish social isolation (Brown et al., 2008).

1.5.3 Social environment

A major aspect when considering perception of the environment is the social environment. It plays a central role for aging in both urban and natural settings, given that social support and networks are essential for well-being of the individual, especially in older adults (Bowling et al., 2002). There is remarkable evidence on the adverse effects of social isolation and lack of close ties with poor health states and risk of mortality (Holt-Lunstad et al., 2010). Reversely, it was shown that frail and pre-frail older adults have a less satisfying social environment compared to their non-frail peers (Herrera-Badilla et al., 2015). The social environment can be divided into proximal (family, friends and peers) and distant (culture, labor market, neighborhood) environment (Berkman et al., 2000). While social networks define the size and frequency of relationship, social support describes the attention obtained in terms of emotional resources within the social environment. Loneliness is pivotal in all notions of the social environment, pointing towards detrimentally affecting health and QoL (Holt-Lunstad et al., 2015).

Furthermore, social engagement is also particularly relevant for older adults. As many critical life events happen during this period, such as retirement or the loss of close friends, an active engagement in social relationships is important. It was shown that not being socially engaged may be associated with adverse HRQoL outcomes resulting in cognitive decline or enhanced risk of mortality (Bennett and Ageing, 2002).

1.5.4 Environmental noise exposure

When considering environmental health hazards, noise is globally ranked on top of all common environmental stressors (WHO, 2011). In the context of demographic aging and with the rapid urbanization, the demand for aircraft, road and railway transportation is increasing (Kotzeva and Brandmüller, 2016). Noise exposure, which is perceived as unwanted or harmful sound affects physiological and psychological health outcomes (Hanninen et al., 2014a). Many pathologies seem to be affected by exposure to transportation noise, ranging from physical pre-morbid risk factors such as obesity (Oftedal et al., 2015, Pyko et al., 2015, An et al., 2018, Foraster et al., 2018) to cardio-metabolic diseases (Eze et al., 2017, An et al., 2018, Sørensen et al., 2013, Van Kempen et al., 2018) and possibly also adverse mental health (Clark and Paunovic, 2018, Dzhambov and Lercher, 2019), as well as HRQoL outcomes (Clark and Paunovic, 2018). Besides the direct effects of objectively measured transportation noise, the individual perception and ability to cope with higher noise levels may be even more important to assess, when looking at the association of noise and QoL as well as morbidity.

Recently, two notions are highly discussed in environmental research: Noise annoyance, which is described as the grade of disturbance and dissatisfaction from noise exposure (Guski, 1999); and noise sensitivity, described as the individual variation in perception of noise effects (Smith, 2003). Noise annoyance is deemed to be a multi-faceted stress response that depends on several personality traits and determines the reaction to actual noise exposure (Guski et al., 2017). Noise sensitivity is presently regarded as a personality trait and is a key concept of psychoacoustics (Dzhambov, 2015). It can be defined as "the internal states (be they physiological, psychological - including attitudinal, or related to life style or activities conducted) of any individual which increase their degree of reactivity to noise in general" (Job and Health, 1999).

Similar to the association with morbidities, higher noise annoyance and sensitivity ratings were mostly associated with lower HRQoL scores (Dratva et al., 2010, Héritier et al., 2014, Shepherd et al., 2016, Shepherd et al., 2010, Urban and Máca, 2013, Welch et al., 2018). A major limitation of most studies mentioned in this paragraph is that they did not combine these three aspects of exposure to noise, where we must again question whether this is not over-simplifying the underlying exposure-outcome relationship. We strongly believe investigating these factors jointly would help to improve the understanding of their independent or joint effects and adequately contribute to the known risks coming from this most prominent environmental stressor (Clark and Paunovic, 2018).

1.6 Cohort studies – the right study design to investigate complex exposure-outcome associations

The prospective cohort is the most suitable design for investigating the long- and intermediate-term effects of exposure risks and environmental influences on defined outcomes as HRQoL, disease-onsets, and health states due to its systematic approach and long-term follow-up of study participants (Manolio et al., 2006). The first concepts of cohorts were used, in the early 20th century, to investigate incidences and mortality rates of tuberculosis in Europe and the US.

The ”Framingham Heart Study”, initiated in 1948, represents the first population-based prospective cohort study investigating 5000 subjects. The study enabled, for the first time, investigations into different exposures and their outcomes, in a time-resolved manner, which eventually resulted in the definition of the term “risk factors”.

In the same century two large-scale cohort studies started, named “Nurses Health Study” and the “Physicians Health Study”, both with high impact in medical sciences representing the basis for the following epidemiological research era (Gaziano, 2010). In 1998 the agreed definition was published, that describes population-based cohort studies as an epidemiological study in which a sample, or even an entirety of a defined population is followed up and longitudinally observed to assess the relationship of several exposures with multiple outcomes (Szklo, 1998).

The most central aspect of these studies is the adherence to follow-up. The tracking of people from exposure to outcome (prospective) defines the uniqueness of this study design yet allows researchers also to conduct retrospective studies by providing data from existing cohorts (or registries) to identify exposed versus non-exposed participants many years back (Grimes and Schulz, 2002). In some cohort settings, where participation rates are above average or the target population is very responsive (often in clinical settings), external validity (generalizability to a target population or region) is seen as a further attribute of cohort studies (Lieb, 2013). However, especially in population-based settings the important questions and trade-off is between being representative versus minimizing loss to follow-up, while the latter seems to be more critical for population-based outcomes (Grimes and Schulz, 2002).

A key advantage of prospective cohorts is the standardized and comprehensive collection of pre-morbid exposure information. This prior-to-outcome information helps to avoid recall bias (systematic error of accuracy due to false recollection of past events). From a statistical point of view the strength of prospective cohorts, is the ability to calculate incidence rates, relative risks, and confidence intervals that are presumably favored ways to present study results, rather than only with p values.

The major concern of population-based cohort studies is the loss-to-follow up, which is the proportion of participants who do not respond to follow-ups - non-responder - or even drop out before the first follow-up. If these loss-to-follow up percentages are too high or too uneven in exposure and outcome categories, the derived statistical results may be affected (Greenland, 2017). A further concern is - the selection bias - the systematic error that arises if the pre-defined target population was recruited non-randomly, due to better or worse responses of specific members of this population (Rothman, 2012). The risk for selection bias is therefore highest for specific groups of the population that are hard to reach. More precisely this group consists of elderly, singles, immigrants, people with low socioeconomic status and low educational levels (Langhammer et al., 2012). A limitation of this study design, when it comes to investigating non-communicable chronic diseases is the need for large sample sizes and the long duration times to detect sufficient disease-onsets in participants. To gather high complex exposure information, the cost of prospective cohorts are often very high but indispensable to predict diseases in early stages (Downey and Peakman, 2008).

Major values of today's large-scale cohorts are the associated biobanks. The prospective storage of biosamples that permits analysis of biomarkers at a later stage, often decades, enables tracing back to specific exposures that led to adverse events or outcomes. Measurements of the development of phenotypes over a long time-period indicate prior unknown etiopathologies of defined outcomes (Downey and Peakman, 2008). Prospective cohorts with associated biobanks have the possibility to identify new biomarkers of exposure and physiological effects. They can use known biomarkers to explore associations with unknown outcomes of these markers such as HRQoL (Chadeau-Hyam et al., 2011). Particularly, in identifying and assessing the entirety of environmental exposures - known as concept of the exposome - prospective population-based cohorts with associated biobanks offer exciting new approaches for research in this field of exposure assessment (Wild et al., 2013).

2 OBJECTIVES

Based on the previously presented scientific background and the accompanied gaps in knowledge, this PhD thesis aims at thoroughly elucidating associations of lifestyle, physiological functioning and the environment with health-related quality of life in the only nation-wide Swiss citizen cohort.

The specific aims for each pillar are described in the following sub-chapters.

1. Health-related quality of life in an aging general population sample: the role of lifestyle patterns and physiological functioning

1.1. to identify clusters of lifestyle habits and physiological functioning related to respiratory and cardio-metabolic health in the SAPALDIA 55+ cohort using latent class analysis

1.2. to describe the socio-demographic characteristics of the clusters and to assess associations of these with HRQoL scores.

2. Elucidating independent and joint associations of the social and perceived built environment with health-related quality of life and differences in usage of medical services

2.1 to investigate independent associations between the social and perceived built environment with HRQoL domains

2.2 to identify clusters consisting of social and perceived environmental attributes that best determine HRQoL

2.3 to investigate associations of these social and built environmental attributes—in single and cluster formats—with different healthcare seeking behaviors

3. The independent association of source-specific transportation noise, noise annoyance and noise sensitivity and its associations with health-related quality of life

3.1 to investigate the mutually independent association of objectively estimated source-specific transportation noise levels (aircraft, railway and road traffic), self-reported noise annoyance and noise sensitivity with HRQoL in a predictive longitudinal manner

3 METHODS

3.1 Study population – Swiss Study on Air Pollution and Lung and Heart Diseases (SAPALDIA)

This PhD thesis is based on data collected in the Swiss Study on Air Pollution and Lung and Heart Diseases (SAPALDIA). SAPALDIA is a population-based cohort with associated biobank initiated in 1991. In SAPALDIA1, 9’651 adults (18-62 years) were randomly recruited from eight study areas in Switzerland representing the country’s geographic and cultural diversity (Ackermann-Liebrich et al., 2005). In the subsequent decades, two follow-ups were carried out including 8’047 subjects in SAPALDIA2 (2001/2002) and 6’088 in SAPALDIA3 (2010/2011) (Endes et al., 2017). All three assessments comprised questionnaires and health examinations of increasing complexity over time. The most recent follow-up (SAPALDIA4, 2017/18) involved 5’189 participants answering to multiple self-administered questionnaires and additional health examination in the sub-group (n=1’753) of participants aged above 55 years and above.

The study is coordinated by Prof. Dr. Nicole Probst-Hensch and primarily funded by the Swiss National Science Foundation (SNSF) since 1991. With over 200 publications, SAPALDIA is generating remarkable scientific impact on public health and medical research.

The SAPALDIA cohort study complied with the Declaration of Helsinki. For each survey, ethics approval was granted by the regional ethics committees and participants provided written informed consent prior to participation.

3.2 Measurements

3.2.1 Health-related quality of life – Outcome metric

The RAND version of the 36-Item Short-Form Health Survey (SF-36) is a widely used HRQoL assessment tool that was validated in large population-based surveys as well as in clinical settings (Hart et al., 2015, Keller et al., 1998). The questionnaire is designed to provide a summary of physical and mental health scores, based on eight domains. The physical component comprises physical functioning (PF), bodily pain (BP), role-physical (RP) and general health perception (GH). The mental component reflects vitality (VT), social role functioning (SF), role emotional (RE) and mental health perception (MH) (Figure 3.1). Scores for each subscale range from 0-100, and higher scores indicate better HRQoL (Framework, 1992).

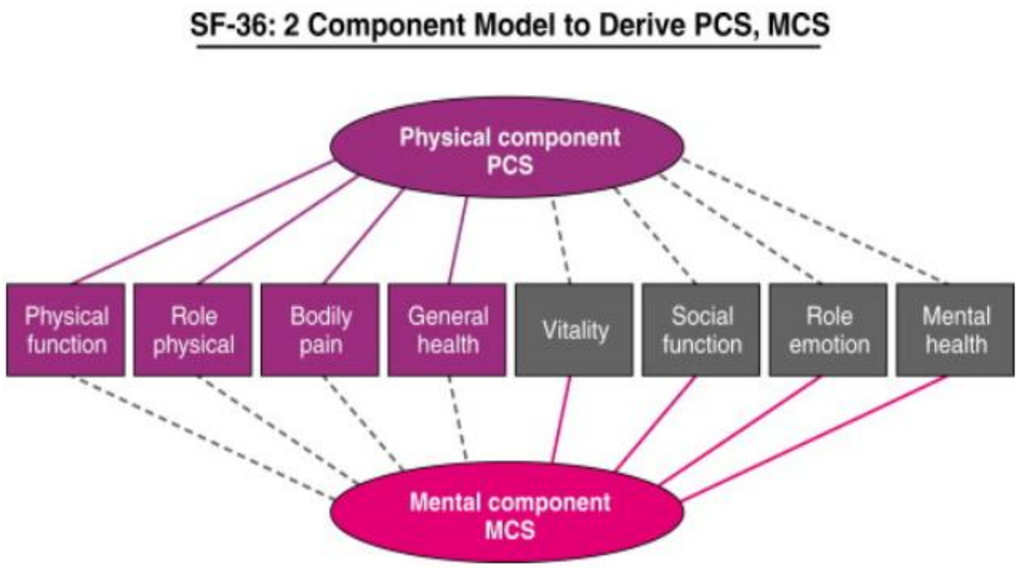

Figure 3.1 SF-36 Component and subscales (Strand and Singh, 2009)

3.2.2 SAPALDIA Questionnaires

Questionnaires are a major component of the SAPALDIA assessments. While in earlier surveys, in-person interviews were conducted, in SAPALDIA 4 they were self-administered on paper and online via state of the art data capture tools. The basic information obtained is on socio-demographic characteristics, lifestyle, psychosocial factors, disease symptoms, diagnoses, medications, as well as health and social service use.

In SAPALDIA4, data collection was questionnaire based for all participants. SAPALDIA participants who were aged 55 years and older and who had answered all SAPALDIA 4 questionnaires were subsequently invited for a health assessment (SAPALDIA 55+) to one of the eight local study centers (Aarau, Basel, Davos, Geneva, Lugano, Montana, Payerne and Wald).

3.2.3 Health examination SAPALDIA 55+

At the fourth follow-up of SAPALDIA, participants aged 55 years and older were invited for a comprehensive health examination. The data collection comprised anthropometric measurements: Weight, height (wall-fixed measuring system), hip and waist circumference, derived body mass index (BMI) and waist to hip ratio parameters. We measured body composition using bio-electrical impedance analysis (BIA). In both epidemiological and clinical settings BIA is considered a useful tool to predict percentage body fat (Böhm and Heitmann, 2013). The results are based on equations from the resistance of the electrical signals to different tissue cells. Hydrated muscle cells encounter a smaller resistance than fat cells, which have lower water content (Nichols et al., 2006).

In SAPALDIA 4, two different BIA devices were used. In two study centers of SAPALDIA (Aarau & Geneva) both a standing (Tanita MC780) and a lying (Helios) BIA device was used. In the other six centers only lying BIAs where performed. The major difference of these two devices – apart from the measurement position – is that they use different electrical frequencies and the Helios devices computes no direct outcome measure, such as percent body fat. To avoid systematic measurement bias we harmonized the data of the two devices and derived a comparable variable considering both measurement values (Appendix 1).

Furthermore, blood pressure and heart rate were measured. We assessed pre- and post-bronchodilation lung function administering 2 puffs 200µg of Salbutamol aerosol (Ventolin©) for bronchodilation according to ATS recommendations (Gerbase et al., 2013) using the same spirometer device type in all study centers. We used point-of-care diagnostics for measurements of HbA1c, lipid panel profile in capillary blood and albumin/creatinine ratio (ACR) in spot urine.

Additional measurements, which were not used for this PhD thesis, were: A short physical performance test battery, including balance, gait speed, chair-rise tests and handgrip strength, pulsoxymetry for oxygen saturation measurements, neurologic screening tests including 12 sniffin' sticks test for olfactory function and digital symbol test part of the Wechsler Adult Intelligence Scale for cognitive function.

3.2.4 Statistical analysis

One of the technical challenges in quantifying HRQoL data is that it may not be normally distributed as seen in Figure 3.2. Therefore, several regression analyses could in principle be taken into consideration. We predominantly used quantile regressions to address the problem of left-skewed distribution. Some sub-domains of HRQoL showed only very few distinct values and most subjects had a perfect score of 100. Those variables were dichotomized (with value 1 for a perfect score of 100 and value 0 for a score of <100) and logistic regression models were used to analyze these outcomes.

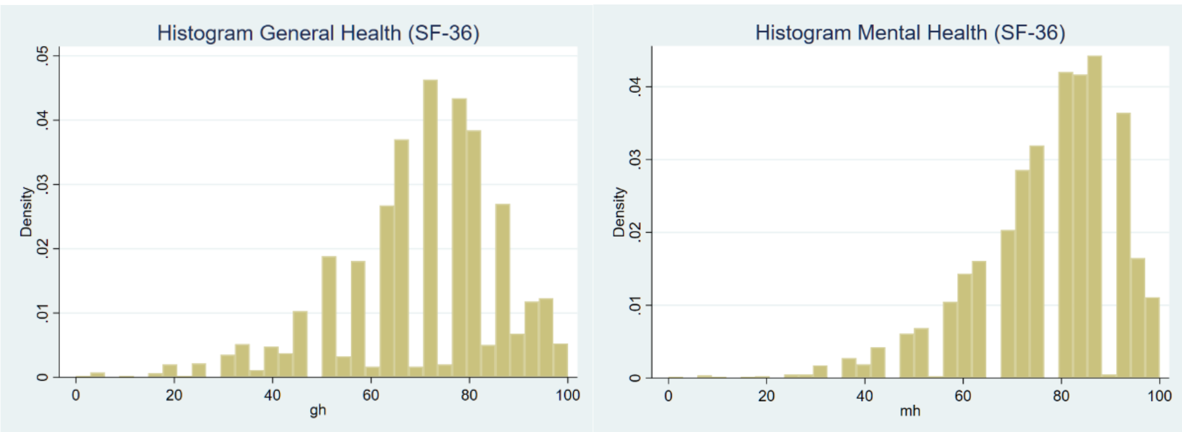

Figure 3.2. Histograms of General Health and Mental Health scores of the SF-36

To quantitatively examine possible synergies and joint associations of several factors such as lifestyle patterns or environmental exposures a clustering approach is frequently used. For this purpose, several methods are available to create clusters (model and non-model-based). We chose Latent Class Analysis (LCA), which is a model-based approach attempting to detect homogeneous groups within a heterogeneous population. It was proven a sophisticated tool to capture and display the complexity of interrelated risk factors (Laska et al., 2009). The models result in groups, which are represented as latent classes. These latent classes define subgroups of the population characterized by a given number of observed categorical variables that are uncorrelated (Larsen et al., 2017). LCA can be therefore well used to cluster high numbers of variables into few categories, which still properly capture the initial input variables (Ghanbari et al., 2018).

4 MANUSCRIPT I

Health-related quality of life in an aging general population sample: the role of lifestyle patterns and physiological functioning

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4.1 Abstract

Background: Lifestyle habits and physiological functioning are known modifiable risk factors for adverse health and quality of life outcomes. Yet, the combined effects of these risk factors on health-related quality of life (HRQoL) are still unknown. The objectives of this study were to identify clusters of lifestyle habits and physiological functioning in a citizen cohort, to study the socio-demographic distribution of these clusters, and to assess their associations with HRQoL scores.

Methods: Latent class analysis (LCA) was used to group participants from the SAPALDIA 55+ cohort based on a set of lifestyle habits and physiological functioning (N=1’167). *A priori* selected categorical LCA input variables consisted of dietary factors, alcohol consumption, smoking, physical activity, body mass index (BMI) as well as percent body fat, glycated hemoglobin, blood triglycerides, blood pressure and lung function. The 36-item Short-Form Health Survey (SF-36) was used to assess HRQoL. Multinomial logistic regression models were used to display socio-demographic characteristics of the clusters. The associations of the clusters with HRQoL scores were assessed by quantile regression and logistic regression models.

Results: The LCA resulted in three classes labeled “Healthy”, “Overweight at risk” and “Obese and unhealthy”. Being female, young and having higher education levels enhanced the probability of belonging to the Healthy class. Compared to the other two classes the Obese and unhealthy class scored lowest in all HRQoL domains except in the mental health and role-emotional domains. The Overweight at risk class differed only substantially in the physical function and vitality domain from the healthy class.

Conclusions: The results point to males and persons of older age or lower educational level as an important target group for health promotion and maintenance of wellbeing. These population groups have a lower HRQoL as a result of their combined occurrence of adverse lifestyle and physiological parameters.

Key words: Latent class analysis, aging, lifestyle, physiological functioning, health-related quality of life

4.2 Introduction

In the Western world, the proportion of people aged 80 years and above is estimated to double by 2080 compared to 2014 (Desa, 2015). At older age disability adjusted life years and years lived with disabilities are increasing considerably (Gao et al., 2015, Vos et al., 2015). This emphasizes the global importance in investing into healthy aging.

A priority in the context of disability prevention and healthy aging promotion is to also understand the factors contributing to quality of life (QoL). Reduced QoL has been associated with older age (Corica et al., 2015, Leadley et al., 2014). The concept of QoL is characterized by high complexity involving as well as influencing several life domains. In the last decades, the notion of *health-related quality of life* (HRQoL) has emerged (Dey et al., 2013) and is on the individual level an expression of physical and mental health perceptions. Understanding the determinants of HRQoL is critical because it is a prerequisite for improving public health strategies promoting healthy aging (Stocks et al., 2019).

Lifestyle behaviors are major modifiable risk factors influencing healthy aging and HRQoL (Stocks et al., 2019). With advancing age and partly as a result of lifestyle, the physiology of numerous organ systems changes significantly and physiological functioning is lastingly altered. These continuous alterations lead to a decrease in several functions, which can again affect lifestyle. For example, from midlife onwards the skeletal muscle mass is affected by aging-induced losses (McGregor et al., 2014). The most often observed changes are increasing body fat and loss of muscle mass that commonly result in sedentary behavior and vice versa. People with unhealthy lifestyles and poor levels of physiological functioning are more likely to become disabled (Beavers et al., 2012, Batsis et al., 2016). In particular, components of the metabolic syndrome, i.e. central obesity, hyperglycemia, dyslipidemia, and hypertension, and thus lifestyle factors related to the metabolic syndrome are prevalent early warning signs in aging populations and increase the risk of a range of common chronic cerebrovascular, cardiovascular, and neurological disorders known to be associated with severe disability. With most of these components being easily detectable they might also be used for targeting interventions (Carriere et al., 2013).

Previous studies have commonly investigated effects of lifestyle and physiological functioning parameters on HRQoL domains one factor at a time. Yet, examining multiple lifestyle behaviors and their joint effects simultaneously provides valuable insights for possible improvements in population health and QoL (Priano et al., 2018, Ford et al., 2011). In particular, many of today's known risk behaviors are highly interrelated and do therefore define population subgroups at high risk of poor health. These linked patterns of lifestyle and physiological alterations bear great potential for improving the understanding of public health relevant pathways contributing to adverse health and QoL outcomes especially in vulnerable life phases (Laska et al., 2009).

A clustering approach is frequently used to examine the possible synergy of several factors and to give insights on important underlying patterns, e.g. related to lifestyle and behavior. Several clustering methods (model and non-model-based) are available for this purpose. Latent Class Analysis (LCA) is a model-based approach that attempts to detect homogeneous groups within a heterogeneous population. It is a sophisticated tool to capture the complexity of interrelated risk factors (Laska et al., 2009). The groups are represented as latent classes and identified by subgroups of the population within a given number of observed categorical variables that are uncorrelated (Larsen et al., 2017). LCA can be well used to cluster lifestyle patterns into categories as living healthy or less healthy (Ghanbari et al., 2018).

Four recent studies have applied LCA to cluster lifestyle behavior (Ghanbari et al., 2018, Atzendorf et al., 2018, Saint Onge and Krueger, 2017). Three recent studies and one systematic-review looked at the association of a set of lifestyle behaviors and physiological functioning with QoL domains (Priano et al., 2018, Gouveia et al., 2017, Knox and Muros, 2017). None of them, however, looked at the association of the identified clusters with the QoL domains in a population-based setting with nation-wide coverage.

The objectives of this study were to classify clusters of lifestyle habits and physiological functioning related to respiratory and cardio-metabolic health in the SAPALDIA (Swiss Study on Air Pollution and Lung and Heart Diseases) 55+ cohort using LCA, to describe the socio-demographic characteristics of the clusters and to assess associations of these with HRQoL scores.

4.3 Methods

4.3.1 Study population

SAPALDIA is a population-based cohort with associated biobank initiated in 1991. In SAPALDIA1, 9’651 adults (18-62 years) were randomly recruited from eight study areas in Switzerland representing the country’s geographic and cultural diversity (Ackermann-Liebrich et al., 2005). In the subsequent decades, two follow-ups were carried out including 8’047 subjects in SAPALDIA2 (2001/2002) and 6’088 in SAPALDIA3 (2010/2011) (Endes et al., 2017). All three assessments comprised questionnaires and health examinations of increasing complexity over time. The current research analyzed data from the third follow-up (SAPALDIA4, 2017/18) involving 5’189 participants answering to multiple self-administered questionnaires and additional health examination in the sub-group (n=1’753) of participants aged above 55 years. The present analysis involved 1’167 of the 55+ participants who provided complete information on all relevant variables (Figure 4.3A).

The SAPALDIA cohort study complied with the Declaration of Helsinki. For each survey, ethics approval was granted by the regional ethics committees and participants provided written informed consent prior to participation.

4.3.2 Questionnaire derived information

For SAPALDIA4, cohort participants were invited to answer multiple self-administered questionnaires on paper or online version. The questionnaires obtained information on socio-demographic characteristics, lifestyle, psychosocial factors, disease symptoms, diagnoses, medications, as well as health and social service use.

Unlike previous SAPALDIA surveys, data collection in SAPALDIA4 was primarily questionnaire based. Only SAPALDIA participants who were aged 55 years and older and who had answered all SAPALDIA4 questionnaires were subsequently invited for a health assessment (SAPALDIA55+) to one of the eight local study centers (Aarau, Basel, Davos, Geneva, Lugano, Montana, Payerne and Wald). The SAPALDIA55+ health visit focused on the collection of healthy aging related determinants and preclinical aging endpoints. The 55+ assessment additionally included a questionnaire specifically addressing aging-related determinants and risk factors. Relevant questionnaire information for this analysis were questions on physical activity levels (frequency of moderate and vigorous physical activity), smoking patterns, alcohol consumption, meat and fish as well as vegetables and fruits consumption.

4.3.3 Health-Related Quality Of Life (HRQoL) measures

Questionnaires also included the 36-Item Short-Form Health Survey (SF-36), a widely used HRQoL assessment tool that was validated in large population-based surveys as well as in clinical settings (Hart et al., 2015, Keller et al., 1998). The questionnaire is designed to provide a summary of physical and mental health scores, based on eight domains. The physical component comprises physical functioning (PF), bodily pain (BP), role-physical (RP) and general health perception (GH). The mental component reflects the vitality (VT), social role functioning (SF), role emotional (RE) and mental health perception (MH). Scores for each subscale range from 0-100, and higher scores indicate better HRQoL (Framework, 1992).

4.3.4 Health examination

The 55+ health examination consisted of measurements of weight (SECA877 flat scale), height (SECA206, wall-fixed measuring system), hip and waist circumference (SECA201 ergonomic measuring tape, SECA, Reinach, Switzerland), bio-impedance analysis (BIA) using two different devices (Helios, Forana GmbH, Frankfurt, Germany; Tanita MC-780MA, TANITACorporation, Tokyo, Japan), blood pressure and heart rate measurements (Omron MC6 or Omron 705-IT, Anandic Medical Systems AG, Bern Switzerland); pre- and post-bronchodilation lung function measurements separated by administering 2 puffs 200µg of Salbutamol aerosol (Ventolin©) for bronchodilation (EasyOne, ndd, Zurich, Switzerland); point-of-care diagnostics for capillary blood HbA1c and triglycerides (Afinion AS100 Analyzer; ALERE, Wädenswil, Switzerland).

Blood pressure measurements were taken after the participant was seated for at least 10 minutes. Two measurements were taken, with a break of 3 minutes between measurements. Spirometry was measured pre- and post-bronchodilation according to ATS recommendations (Gerbase et al., 2013). The blood measurements for the point-of-care tests were taken in a non-fasting state. From the anthropometric measurements, body mass index (BMI) and waist to hip ratio were derived.

4.3.5 Lifestyle patterns and physiological functioning clustered in latent classes

Twelve categorical variables which reflect overall lifestyle behavior and physiological functioning were considered for identifying latent classes. Variables that have evidence-based thresholds or recommendations were categorized accordingly, namely systolic blood pressure (Reboussin et al., 2018) (diastolic blood pressure was omitted due to its high correlation with systolic blood pressure), BMI (Nishida and Mucavele, 2005), HbA1c (Cohen et al., 2010), triglycerides (Jessani et al., 2006), physical activity (WHO guidelines) and smoking. For other variables (percentage body fat, FEV1 % predicted, alcohol consumption and the nutrition variables), tertiles were calculated in the absence of a reference for categorization (Supplement Table 1).

4.3.6 Statistical analyses

In a first step latent class analysis was carried out to empirically classify lifestyle behaviors and physiological functioning. Subjects were characterized based on their values of the 12 predictor variables. LCA was used as an explorative tool (unconstrained LCA) without *a priori* expectation about the number of classes.

In order to detect the appropriate number of classes and maximize model fit, we started with a one-class model and increased the number of latent classes up to six. The final model was selected by examining the Bayesian information criterion (BIC) and the Akaike Information Criterion (AIC) in the first place. These indices have shown to be useful for determining the appropriate number of classes for LCA (Yang and Analysis, 2006). We checked whether there was a good discrimination between the final definition of latent classes and the twelve predictor variables. Two additional model fit indices, the adjusted BIC and the consistent AIC, were considered along with the proportions of the single classes to further support the decision on the final model.

To assess associations of the derived latent classes with socio-demographic characteristics of the study population, multinomial logistic regression models with latent class membership as outcome variable and sex, age, educational level and study area as simultaneous predictor variables were used.

Associations of median SF-36 scores with the latent classes were analyzed using quantile regression models with adjustment for basic individual predictor variables (e.g. sex, age and educational level). Quantile regression models were chosen to address the problem of left-skewed distribution of QoL measures. As three domains of the SF-36 (SF, RP & RE) had only very few distinct values and the proportion of subjects with the perfect score 100 ranged between 72% and 85%, those variables were dichotomized (with value 1 for a perfect score of 100 and value 0 for a score of <100) and logistic regression models were used to analyze the associations of the rates of suboptimal scores with the latent classes.

4.4 Results

4.4.1 Characteristics of the study population

The descriptive characteristics of the study population can be seen in Table 4.1 (for comparison of characteristics at baseline among participants included in our sample versus those not included in our sample see Supplement Table 2). Women and men were equally distributed among the subjects (n=1'167) and the mean age was 67.56 ± 7.88 (range: 55-88 years). Approximately 63% of the subjects had medium education levels, which refers to having completed middle school. The mean score of the overall HRQoL domain (GH) showed no difference by sex but with advancing age and declining education the score decreased. The physiological functioning variables (blood pressure, glycemia, body fat, FEV1, BMI and triglycerides) all showed lower scores for values below and above the desirable values, respectively. The lifestyle variables (smoking status, physical activity, alcohol consumption and nutrition) display higher scores for the healthy classifications.

Table 4.1 Characteristics of the study population

Variable	Total n=1161	Percent (%)	Mean score of overall HRQoL (General Health)
Sex			
Male	584	50.0	70.2
Female	583	50.0	70.6
Age (Mean, SD)	1167	67.6 ± 7.9	70.4
Age (years)			
55-64	478	41.0	72.0
65-74	476	40.8	70.3
75+	213	18.3	67.0
Education			
Low	66	5.6	65.5
Middle	730	62.6	70.4
High	371	31.8	71.3
Smoking Status			
Never	493	42.3	71.9
Former	516	44.2	69.4
Current	158	13.5	68.8
Physical Activity Guidelines (WHO)			
Inactive	370	31.7	66.0
Sufficiently active	797	68.3	72.5
BMI			
Low (<18.5)	11	0.9	61.9
Normal (20-25)	482	41.3	72.6
Overweight (25-30)	467	40.0	70.5
Obese (>30)	207	17.7	66.0
Body Fat (%)			
Low	414	35.5	72.8
Intermediate	390	33.4	71.4
High	363	31.1	67.8
Alcohol Consumption			
Never – 4x a month	556	47.6	69.8
2-4x a week	339	29.1	72.5
>4x a week	272	23.3	69.6
Meat Consumption			
Lowest tertile	618	53.0	70.4
Medium tertile	233	20.0	71.4
Highest tertile	316	27.1	69.8
Fish Consumption			
Lowest tertile	412	35.3	70.4
Medium tertile	495	42.4	70.1
Highest tertile	260	22.2	71.5
Vegetables & Fruits			
Lowest tertile	353	30.3	69.5
Medium tertile	377	32.3	71.4
Highest tertile	437	37.5	71.7
Triglycerides			

Normal	692	59.3	71.0
Borderline	134	11.5	70.8
High	341	29.2	68.5
Glycemia (HbA1c)			
Desirable	803	68.8	71.4
Borderline	311	26.7	68.5
High	53	4.5	65.8
Blood pressure (systolic)			
Normal	471	40.4	70.9
Elevated	242	20.7	69.1
Hypertensive	454	38.9	70.2
FEV1 % predicted			
Lowest tertile	379	32.5	67.7
Medium tertile	398	34.1	72.2
Highest tertile	390	33.4	71.8

Education: Low= Primary School (≤ 9years), Middle= Secondary school, middle school or apprenticeship (≤12 years), High= Technical College or University (≥12 years);
Physical Activity Guidelines (WHO):
Inactive: <150 min of MPA and <75 VPA per week
Sufficient: >150 min of MPA or >75 VPA per week

4.4.2 Model Fit Statistics for LCA

The value of the BIC reached its minimum in the model consisting of two and three classes. The adjusted BIC was lowest in the three-class model. The AIC constantly decreased with the augmentation of numbers of classes (Table 4.5A). Yet, Figure 4.1 shows that the curve indicating the values of the AIC reached a plateau at three classes and did not decrease substantially with higher numbers of classes. By considering these goodness-of-fit indices, the model with three latent classes was chosen to be the final model. The model with three classes also generated a relatively even distribution (N_1=353 N_2=476, N_3=338) within the study sample, potentially favoring increased statistical power.

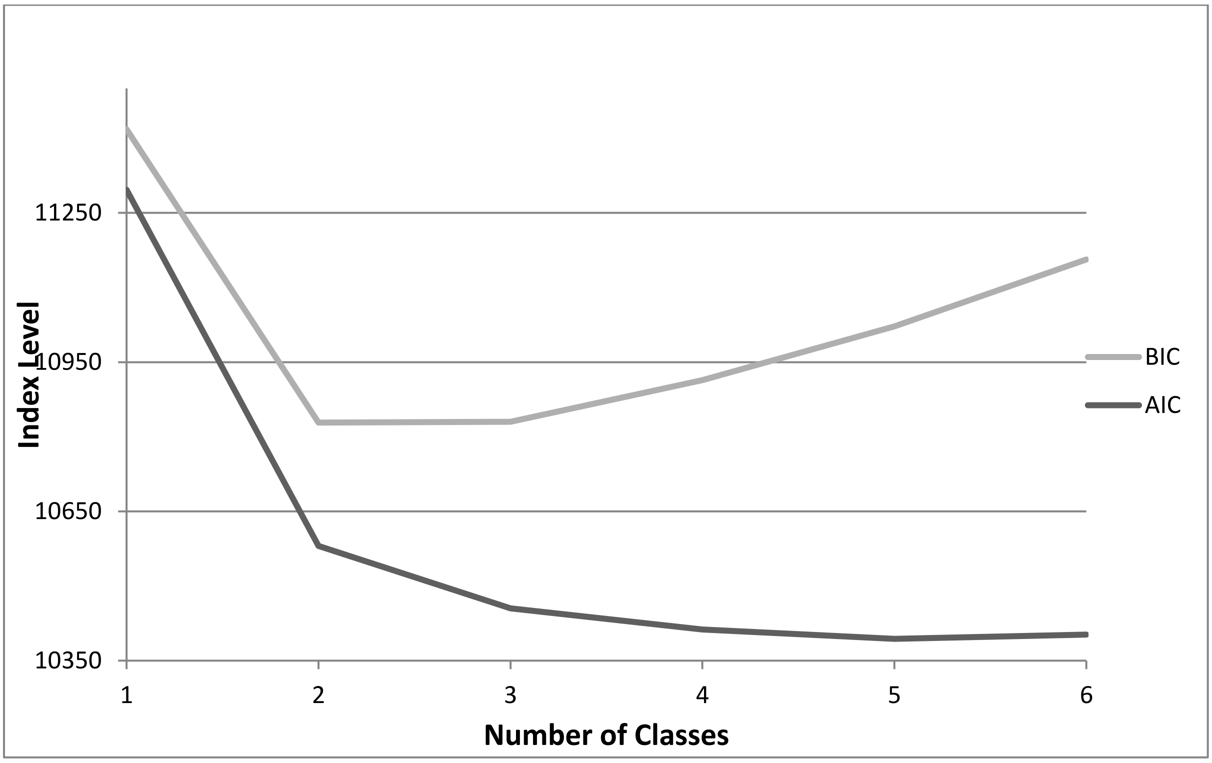

Figure 4.1 Bayes and Akaike information criterion according to number of latent classes

4.4.3 Three lifestyle and physiological functioning clusters defined by LCA

The proportion of the different classes and the estimated class-specific probabilities for the predictor variables are shown in Table 4.2.

Class 1, labeled “Healthy” consisted of individuals having mainly normal physiological functioning measured as blood pressure, glycemia, triglycerides, lung function and percentage body fat or BMI. These beneficial physiological profiles agree with the healthy lifestyle profile of this class, consisting of a high proportion of persons being sufficiently active, having low alcohol and meat, but high vegetable, fruit and fish consumption. This class included 30% of participants.

In Class 2, labeled “overweight at risk”, 70% respective 66% of individuals were overweight and had intermediate percentages of body fat. The prevalence of high blood pressure, hyperglycemia, and dyslipidemia in this group were intermediate compared to those observed for classes 1 and 3. In contrast, the distributions of lung function, physical activity, and smoking were not substantially different from those in class 1. Yet, alcohol consumption appeared to be highest in this group. Participants in this class were most likely to be in the highest tertile of meat consumption, in the middle tertile of fish consumption and in the lowest tertile of fruit and vegetable consumption. Most subjects were categorized into this class (41%).

Class 3, labeled “Obese and unhealthy” had an overrepresentation of individuals that were obese (61%), in contrast to the other classes that contained no obese participants. Accordingly, participants in class 3 were more likely to have a high percentage of body fat, to be hypertensive, to have high glycemia and triglyceride values, lower FEV1 % predicted and to be insufficiently active than those in class 1 and 2. The diet of class 3 participants did not differ substantially from that of class 1 individuals, except for meat consumption, which was more like class 2. 29% of the sample was assigned to this class. The three classes showed differences in smoking habits.

Table 4.2. Proportions and class-specific probabilities for the 3 latent classes

Variables	Healthy n=353 (30%)	Overweight at risk n= 476 (41%)	Obese and unhealthy n=338 (29%)
Smoking Status			
Never	0.48	0.39	0.41
Former	0.39	0.45	0.48
Current	0.12	0.16	0.11
Physical Activity			
Insufficient	0.24	0.28	0.46
Sufficient	0.76	0.72	0.54
BMI			
Low	0.03	0.00	0.00
Normal	0.96	0.30	0.01
Overweight	0.01	0.70	0.38
Obese	0.00	0.00	0.61
Body Fat			
Low	0.87	0.21	0.02
Intermediate	0.13	0.66	0.09
High	0.00	0.12	0.89
Alcohol Consumption			
Never – 4x a month	0.51	0.39	0.57
2-4x a week	0.32	0.30	0.25
>4x a week	0.18	0.31	0.18
Meat Consumption			
Lowest tertile	0.65	0.48	0.46
Medium tertile	0.18	0.19	0.24
Highest tertile	0.17	0.33	0.30
Fish Consumption			
Lowest tertile	0.38	0.32	0.38
Medium tertile	0.37	0.51	0.36
Highest tertile	0.26	0.17	0.26

Vegetables and Fruits Consumption			
Lowest tertile	0.21	0.37	0.30
Medium tertile	0.32	0.34	0.30
Highest tertile	0.46	0.29	0.40
Triglycerides			
Normal	0.78	0.57	0.44
Borderline	0.09	0.11	0.15
High	0.13	0.33	0.41
Glycemia (HbA1c)			
Desirable	0.84	0.72	0.48
Borderline	0.16	0.25	0.40
High	0.01	0.03	0.11
Blood pressure			
Normal	0.66	0.33	0.24
Elevated	0.12	0.27	0.20
Hypertensive	0.21	0.40	0.55
FEV1 % predicted			
Lowest tertile	0.29	0.30	0.40
Medium tertile	0.35	0.34	0.33
Highest tertile	0.36	0.36	0.27

Values represent class-specific probabilities for each variable;

BMI= Body Mass Index; Hba1C= Glycated hemoglobin; FEV1= Forced Expiratory Volume

4.4.4 Socio-demographics across the clusters

Table 4.3 shows the comparison of socio-demographic characteristics across the three latent classes. The results of the multinomial logistic regression showed that females were less likely than men to belong to the Obese and unhealthy or the Overweight at risk class. The likelihood of being categorized as “Healthy” decreased with age and lower educational level. Persons aged 75+ or with low educational level were particularly likely to be categorized as Obese and unhealthy.

Table 4.3 Socio-demographic characteristics of the latent classes

	Healthy (Reference)	Overweight at risk	Obese and unhealthy
Characteristics		RRR (95% CI)	RRR (95% CI)
Gender			
Male		1.00	1.00
Female		0.40* (0.20; 0.54)	0.47* (0.34; 0.64)
Age (years)			
55-65		1.00	1.00
65-75		1.14 (0.84; 1.56)	2.00* (1.42; 2.83)
75+		1.57* (1.03; 2.40)	2.80* (1.78; 4.40)
Education level			
Low		1.00	1.00
Middle		0.57 (0.27; 1.23)	0.36* (0.17; 0.77)
High		0.35* (0.16; 0.77)	0.22* (0.10; 0.49)

RRR= Relative Risk Ratio; *= p<0.05;
Relative risk ratios are mutually adjusted for all variables included in the model as well as for study area

4.4.5 Associations of clusters and HRQoL domains

The results of the quantile regression analyses (Table 4.4) showed that, compared with the reference class (Healthy) median HRQoL-scores were lower in the Obese and unhealthy class, i.e., with differences of -3.21(95%CI: (-5.59, -0.84) in the general health domain, of -6.25 (-7.50, -5.01) in the physical functioning domain, of -9.40 (-13.78, -5.04) the bodily pain domain and of -5.0 (-7.92, -2.08) in the vitality domain.

The Overweight at risk class only had lower scores in the physical functioning domain (-1.42; -2.40, -0.45)) and the vitality domain (-5; (-7.59, -2.41)), compared to the reference class. Figure 4.2 shows the median scores of the HRQoL domains stratified by the latent classes. It documents the prevailing pattern of lower median scores in the Obese and unhealthy class compared to the Healthy class, with the exception of the mental health domain where the three classes showed almost no difference. Sensitivity analysis testing the additional inclusion of each risk factor separately in the analysis confirmed the independent association of the LCA classes with HRQoL scores (Table 4.8A).

Table 4.4 Differences in median levels of SF-36-scores between the three latent classes derived

	General Health (GH)		Physical Functioning (PF)		Bodily Pain (BP)		Vitality (VT)		Mental Health (MH)	
Latent classes	Coefficient (95% CI)	P-value	Coefficient (95% CI)	P-value	Coefficient (95% CI)	P-value	Coefficient (95% CI)	P-value	Coefficient (95% CI)	P-value
Healthy	Reference									
Overweight at risk	-1.13 (-3.43; 1.18)	0.338	-1.42 (-2.40; -0.45)	0.004	-2.06 (-5.00; 0.89)	0.172	-5 (-7.59; -2.41)	<0.001	-0.90 (-2.54; 0.75)	0.284
Obese and unhealthy	- 3.21 (-5.59; -0.84)	0.008	-6.25 (-7.50; -5.01)	<0.001	-9.40 (-13.78; -5.04)	<0.001	-5 (-7.92; -2.08)	0.001	-1.22 (-3.33; 0.89)	0.258

CI= Confidence interval;

Differences in median levels were analysed with quantile regression models;

Adjustued Variables: Sex, age, education level and study area

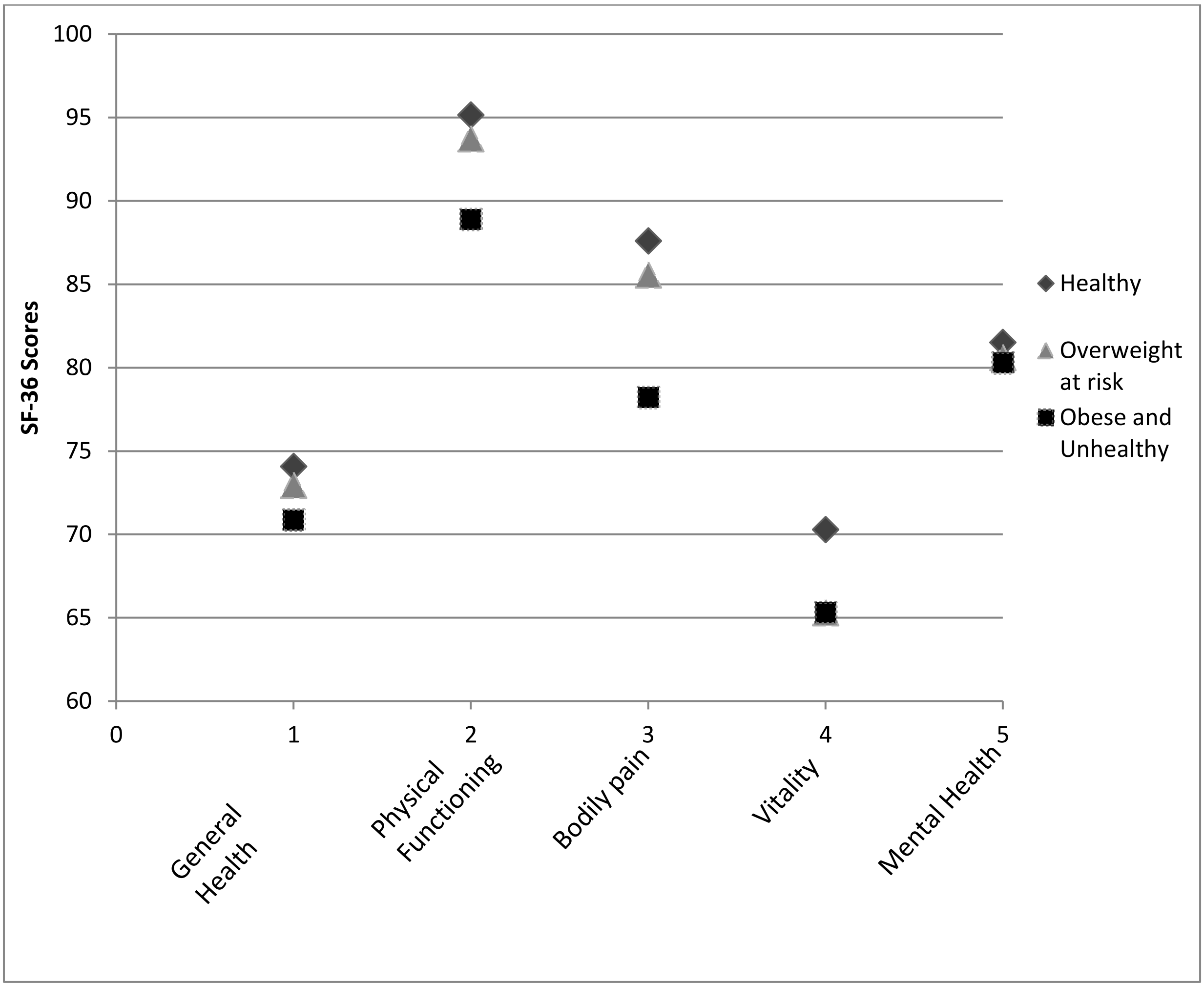

Figure 4.2 Adjusted (sex, age, education level and study area) median HRQoL scores according to the three latent classes

The Overweight at risk class showed no differences to the healthy class in the three HRQoL subdomains that were dichotomized (SF, RP & RE). Whereas, the Obese and unhealthy class showed a lower probability of reaching a perfect score of 100, compared to the Healthy reference class, for the domain RE (OR=0.64; 95%CI: (0.64; 0.92)) (Table 4.9A).

4.5 Discussion

In this general population sample from Switzerland aged 55 years and older, HRQoL derived from SF-36 was generally high compared to similar settings (Hopman et al., 2000).

To improve understanding of HRQoL and well-being in aging residents of a country where disease control weights the treatment over the prevention of disease (Berset et al., 2015), the use of latent class analysis enabled us to cluster lifestyle patterns and physiological functioning of the SAPALDIA 55+ population and identify three latent classes within the sample. The three classes identified appeared to represent increasing levels of disease risk. They were termed “Healthy”, “Overweight, at risk” and “Obese and unhealthy”. Obesity and a high percentage of body fat in the presence of unhealthy lifestyles as well as respiratory and cardio-metabolic pathophysiology was associated with considerably lower HRQoL scores in all domains except for MH and RE. The largest difference to the Healthy reference class in terms of median scores was found for the PF and VT domains, the two only domains that were also lower in the “Overweight” class. Differences in HRQoL between classes were larger for the physical compared to mental health components. Yet, the VT subdomain, belonging to the mental health component also showed considerable differences for both, the Obese and unhealthy and the Overweight at risk class compared to the Healthy Class.

Results from previous research on the association of single components making up the “Obese and unhealthy” class with HRQoL domains are mostly consistent with our findings(Gouveia et al., 2017, Knox and Muros, 2017). Even after controlling for other important health-risk behaviors, an increased BMI seems to be most strongly associated with adverse HRQoL outcomes (Dey et al., 2013). A recent systematic review supports these findings and stated that obesity is associated with lower HRQoL outcomes (Kolotkin and Andersen, 2017). Another systematic review showed that being overweight or obese resulted in fewer points in the main domains of HRQoL (Corica et al., 2015), in line with our results. In populations aged 55 and older higher levels of physical activity have been shown to be associated with greater HRQoL (Bouaziz et al., 2017, Abdelbasset et al., 2019). Physical activity even acts as mediating factor for hypertension and QoL, as medical treatment of hypertension in older ages often results in reduced QoL (Setters and Holmes, 2017). The improvement of QoL was also detected by randomized controlled trials, looking at the benefit of exercise-based rehabilitation programs in hypertensive individuals (Morris et al., 2017). Hyperglycemia was shown to have direct and indirect effects through inadequate glycemic control on HRQoL outcomes in diabetic elderly (Atif et al., 2018). Intervention plans to promote lifestyle changes prevented frailty in diabetic individuals and enhanced life expectancy and QoL (Cobo et al., 2016).

The risk factors being more prevalent in members of the "Obese and unhealthy Class" agree well with the cluster of risk factors defining the metabolic syndrome (Carriere et al., 2013). Although there is not yet much evidence on an association of metabolic syndrome with QoL, most studies showed a worsening effect of the metabolic syndrome on QoL. However, it was also observed that the metabolic syndrome alone without accompanying comorbidities such as depression had little or no effect on QoL (Ford and Li, 2008, Mahambetalieva et al., 2018, Saboya et al., 2016).

In this study, we observed a clear socio-economic gradient across the three latent classes, with participants at the lowest educational level being over-represented in the class with the lowest QoL scores ("Obesity and unhealthy"). Socio-economic gradients have previously been identified for obesity and associated lifestyles (Ball et al., 2015, Bonaccio et al., 2012, Livingston and review, 2014, Newton et al., 2017, Prince et al., 2017, Thebault et al., 2018, Volaco et al., 2018), for the metabolic syndrome (Alkerwi et al., 2012, Pucci et al., 2017, Santos et al., 2008), and for HRQoL (Read et al., 2016, Stojanović et al., 2018). Factors that are likely to contribute to these social gradients include understanding of healthy habits, access to healthy habits (e.g. access to fitness centers; prices for healthy vs. unhealthy food; green spaces and built environment) and access to screening for disease (i.e. regular testing of blood pressure, glycemia, lipids), and adequate control of disease (i.e. blood pressure medication) (Ball et al., 2015, Livingston and review, 2014, Bonaccio et al., 2012). In a country like Switzerland with sufficient economic resources, the lack of investments into primary and secondary prevention seems to come at the cost of poor wellbeing in persons in the second half of their life. This may lead to high treatment costs later in life and to loss of productivity in persons still actively engaged in the workforce (Goettler et al., 2017, Hämmig and Bauer, 2013).

Strength and Limitations

The cross-sectional nature of the study does not allow inferring causality. The information on socio-economic status, physical activity, and nutrition, smoking status and alcohol consumption were self-reported by the participants, which could lead to measurement errors. However, all other variables included in the analysis were objectively assessed. Because the self-reported data was highly associated with the objectively measured data – tested in the LCA, we believe that the subjective nature of these assessments did not substantially bias our results. The variables reflecting lifestyle behavior and physiological functioning were chosen based on the evidence reported in the literature. The availability of additional physiological and lifestyle variables could help to improve the definition of latent classes. The current LCA may furthermore be sensitive to the chosen categories for the predictor variables. The generalizability of our findings to other study settings needs testing.

Despite these limitations, the findings of this study strongly support that it is possible to reduce the number of lifestyle behavior and physiological functioning variables using LCA. Even after adjusting for their input variables the differences between the three classes remained almost unchanged with regard to the overall HRQoL score (GH) (Table 4.8A). Hence, the latent classes seem to comprehensively represent the predictor variables for relationship-analysis with HRQoL domains.

The LCA was facilitated by access to data from the SAPALDIA participants, who are deeply characterized on various lifestyle and physiological domains. The population-based design of the study is an important prerequisite for the generalizability of the findings, at least within the Swiss setting, although participation and survivor bias always pose a threat to validity and generalizability of any long-running cohort.

Conclusion

This study, investigating combined lifestyle and physiological functioning parameters for health-related quality of life in a general population sample, emphasizes the relevance of promoting primary and secondary prevention to maintain wellbeing in aging populations. The broad absence of organized primary prevention and screening programs in the strong economy of Switzerland leads to the clustering of factors among the lower social classes and therefore to inequity in HRQoL. In the light of increased promotion of personalized medicine as opposed to public health and prevention programs, as well as imbalanced investments into medical treatments, our results may help understand and guide how to avoid further widening of medical inequalities. This study provides new insights for delivering health promotion, by suggesting a linked approach aimed at preventing risk behavior in general rather than focusing on individual single risk factors.

Acknowledgements

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Conflict of interest

The authors declare that they have no conflict of interest.

Appendix A. Supplement information

4.6 Supplement information

Supplement Figures:

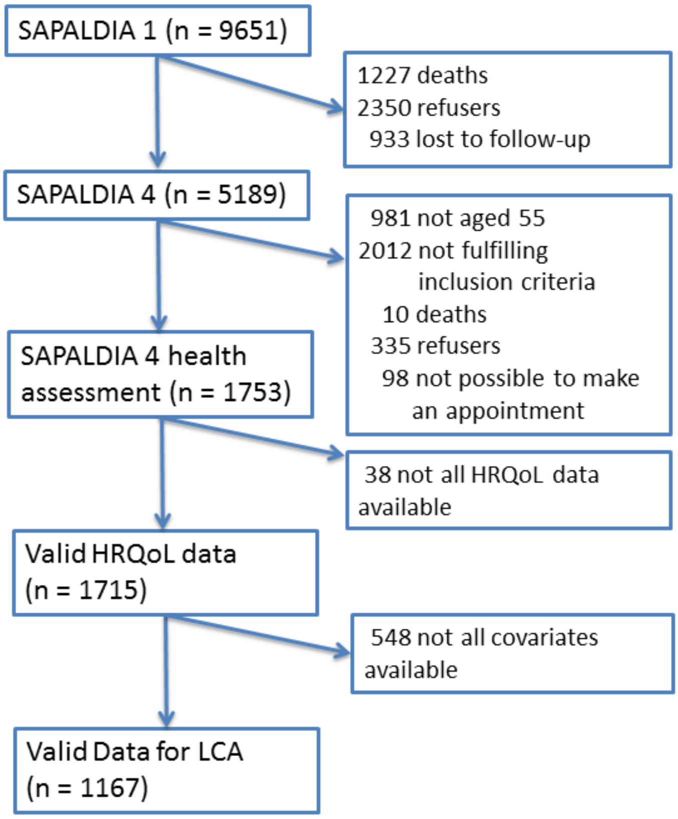

Figure 4.3A Participation from SAPALDIA 1 to the current study (1991 – 2018)

Supplement Tables:

Table 4.5A Categorization of lifestyle and physiological functioning variables for LCA

Variables	Categorization for LCA
Systolic blood pressure	120 -129 (normal), 130 – 139 (elevated), ≥140 (hypertensive)
BMI	<18.5 (underweight), 20-25 (normal weight), 25-30 (overweight), >30 (obese)
HbA1c (%)	<5.7 (desirable), 5.7-6.5(borderline), >6.5 (high)
Triglycerides (mmol/l)	<1.7 (desirable), 1.7-2.0 (borderline), >2.0 (high)
Percentage Body fat (%)	Male: 10-26 (low) , 26-31 (intermediate), >31 (high) Female: 9-36(low), 36-40 (intermediate), >40 (high)
Physical Activity (WHO)	Inactive: <150 min of MPA and <75 min VPA per week Sufficient: ≥150 min of MPA or ≥75 min VPA per week
FEV1 % predicted (pre-bronchodilation)	Lowest tertile, Medium tertile, Highest tertile
Smoking	Never, Former, Current
Alcohol Consumption	Never – 4x a month, 2-4x a week, >4x a week
Meat Consumption	Lowest tertile (0-2 days/week), Medium tertile (3-4), Highest tertile (5-7)
Fish Consumption	Lowest tertile (0-2 days/week), Medium tertile (3-4), Highest tertile (5-7)
Vegetables (raw, cooked, juice) and Fruits (including juice)	Lowest tertile (0-20 portions/week), Medium tertile (20-41), Highest tertile (>41)

BMI= Body Mass Index; HbA1C= Glycated hemoglobin; MPA=Moderate physical activity; VPA=Vigorous physical activity; FEV1 % predicted= Forced Expiratory Volume in one second percent predicted according to ECSC equations [37]

Table 4.6A Baseline characteristics at SAPALDIA 1 of participants who reached the age of 55+ at the time of the health assessments, stratified by participation status.

	Non-participation in 55+ health assessment		Participation in 55+ health assessment		
	N	%	N	%	p-value
Sex					
male	3266	48.0	584	50.0	0.187
female	3545	52.1	583	50.0	
Language					
German	3607	53.0	597	51.2	
French	2224	32.7	468	40.1	<0.001
Italian	980	14.4	102	8.7	
BMI [kg/m^2}					
<18.5	196	2.9	54	4.6	
<25.0	3842	57.1	828	71.2	<0.001
25-30	2090	31.7	246	21.2	
>30	599	8.9	35	3.0	
Age (years)					
30-40	1858	27.3	490	42.0	
40-50	2338	34.3	440	37.7	<0.001
50-60	2333	34.3	178	15.3	
Education Level					
low	1371	20.2	99	8.5	
middle	4335	63.8	766	65.8	<0.001
high	1086	16.0	300	25.8	
Smoking Status					
never	2708	39.8	568	48.8	
former	1736	25.5	317	27.2	<0.001
current	2361	34.7	280	24.0	

Table 4.7A Summary of model fit indices for 1 to 6 latent classes

Number of latent classes	BIC	Adjusted BIC	AIC	CAIC	Entropy
1	11417.948	11341.715	11296.455	11441.948	1
2	10828.436	10672.796	10580.389	10877.436	0.74376393
3	10829.937	10594.888	10455.335	10903.937	0.68208626
4	10913.766	10599.308	10412.609	11012.766	0.67505983
5	11021.537	10627.67	10393.825	11145.537	0.66529533
6	11156.365	10683.09	10402.098	11305.365	0.69436677

BIC= Bayesian Information Criterion; AIC= Akaike Information Criterion; CAIC= Consistent AIC

To examine if the latent classes still showed an effect on the overall HRQoL score (GH) after adjusting for their input variables, i.e., the categorical variables having been used to derive them, the main model of this study looking at the differences in the median values of the GH-scores between the three latent classes was compared with a model additionally containing all indicator variables associated with the different levels of the input variables. For this purpose, these indicator variables were centered at their mean values in the respective latent classes. Supplement table 4 shows that the differences between the three classes remain almost unchanged after this further adjustment.

Table 4.8A Differences in median levels of GH score between the three latent classes with and without adjustment for input variables

	General Health (GH) without adjustment for input variables		General Health (GH) with adjustment for input variables	
Latent classes	Coefficient (95% CI)	P-value	Coefficient (95% CI)	P-value
Healthy	Reference		Reference	
Overweight at risk	-1.13 (-3.43; 1.18)	0.338	-1.28 (-3.83; 1.26)	0.322
Obese and unhealthy	- 3.21 (-5.59; -0.84)	0.008	-3.56 (-6.34; -0.79)	0.012

CI= Confidence interval;
Differences in median levels were estimated using quantile regression models;
Both models were adjusted for sex, age, education level and study area;
Input variables (Number of categories): Blood pressure (3), HbA1c (3), Smoking status (3), Body fat (3), BMI (4), Physical Activity Guidelines (2), FEV1 % predicted (3), Triglycerides (3), Alcohol (3), Meat (3), Fish (3), Vegetables and Fruit (3)

Table 4.9A Differences in the rates of suboptimal scores in three of the SF36 domains SF, RP and RE between the three derived latent classes

	Social role functioning		Role physical		Role emotional	
Latent classes	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Healthy	Reference					
Overweight at risk	1.12 (0.81; 1.55)	0.497	1.05 (0.75; 1.48)	0.759	0.92 (0.61; 1.40)	0.696
Obese and unhealthy	0.77 (0.55; 1.08)	0.133	0.64 (0.45; 0.92)	0.015	0.66 (0.43; 1.01)	0.058

OR= Odds ratio; CI= Confidence interval;
The outcome variables were dichotomized with value 1 representing a perfect score of 100 and value 0 representing a score of <100;
Differences in rates of SF, RP and RE were analyzed using logistic regression models and adjusted for sex, age, education level and study area

5 MANUSCRIPT II

Elucidating independent and joint associations of the social and perceived built environment with health-related quality of life and health service utilization

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Journal: Health & Place – Ready to submit

5.1 Abstract

Previous research has shown that the built and social environment play a crucial role for residents' health-related quality of life and could influence health service utilization. However, many studies have failed to link these environmental factors and investigate the involved mechanisms associated with health-related quality of life and differences in health service utilization.

This study used data from the third follow-up of SAPALDIA (initiated in 1991), a population based cohort with associated biobank. Latent Class Analysis were used to group subjects by the environmental parameters and multiple quantile regressions as well as logistic regressions were used to identify associations with SF-36 derived HRQoL and health service utilization.

Results suggested that among all measured environmental parameters, living with a partner compared to solitary living as well as high noise annoyance ratings showed strongest associations with health-related quality of life and health service utilization. **Key words: Social, perceived built, environment, health-related quality of life, health service utilization**

5.2 Introduction

The environment, which can range from the built or physical environment to the social environment, serves as the context of life, and contributes to its quality in terms of health, well-being and diseases (Guite et al., 2006, Bowling et al., 2002). The built environment comprises exposures such as noise, environmental pollutants and general neighborhood conditions as infrastructural adequacy, which can facilitate or hinder physical and psychological functioning (Bowling et al., 2002, Tse, 2005, Schootman et al., 2006, Guite et al., 2006, Moore et al., 2018, Rautio et al., 2018). By comparing different studies from five cities, a number of health outcomes were linked to characteristics of the built environment (Goldberg et al., 2012). Lower obesity rates were associated with higher land-use diversity. Headaches, arthritis and various respiratory morbidities were also attributed to the built environment (Hogan et al., 2016b).

At the same time, the social environment is pivotal given that social support and networks are crucial for well-being of the individual, especially in frail older adults

(Bowling et al., 2002, Herrera-Badilla et al., 2015). Frailty is thought to contribute to poorer social functioning with increasing loneliness over time. By being an important risk factor for morbidity and early mortality, loneliness could be detrimental for HRQoL (Cacioppo et al., 2015). Furthermore, social support was predictive of lower all-cause mortality risk and improved physical and mental health (Liu, 2011, Shye et al., 1995, Birmingham and Holt-Lunstad, 2018). It has relevant protective effects on health and longevity in every period of the lifecycle, starting with the support of parents at younger ages to the care of older adults by family members, peers and care givers (Holt-Lunstad, 2018, Gariépy et al., 2016).

As demonstrated by previous studies (Foraster et al., 2016, Eze et al., 2018, Héritier et al., 2014, Dratva et al., 2010, Martens et al., 2018, Wang et al., 2018, Del-Pino-Casado et al., 2018), the perception of the social and built environment plays an important role in understanding environmental links to health, and therefore underlines its relevance for investigation in health-related outcomes. The perception of the built environment seems to affect health-related quality of life (HRQoL) where better perceptions of neighborhood aesthethics, accesses to shops, services, public transportation and natural open spaces were associated with higher HRQoL scores (Byles et al., 2014, Sugiyama et al., 2009). It is expected that socially disadvantaged older adults are vulnerable to limitations caused by the built environment given their greater need for accessing health and social services (Clarke and Nieuwenhuijsen, 2009). Moreover, individuals with poor perceptions of social support seem to evolve worse mental health issues with stronger symptoms in disease-outcomes compared to individuals perceiving their social support positively (Del-Pino-Casado et al., 2018, Wang et al., 2018). Hence, the perception of these environmental attributes, in addition to individual perception of health and socio-demographic factors, could influence the health-seeking behaviors of older adults and their HRQoL (Vedsted et al., 2004, Busato et al., 2005).

The evidence linking the social and built environment to HRQoL, remains limited, with poor and unclear understanding of the involved mechanisms (Hajek et al., 2016). In particular, an integrated approach investigating environmental attributes that determine HRQoL and well-being is critical to the advancement of public health policies and urban planning towards healthy aging. Furthermore, there are also very few studies that have linked even single aspects of the physical and social environment to health service utilization as a downstream consequence of poor HRQoL (Zhou et al., 2014, Sabbath et al., 2018). From a health-all-policy perspective (Waring et al., 2016, Zeeb et al., 2018), it seems important though to link the social and physical environment to the use of medical services and to thereby add a price tag to inadequacies related to environmental and social policies.

To the best of our knowledge, no study so far has investigated the association of the perceived built and social environment with HRQoL and health service utilization in a combined manner. Therefore, the objectives of this cross-sectional study done in the context of the Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults (SAPALDIA) were: (1) to investigate independent associations between the social and perceived built environment with HRQoL domains; (2) to identify clusters of environmental and social attributes that best determine HRQoL and finally (3) to investigate associations of the social and perceived built environment—in single and cluster formats—with differences in health service utilization.

5.3 Methods

5.3.1 Study population

SAPALDIA, initiated in 1991 (SAPALDIA1), is a population-based cohort with associated biobank involving 9’651 adults (18-62 years) drawn from eight representative Swiss areas aimed primarily at understanding the respiratory impact of air pollution exposure in the Swiss population (Ackermann-Liebrich et al., 2005). In the subsequent three follow-ups completed over 25 years (SAPALDIA2, 2001/2002, 8’047 participants; SAPALDIA3, 2010/2011, 6’088 participants (Endes et al., 2017); and SAPALDIA4, 2017/2018, 5’189 participants) the study expanded into cardio-metabolic outcomes, well-being and healthy aging. The current study was based on SAPALDIA4 where all the relevant variables required for the present research questions were collected. We therefore included 1962 SAPALDIA4 participants who had complete data on the perceived built and social environment, HRQoL, healthcare utilization as well as other relevant covariates. The SAPALDIA cohort study complies with the Declaration of Helsinki. For each survey, ethics approval was granted by the regional ethics committees and participants provided written informed consent prior to participation.

5.3.2 Measures of Health-Related Quality Of Life (HRQoL)

The SAPALDIA 4 questionnaires included the 36-Item Short-Form Health Survey (SF-36), a widely-used and validated tool for measuring HRQoL in both population-based and clinical settings (Hart et al., 2015, Keller et al., 1998). The questionnaire provides a summary of physical and mental health component scores, based on eight domains. The physical component comprises physical functioning (PF), bodily pain (BP), role-physical (RP) and general health perception (GH). The mental component comprises vitality (VT), social role functioning (SF), role emotional (RE) and mental health perception (MH). Scores for each subscale range from 0-100, and higher scores indicate better HRQoL (Framework, 1992). We excluded three domains of the SF-36 (SF, RP & RE), as they had only very few distinct values in our sample. These variables represent minor sub-scales of the SF-36, their exclusion still allows an assessment of MCS and PCS of HRQoL outcomes.

5.3.3 Measures of perceived built and social environment

We extracted relevant information on the perceived built and social environment from the SAPALDIA4 questionnaire. For the perceived built environment, we considered personal satisfaction with apartment and neighborhood (score out of four questions); proximity to supermarkets, local services, restaurants and cafés, public transportation services, sports facilities, parks and green spaces as well as quite places (minutes to places 5-30 min.); transportation noise annoyance (standardized rating Scale 0-10) (Fields et al., 2001). For the social environment measures, we considered the living status of the participants (living alone vs. living with a partner); occupational status (full-time job, part-time job, retired, retired but still working); social engagement (score out of eleven questions); daily peer support (dichotomized by median = low/high); peer support in emergencies (dichotomized by median = low/high); peer compassion (tertiles). The questions are displayed in the Table 5.7A.

5.3.4 Health service utilization

We assessed health service utilization as use of medical services measured using the SAPALDIA4 questionnaire. We defined three health service utilization variables including a visit to physician(s), hospital(s) or therapist(s) (i.e. psychologist, physiotherapists, alternative practitioners) in the 12 months preceding the survey (yes vs. no for each). We also defined a clinical use variable, which combined the visit of either physician(s) or hospital(s) in the 12 months preceding the survey (yes vs. no). We treated these response variables as binary because nearly all participants (94-100%) reported 1 or 0 visits in the specified period.

5.3.5 Potential confounders and effect modifiers

We *a priori* selected the following potential confounders and effect modifiers measured at SAPALDIA4, based on existing literature and prior knowledge: age (years), sex (male/female), years of formal education (≤9/≤12/>12 years equivalent to primary, secondary and tertiary education), study area (Basel, Wald, Geneva, Payerne, Lugano, Aarau, Davos, Montana), smoking status (never/former/current), sufficient moderate to vigorous physical activity (<150/≥150 minutes per week) and body mass index (BMI; kg/m2).

5.3.6 Statistical analysis

In a first step (see 5.4.1), we described the characteristics of the study population, summarizing continuous variables as means and interquartile ranges (SF-36), and categorical variables as proportions. The median HRQoL GH score and the % of persons with at least one physician or hospital visit in the last 12 month are reported according to the levels of the characteristics.

In a second step (see 5.4.2), we investigated associations of perceived built environment and social environment variables with HRQoL using separate multiple quantile regression models while adjusting for covariates. We chose this approach as values of SF-36 derived HRQoL scores are highly left-skewed (Figure 5.4A).

In a third step (5.4.3), we performed Latent Class Analysis (LCA) to empirically classify perceived built environment and social environment variables. We used unconstrained LCA as an explorative tool without a priori expectation about the number of classes. To detect the right number of classes, prominent goodness-of-fit indices were used, including the Bayesian information criterion (BIC) and the Akaike Information Criterion (AIC) (Yang and Analysis, 2006). We further considered two additional model fit indices, the adjusted BIC and the consistent AIC, to support the decision on the final model. Each participant was assigned to the best fitting Latent Class (LC) according to his/her characteristics profile.

In a fourth step (5.4.3) we examined the associations of the LC derived from variables reflecting the perceived built environment and social environment with HRQoL in the context of covariate adjusted multiple quantile regression models. Separate models were run for each of the HRQoL domains. The LC variable was included in the regression models as a categorical variable with one of the LCs as reference category.

In a fifth step (5.4.4) we examined the independent and covariate adjusted associations of the perceived built and social environment, respectively, with health service utilization by including all relevant variables in two separate multiple logistic regression model. In a sixth step (5.4.4) we also examined the covariate adjusted association of the LCs with health service utilization with the help of multiple logistic regression models.

Lastly (5.4.5), we stratified the main results by noise annoyance as this variable turned out to be persistently dominant and worth investigating in more detail.

In the multiple regression models, and for LC formation we assessed some variables (noise annoyance, social engagement & peer compassion) along their tertiles (low, medium and high), all others on a two-level (low vs. high) categorical scale. All of the above models were adjusted for potential individual-level and context-level confounders measured, including sex, age, education, smoking status, physical activity, BMI and study area.

We performed all analyses using Stata 15 (Stata Corporation, College Station, Texas) and considered associations as statistically significant at an alpha-level of 0.05.

5.4 Results

5.4.1 Characteristics of the study population

The characteristics of the study population are presented in Table 5.1. The mean age of the included participants was 64 years (43 to 87 years), with an equal distribution by sex. Approximately 61% of the subjects reported medium education levels. Relatively few participants were current smoker (15%) and nearly two third (64%) met the WHO guidelines for physical activity. A majority of the study population (62%) reported being satisfied with their apartment and neighborhood. With regards to perceived proximity measures, about half of the study participants reported high levels of proximity to social places and quite/green places, whereas most subjects (84%) reported public transportation to be available in proximity to their residence. In contrast, more than two third (72%) reported living distant to sports facilities. Most subjects (75%) lived with a partner. About one third were working full-time and another third were retired. More than half of the participants reported a high level of social support.

On average participants reported high HRQoL scores across all domains. The median score of the GH HRQoL domain showed small or no differences by sex, proximity to social places, sports facilities and public transportation and peer support for daily activities. Most subjects (84%) visited a physician, but only few visited a hospitals within the last 12 months. Descriptive differences in visits to either physicians and/or hospitals the last 12 months were detected for sex, age categories, noise annoyance ratings, occupational status, education and smoking status. The correlations between the social and perceived built environment variables are summarized in Table 5.8A.

Table 5.1 Characteristics of the study populations and sub-group specific mean scores of overall HRQoL score (GH) and physician and/or hospitals visits within the last 12 months

Variable	Total n=1962	Percent (%)	Median score of overall HRQoL (GH)	Visited physician / hospital ≥1 (%)
Sex				
Male	1001	51	71	80
Female	961	49	72	90
Age (Mean, SD)	64.22 (10.20)			
Age (years)				
55-64	1014	52	74	81
65-74	648	33	70	89
75+	300	15	67	88
Education				
Low	57	3	69	93
Middle	1201	61	72	84
High	704	36	72	84
Smoking Status				
Never	870	44	73	83
Former	805	41	70	87
Current	287	15	71	82
Physical Activity Guidelines (WHO)				
Inactive	700	36	67	84
Sufficiently active	1262	64	74	85
BMI (Mean, SD)	26.05 (4.44)			
Satisfaction with apartment and neighbourhood				
Low	740	38	68	85
High	1222	62	73	84
Proximity to social places				
Low	1003	51	72	83
High	959	49	71	86
Proximity to public transportation				
Low	315	16	71	84
High	1647	84	71	85
Proximity to sports facilities				
Low	1411	72	72	85
High	551	28	71	83
Proximity to quite/green places				
Low	1107	56	70	84
High	855	44	73	84
Noise annoyance				

Low	804	41	73	81
Mid	595	30	70	87
High	563	29	71	86
Living alone	496	25	70	85
Living with a partner	1466	75	72	84
Occupational status				
Full-time	667	34	74	78
Part-time	291	15	74	86
Retired	753	38	68	89
Retired & Working	251	13	72	86
Social engagement				
Low	719	37	70	84
Medium	666	34	72	84
High	577	29	73	86
Peer support for daily activities				
Low	286	15	72	84
High	1676	85	72	84
Peer support in emergencies				
Low	624	32	71	83
High	1338	68	73	85
Peer compassion				
Low	199	10	67	83
Middle	592	30	70	85
High	1171	60	71	85
Physician visit last 12 months				
0	320	16	76	n.a
≥1	1642	84	71	n.a
Hospital visit last 12 months				
0	1648	84	73	n.a
≥1	314	16	68	n.a

Education: Low= Primary School (≤ 9years), Middle= Secondary school, middle school or apprenticeship (≤12 years), High= Technical College or University (≥12 years);
Physical Activity Guidelines (WHO):
Inactive: <150 min of MPA and <75 VPA per week
Sufficient: >150 min of MPA or >75 VPA per week

5.4.2 Associations of the social and perceived built environment with HRQoL

5.4.2.1 The perceived built environment and HRQoL

The results on the independent and covariate adjusted associations of variables describing the perceived built environment with HRQoL domains are illustrated in Figure 5.1. We observed statistically significant positive associations of self-reported satisfaction with the apartment and neighbourhood on all HRQoL domains. We found no association between proximity measures and HRQoL apart from a positive association of reported proximity to sports facilities with BP. We found a negative trend between tertiles of noise annoyance and HRQoL parameters. Compared to participants in the lowest tertile of noise annoyance, those in the middle and highest tertiles of noise annoyance showed statistically significant lower scores for BP, VT and MH, with the highest tertile group having the lowest scores of these HRQoL parameters.

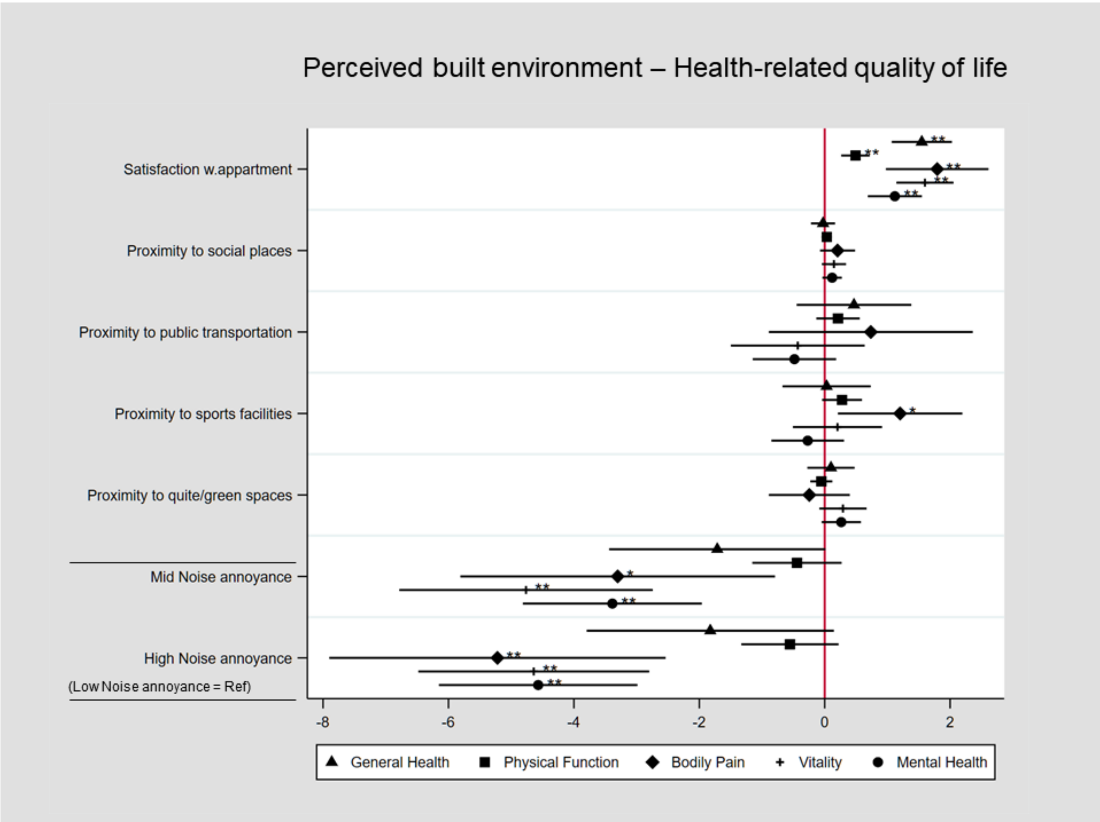

Figure 5.1 Independent association of variables describing the perceived built environment with health-related quality of life domains, adjusted for covariates

5.4.2.2 The social environment and HRQoL

We observed statistically significant independent and covariates adjusted associations of living with a partner with higher scores of BP, VT and MH compared to living alone. Retirement with occupational activity was associated with higher vitality, but also higher bodily pain compared to working full-time. There was a positive association of daily peer support and PF, and participants within the highest tertile of peer compassion had higher scores of VT and MH compared to those in the lowest tertile. We observed no associations between social engagement and parameters of HRQoL (Figure 5.2).

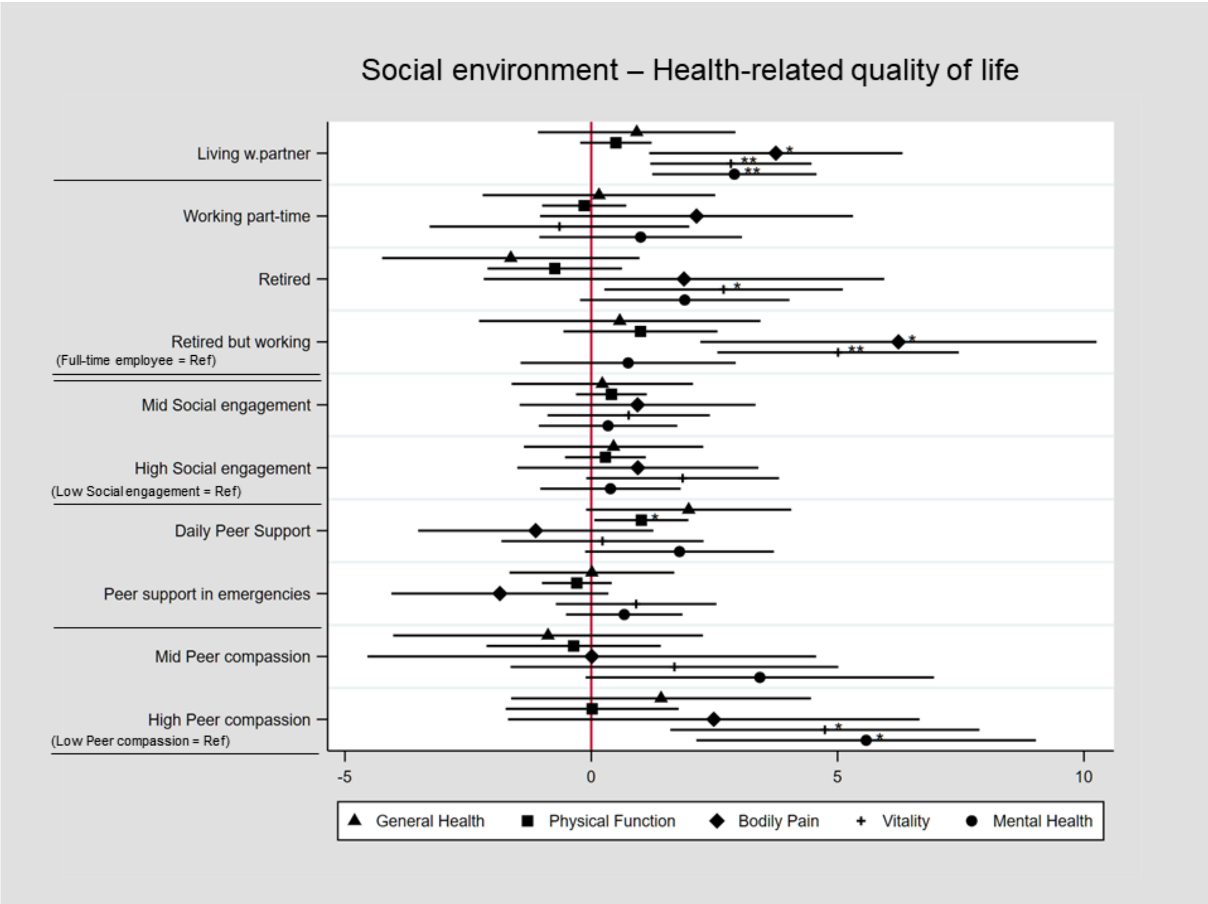

Figure 5.2 Independent association of variables describing the social environment with health-related quality of life domains, adjusted for covariates

5.4.3 Latent Class Analysis (LCA) of combined perceived built and social environment

5.4.3.1 Model fit indices for LCA

We observed that the BIC reached its minimum in the model with three latent classes. The AIC decreased with the augmentation in numbers of classes (Table 5.9A). Yet, as illustrated in Figure 5.3, the curve indicating values of the AIC approached a plateau at three classes and did not decrease substantially with higher numbers of classes. Moreover, the adjusted BIC as well as the CAIC showed lowest values (or plateaus) for the model consisting of three classes. Therefore, we selected the model consisting of three latent classes for further analyses.

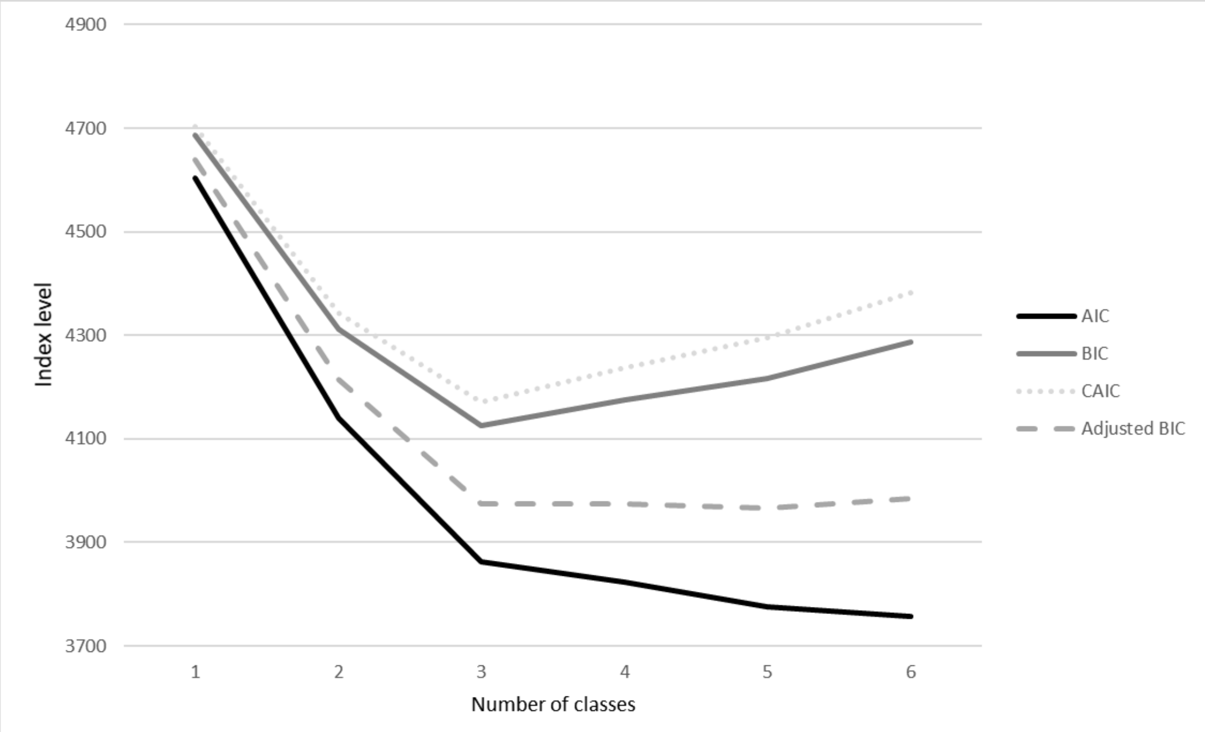

Figure 5.3 Goodness-of-fit indices for establishing correct number of latent classes

5.4.3.2 *Three latent classes describing clusters of perceived built and social environment*

The estimated class-specific probabilities as well as the proportion of the different classes for the variables describing the perceived built and social environment are shown in Table 5.2. The latent class 1 (LC1) consisted mainly of retired individuals reporting low social engagement, high peer support for daily activities, but low support for emergencies and lower scores in peer compassion. Most individuals of this class reported being unsatisfied with their living situation (58%) and living proximal to public transport facilities, but distal to sports facilities and quiet/green places (85%). This class was the smallest with 22% of the study population.

In latent class 2 (LC2), 75% of individuals lived with a partner. This class showed similar values to the LC3 for the occupational status and the social environment. All members of this class were living close to social places and most lived close to public transportation (95%) but showed no difference across the proximity to sports facilities. 37% of the study population was categorized to this class.

Latent class 3 (LC3) consisted of individuals, who predominantly lived with a partner (82%) and were working full-time (37%) or retired (30%). Members having high values in social environment variables characterized the class. Nearly all participants reported living distant to social places (99%) and sports facilities (86%), but close to public transportations (73%). The highest proportion of participants was clustered in this class (41%).

Both the LC2 and LC3 were not different across values of social engagement and proximity to quite/green places and showed high values of satisfaction with the living situation (apartment and neighbourhood). Compared to the LC3, female were less likely to belong to the LC1. Being older increased the probability of belonging to LC1, while higher education decreased the probability of belonging to the LC1 (Table 5.10A).

Table 5.2 Latent class analysis of social and perceived built environment

Variables (n=1962)	**LC1 (n=432, 22%)**	**LC2 (n=720, 37%)**	**LC3 (n=810. 41%)**
Living alone vs with partner			
Alone	40	25	18
Partner	60	75	82
Occupational status			
Full-time	25	37	37
Part-time	6	15	20
Retired	63	32	30
Retired & Working	7	16	13
Social engagement			
Low	59	31	30
Medium	29	33	38
High	13	36	32
Peer support for daily activities			
Low	38	10	6
High	62	90	94
Peer support in emergencies			
Low	90	14	16
High	10	86	84
Peer compassion			
Low	38	2	2
Middle	41	23	30
High	21	75	67
Satisfaction apartment & neighbourhood			
Low	58	36	29
High	42	64	71
Proximity to social places			
Low	46	0	99
High	54	100	1
Proximity to public transportation			
Low	15	5	27
High	85	95	73
Proximity to sports facilities			
Low	72	56	86
High	28	44	14
Proximity to quite/green places			
Low	74	55	49
High	26	45	51

Values represent class-specific proportions for each variable
LC=Latent Class

5.4.3.3 Latent classes and HRQoL

We observed differences in SF-36 derived median HRQoL scores between the LCs for PF, VT and MH, with consistently lower scores for LC1 (Figure 5.5A). The quantile regressions models showed statistically significant lower scores for LC1, compared to LC3 for VT -3.73 (95%CI:-5.83; -1.63) and MH -2.72 (95%CI: -4.97; 1.86). The LC2 scored statistically significant higher for PF 0.67 (95%CI: 0.03; 1.31), BP 3.50 (95%CI: 1.67; 5.43) and VT 2.24 (95%CI: 0.52; 3.95) (Table 5.4).

Table 5.3 Adjusted association of latent classes derived from built and social environment variables with SF-36 derived HRQoL domains

LCs	GH Coef (95% CI)	PF Coef (95% CI)	BP Coef (95% CI)	VT Coef (95% CI)	MH Coef (95% CI)
1	-1.88 (-4.31; 0.54)	-0.03 (-1.01; 0.94)	-1.33 (-3.86; 1.21)	-3.73 (-5.83; -1.63)**	-2.72 (-4.97; 1.86)*
2	0.24 (-1.37; 1.86)	0.67 (0.03; 1.31)*	3.50 (1.67; 5.43)**	2.24 (0.52; 3.95)*	1.33 (-0.05; 2.71)
3	Reference				

**p<0.05 **p<0.001*
Results were calculated using separate multivariate quantile regression model for each HRQoL domain and adjusting for confounders.
HRQoL was assessed using the SF-36: GH, General Health; PF, Physical functioning; BP, Bodily Pain; VT, Vitality; MH, Mental Health
Confounders: Sex, age, education, smoking status, study area, physical activity guidelines, BMI
Categorical variables represent tertiles
LC1=Retired, low values of social environment & low perception of built environment
LC2= Working full-time or retired, living with a partner, high perception of social- and perceived built- environment – proximate to social places
LC3=Working full-time or retired, living with a partner, high perception of social- and perceived built- environment – distant to social places and sports facilities

5.4.4 Social and perceived built environment and health service utilization

The results of the independent and covariate adjusted associations of the social and perceived built environment variables, respectively with health service utilization are shown in Table 5.4 and Table 5.5. Participants reporting higher satisfaction with apartment and neighbourhood had lower probabilities of visiting therapists in the last 12 months OR=0.92 (95%CI: 0.88; 0.98). We observed consistent positive associations of noise annoyance with all medical services in a dose-response manner.

Table 5.4 Independent associations of variables defining the perceived built environment with health service utilization in the last 12 months

Perceived built environment	Physician visit OR (95% CI)	Hospital visit OR (95% CI)	Therapy visit OR (95% CI)	Combined (physician & hospital) OR (95% CI)
Satisfaction with Apartment and Built Environment	1.02 (0.95; 1.10)	1.04 (0.97; 1.12)	0.92 (0.88; 0.98)*	1.02 (0.94; 1.09)
Proximity to social places	1.02 (0.99; 1-04)	1.00 (0.97; 1.02)	0.99 (0.97; 1.02)	1.01 (0.98; 1.04)
Proximity to public transportation	0.99 (0.86; 1.13)	1.12 (0.97; 1.28)	0.98 (0.97; 1.08)	0.95 (0.83; 1.03)
Proximity to sports facilities	0.95(0.84;1.05)	0.95 (0.86; 1.05)	1.06 (0.98; 1.11)	0.97 (0.82; 1.02)
Proximity to quite/green	1.04 (0.99: 1.11)	0.97 (0.92; 1.03)	0.99 (0.96; 1.04)	1.02 (0.98; 1.09)
Noise annoyance				
Low	Ref			
Middle	1.42 (1.08; 1.89)*	1.00 (0.75; 1.31)	1.25 (1.01; 1.54)*	1.50 (1.12: 1.98)*
High	1.54 (1.27; 2.38)*	1.14 (0.85; 1.54)	1.33 (1.07; 1.67)*	1.67 (1.20: 1.89)*

*p<0.05 **p<0.001
Results were calculated using logistic regression model mutually adjusted for all exposure variables and confounders.
HRQoL was assessed using the SF-36.
health service utilization was self-reported for the last 12 months
Confounders: Sex, age, education, smoking status, study area, physical activity guidelines, BMI
Categorical variables represent tertiles

For the social environment variables, we only observed positive significant associations between social engagement and therapy visits. Participants at middle OR=1.28 (95%CI: 1.01; 1.56) or highest tertile OR=1.29 (95%CI: 1.01; 1.65) of social engagement had higher probabilities of visiting a therapist in the last twelve months.

Table 5.5 Independent associations of the social environment with health service utilization in the last 12 months

Social environment	Physician visit OR (95% CI)	Hospital visit OR (95% CI)	Therapy visit OR (95% CI)	Combined (physician & hospital) OR (95% CI)
Living alone vs. with Partner	1.31 (0.98; 1.76)	0.90 (0.67; 1.20)	1.05 (0.84;1.31)	1.30 (0.98; 1.76)
Occupational status				
Working full-time	Ref			
Working part-time	1.35 (0.90; 1.03)	0.81 (0.50; 1.29)	1.11 (0.83; 1.49)	1.32 (0.89; 2.02)
Retired	1.23 (0.80; 1.88)	1.47 (0.95; 2.28)	0.88 (‘.63; 1.11)	1.25 (0.82; 1.94)
Retired but working	1.09 (0.66; 1.82)	0.84 (0.50; 1.40)	0.74 (0.51; 1.08)	1.10 (0.66; 1.88)
Social engagement	Ref			
Low				
Middle	1.06 (0.79; 1.43)	0.94 (0.69; 1.27)	1.28 (1.01; 1.56)*	1.05 (0.78; 1.42)
High	1.11 (0.80; 1.54)	1.12 (0.81; 1.55)	1.29 (1.01; 1.65)*	1.12 (0.81; 1.57)
Daily Peer Support	0.98 (0.68; 1.40)	1.27 (0.86; 1.87)	1.04 (0.78; 1.38)	1.00 (0.69; 1.45)
Peer support in emergencies	1.22 (0.91; 1.62)	1.28 (0.96; 1.72)	0.97 (0.78; 1.20)	1.12 (0.92; 1.66)
Peer compassion				
Low	Ref			
Middle	1.41 (0.89; 2.22)	0.67 (0.43; 1.07)	0.78 (0.54; 1.11)	1.29 (0.81; 2.06)
High	1.19 (0.76; 1.84)	0.82 (0.96; 1.72)	0.77 (0.56; 1.09)	1.13 (0.72; 1.79)

*p<0.05 **p<0.001
Results were calculated using logistic regression model mutually adjusted for all exposure variables and confounders.
HRQoL was assessed using the SF-36.
health service utilization were self-reported for the last 12 months
Confounders: Sex, age, education, smoking status, study area, physical activity guidelines, BMI
Categorical variables represent tertiles

We did not observe any association for the different latent classes with health service utilization (Table 5.6).

Table 5.6 Differences in health service utilization of latent classes

LCs	Physician visit OR (95% CI)	Hospital visit OR (95% CI)	Therapy visit OR (95% CI)	Combined (physician & hospital) OR (95% CI)
1	0.82 (0.59; 1.14)	0.95 (0.68; 1.33)	1.18 (0.92; 1.52)	0.81 (0.58; 1.14)
2	1.10 (0.82; 1.47)	1.00 (0.75; 1.33)	0.97 (0.78; 1.20)	1.06 (0.79; 1.42)
3	Reference			

**p<0.05 **p<0.001*
Results were calculated using logistic regression models for the respective outcomes, adjusting for confounders.
HRQoL was assessed using the SF-36.
health service utilization were self-reported for the last 12 months
Confounders: Sex, age, education, smoking status, study area, physical activity guidelines, BMI
LC1=Retired, low values of social environment & low perception of built environment
LC2= Working full-time or retired, living with a partner, high perception of social- and perceived built- environment – proximate to social places
LC3=Working full-time or retired, living with a partner, high perception of social- and perceived built- environment – distant to social places and sports facilities

5.4.5 Stratification of outcomes by noise annoyance

Due to its dominant association with HRQoL noise annoyance was not included in the LCA. Instead, the association between the LCs with HRQoL scores were stratified by tertiles of noise annoyance (Table 5.11A). There was a suggestion, albeit not entirely consistent, for the inverse association of LC1 with HRQoL to be stronger among participants with high levels of noise annoyance. We also observed quite consistently that the positive association of LC1 with health service utilization was stronger in persons belonging to the highest tertile of noise annoyance (Table 5.12A).

5.4.6 Sensitivity analysis

We observed no relevant change in associations of variables describing the perceived built- and social- environment with HRQoL after mutually adjusting for all variables (social and built environment variables jointly) in the model (Table 5.13A). When considering health service utilization as outcome, the association with the perceived built environment and the social environment did not substantially change when analysing these domains in a combined model (Table 5.14A).

5.5 Discussion

This study is the first to investigate independent and joint associations of the perceived built and social environment with HRQoL as well as health service utilization.

Perceived built environment

A critical component of the perceived built environment was the satisfaction with the apartment and neighbourhood. This variable associated most strongly with higher scores in all HRQoL domains. The results were consistent after mutually adjusting for variables describing the social environment. The association was visible for both the PCS and MCS. The findings of Wong et al., 2018 agree with our results, even though the study was conducted in a cultural and geographical different region (Hong Kong) and with somewhat younger populations (on average 45 years) compared to the current study (Wong et al., 2018). This implies that the perception of the environment, in this case expressed as the satisfaction with the neighbourhood might affect HRQoL more directly compared to the actual built environment. This implication is underlined by the fact that the mentioned study and the current study were conducted in substantial different settings yet showed similar results.

We further observed a positive association of living proximate to sports facilities with higher HRQoL scores of BP, agreeing with a systematic review showing the importance of access to sports facilities for mobility, physical functioning and ultimately HRQoL (Levasseur et al., 2015). Yet, in this cross-sectional study, we cannot exclude that persons with a better health state and therefore high HRQoL, report the proximity to sports facilities differently. In other words, reverse causation remains a possible explanation.

The observation of higher noise annoyance being associated with poorer HRQoL, especially for MCS, agrees with similar findings from several previous studies (Dratva et al., 2010, Shepherd et al., 2016, Urban and Máca, 2013). In addition, we observed an association of noise annoyance with BP, suggesting that there might be an influence on poorer HRQoL aspects related to PCS. Interestingly, the positive dose-response relationship of this association stayed stable after adjustment for social environment variables. The stratification by noise annoyance showed a clear and strong dose-response relationship towards higher probabilities of seeking healthcare for higher noise annoyance ratings. This findings not only add to the amounts of literature showing adverse health effects of noise annoyance (Hanninen et al., 2014a, An et al., 2018, Dzhambov and Lercher, 2019), but go a step further in showing increased need of healthcare and use of medical services for individuals reporting high noise annoyance ratings.

Our findings indicate that the perceived proximity to cultural, sports and green amenities as well as public transportation may not be major determinants of HRQoL. Regarding these proximity measures, our results contradict some studies (Parra et al., 2010, Roh et al., 2011, Byles et al., 2014), yet agree with another study, assessing 5000 adults in Berlin, Paris, London, New York and Toronto, which suggests no direct association of neighbourhood proximity characteristics with HRQoL for older adults (same age as this study) (Hogan et al., 2016a). On the contrary, the same study found relevant association of proximity measures for younger adults and declare that older adults valued provision of services and healthcare facilities more, compared to proximity to social and recreational amenities. There might be several explanations for the lack of associations with proximity characteristics. Residents with very low HRQoL could be less aware of a city's attractiveness as they leave their apartment less frequently. A hypothesis of Machón et al. 2017 stated that if people live for many decades in the same city they get used to the environment, which could lead to a lack of associations with HRQoL (Machón et al., 2017). However, we can only hypothesize about these clarifications, as there may be numerous unknown factors contributing to individual preferences or aversions when dealing with perceptions of environments. Also, the cross-sectional nature of the study does not allow investigation in the directionality of the associations.

Social environment

The observed positive association of living with a partner, compared to living alone, with MCS and PF of HRQoL - therefore also touching on PCS - was remarkably unaltered when adjusting for variables describing the perceived built environment. These findings were supported by other studies in very different settings highlighting the relevance of solitary living for poorer HRQoL (Liu et al., 2013, Kim and Lee, 2018, Harada et al., 2018).

Compared to full-time working, being retired and moreover being still occupationally active showed constant positive associations with VT, also when adjusting for variables describing the perceived built environment. This association seems quite notable as it surpasses 5 points in effect scores, which in many cases is seen as a clinical cut-off value (Maruish, 2011). The employment status seems to be a critical component, as other studies found also strong associations of differences in occupational status with HRQoL mostly covering MCS (Kim et al., 2018, Kwak and Kim, 2017). A longitudinal study conducted in Italy found that differences in occupational status widen the gap of health inequalities over time (Minelli et al., 2014), which was underlined by a European study finding similar results (Bacci et al., 2017). The consistency in findings with previous studies from different settings indicate a pivotal role of occupational status in phases of pre-retirement and retirement for aging populations. However, evidence also points in the direction that especially young people are vulnerable to health hazards when unemployed or working in precarious conditions (Vancea and Utzet, 2017).

With regard to the variables describing social support and environments, we discovered associations of receiving compassion from peers with MCS of HRQoL. In contrast to other studies (Hassanzadeh et al., 2016, Hong et al., 2018, Salihu et al., 2017), we did not find any significant association with social support, expressed in support from peers for daily activities and in emergencies as well as social engagement.

Combined analysis of the social and perceived built environment – LCA

To improve the understanding and gain a holistic view on the perception of the social and physical environment we applied LCA to define clusters of these describing variables. Two of the three resulting latent classes (LC2 & LC3) seemed to be quite homogenous apart from their level of proximity to sports facilities and quite/green places, while LC1 showed substantial differences in member characteristics. Compared to LC2 & LC3 members of LC1 were mostly retired, reported low perceived values of social environment and low perceptions of the built environment. The further detected differences in socio-demographic characteristics point towards a negative gradient for LC1, meaning that this class might consists of individuals with lower educations, worse lifestyles and overall poorer living situations (Table 5.10A). Yet, the observed associations withstood adjustment for these variables, suggesting that these differences in participant's socio-demographic characteristic did not fully explain the poorer HRQoL of the LC1. Interestingly, the study of van Wijk et al., 2017 reported that the built environment – measured objectively in this case – contributed little to educational inequalities (van Wijk et al., 2017). Nonetheless, our findings of the LCA showed that individuals with lower perceptions of built environments, receive less support from social environments and show lower socio-demographic values. Therefore, combining these parameters and strive towards understanding the complexity of these associations seems critical to us and research should further point in this direction.

We decided to exclude noise annoyance from the LCA analysis as it demonstrated to be a dominant variable in the prior single analysis. Instead we stratified the associations of the LCs with HRQoL by noise annoyance. Higher tertiles of noise annoyance showed stronger inverse associations of LC1 and HRQoL. These findings suggest that in this specific context, noise annoyance does not linearly affect the relationship of environmental perceived parameters with HRQoL but may modify the effect size.

Health service utilization

We observed associations of satisfaction with resident's living situation and a decreased probability to visit therapists in the last 12 months. Similarly to HRQoL analysis, noise annoyance seemed to be a most critical variable, as the association with health service utilization showed an enhanced probability of seeking healthcare covering all measured domains (physician, hospital and therapists). Regarding social environmental variables, social engagement enhanced the probability of visiting therapists. These relations seem to point in different directions, as higher noise annoyance ratings indicate an enhanced health service utilization and on the contrary social engagement points in a positive direction of seeking healthcare. We believe there is a fine line between seeking healthcare due to occurring health issues – for instance due to high noise annoyance ratings - versus not seeking healthcare because of socio-economic barriers. It was shown that stronger support networks contributed to better access to healthcare and overcoming the latter mentioned barriers (Holanda et al., 2015, Yang et al., 2017)

When investigating dissimilarities in seeking healthcare for the LCs, we did not detect relevant associations. These findings imply that even though a cluster showed substantial differences in perceptions of the environment, social support and socio-demographic characteristics, the same cluster did not show associations with the use of medical services. Our findings are contradicting results showing that good neighbourhood characteristics as well as positive social cohesion to peers may contribute to appropriate care seeking behaviour (Zhang et al., 2016). Comparing these clustered analysis to the single domain (perceived built- and social- environment) analysis showed that in this context, single factors, such as noise annoyance and living with a partner predict explained healthcare seeking behaviours better than combined clusters of perception variables.

Strength and limitations

A major strength of this study is the comprehensive consideration of the perception of physical and social environmental parameters with HRQoL outcomes and healthcare seeking behavior. Exhaustive analysis were conducted to investigate independent and joint associations of these parameters. In addition, the investigation with health service utilization, facilitates the transfer of our results to clinical relevant domains plus builds a basis for health economic evaluation of environmental risks and burdens for healthcare systems. The population-based design of this study favors the generalizability of the findings within the Swiss setting. However, due to participation and survivor bias, validity and generalizability are always at risk in longitudinal cohort settings.

Due to the cross-sectional nature of the study, inferring causality and directionality of the associations is not possible. We might have over adjusted certain models and therefore lost some minor associations, for example if physical activity or BMI are in the pathways from perceived social and physical environment to HRQoL and health service utilization. Furthermore, the LCA was showing two quite homogenous classes, which did not add the expected power to our analysis. Finally, due to the restricted sample size there is a chance that some relevant associations went unnoticed.

Conclusion

With this study we confirmed the relevance of perceived social and built environment as important contributing factors to residents' HRQoL. We were able to show that these perceived environmental factors are also associated with health service utilization, pointing to the important contribution that environmental and social policies have on health care costs. Among all measured parameters, living with a partner versus living alone as well as high noise annoyance ratings showed strongest associations with HRQoL and health service utilization.

Competing interests

The authors declare no conflict of interest.

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Appendix A. Supplementary information

5.6 Supplementary information

Table 5.7A Questions on the perceived built and social environment

Satisfaction with Apartment / Neighborhood 0-4 rating scale	How satisfied are you with…
	Your apartment
	Your immediate living environment
	Your residential community
	Your neighborhood
Proximity 1=1-5min 2=6-10min 3=11-20min 4=21-30min 5=>30min	How long does it take to walk from your house to the nearest shops, public facilities or recreation areas?
	Local Shops
	Supermarkets
	Local facilities
	Restaurants, Café, Bars
	Fast-Food-Restaurant
	Public Transportation
	Sports facilities
	Recreation areas
	Quite/Green Places
Noise annoyance 0-10 rating scale	How much are you annoyed by transportation noise in your home when the windows are open?
Living alone / with partner	As the marital status does not necessarily correspond to the way of life at the present time, we ask you to indicate whether you live alone or in partnership
Occupational status	What best describes your current job situation?
	Full-time working (>80%)
	Full-time Housewife/man (<80%)
	Part-time working (<80%)
	Hourly or irregularly employed
	Unemployed
	Not in employment because of education or longer vacation
	Not employed because sick or disabled
	Retired
	Retired but still occupationally active
Social engagement 0-6 rating scale	The following list contains a number of groups or clubs that are visited during leisure time, as well as activities that can be carried out during leisure time. How often do you actively participate in the listed activities?
	Sports Clubs & Fitness Centers
	Hobby clubs, allotment garden clubs, shooting clubs, choirs, music and theater clubs
	Professional organizations, professional associations, unions
	Parish, religious associations
	Political groups/parties
	Self-help groups
	Visits to cultural events, museums
	Hiking groups, card game groups
	Family/Friends/Neighbours Meetings
	Voluntary work
Support in daily activities (No/Yes)	If you need help, can you count on someone to help you with your daily chores (e.g. shopping, cleaning, cooking, or if you should be driven anywhere)
Close peer support 0-4 rating scale	How many people are so close to you that you can rely on them if you have a serious personal problem?
Peer compassion 0-5 rating scale	How much interest and sympathy do other people show in what you do?

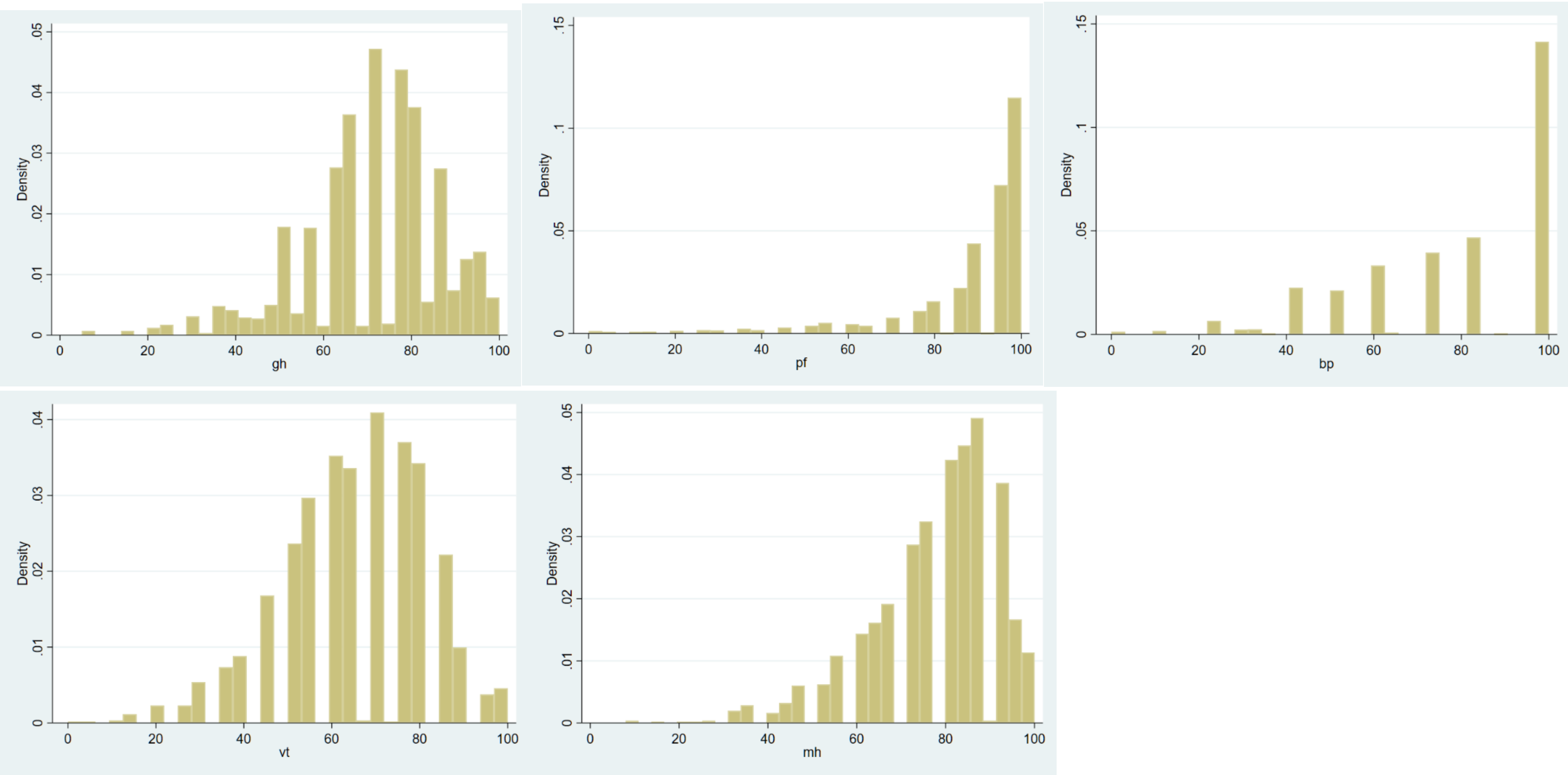

Figure 5.4A Histograms of SF-36 derived health-related quality of life measures (GH, General Health; PF, Physical functioning; BP, Bodily Pain; VT, Vitality; MH, Mental Health)

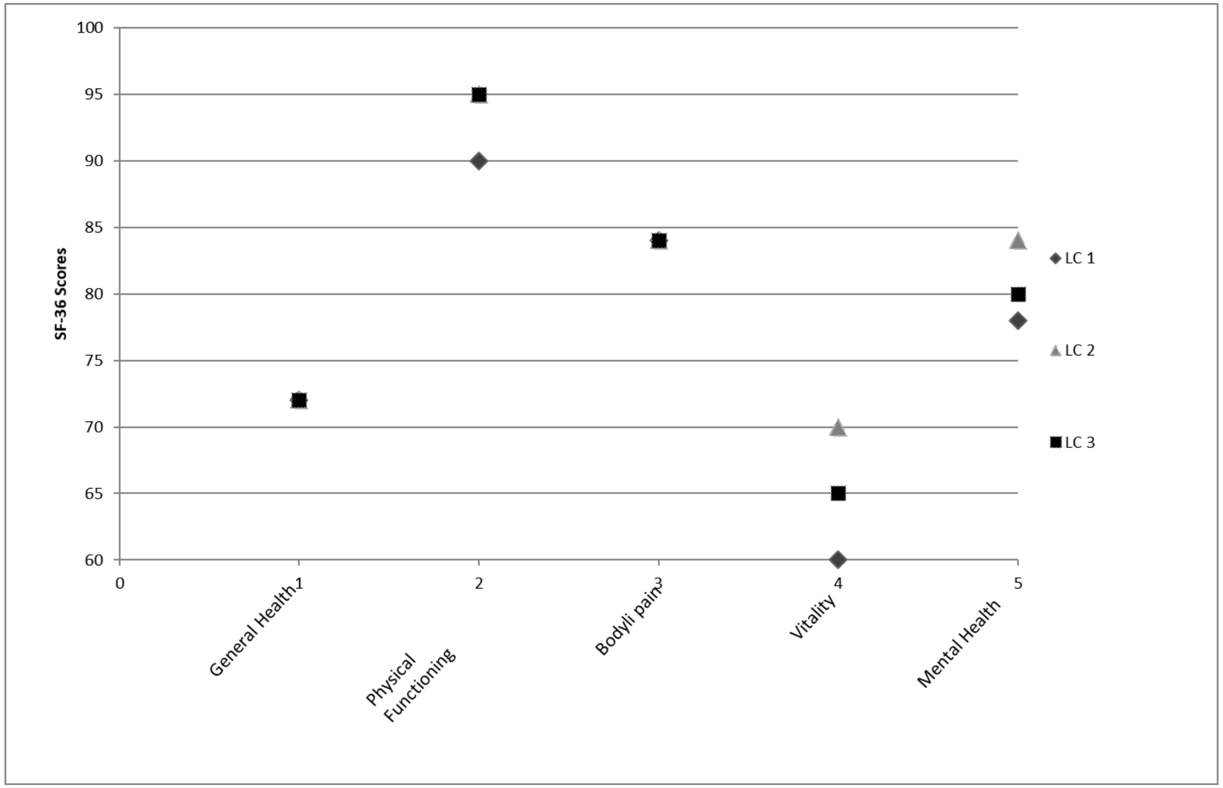

Figure 5.5A Median SF-36 scores of latent classes (LC=Latent Classes)

Table 5.8A Spearman’s rank correlation of perceived built and social environment variables

	Satisfaction neighborhood	Proximity Social Places	Proximity Public Transportation	Proximity Sports Facilities	Proximity Quite/Green Places	Noise annoyance	Living alone vs. with partner	Occupational status	Social engagement	Daily Peer Support	Peer support in emergencies	Peer compassion
Satisfaction neighborhood	1.0000											
Proximity Social Places	-0.0803*	1.0000										
Proximity Public Transportation	-0.0467*	0.2583*	1.0000									
Proximity Sports Facilities	0.0149	0.5275*	0.1701*	1.0000								
Proximity Quite/Green Places	0.1623*	-0.0256	0.0825*	0.1272*	1.0000							
Noise annoyance	-0.1680*	0.0213	-0.0258	-0.0286	-0.0068	1.0000						
Living alone vs. with partner	0.0799*	-0.0995*	-0.0432	-0.0062	0.0602*	-0.0430	1.0000					
Occupational status	0.0134	0.0110	0.0083	-0.0494*	-0.0717*	-0.0614*	-0.1172*	1.0000				
Social engagement	0.0575*	-0.0036	0.0017	0.0506*	0.0368	-0.0116	-0.0068	0.0614*	1.0000			
Daily Peer Support	0.0422	-0.0725*	-0.0275	-0.0190	0.0528*	0.0071	0.1020*	-0.0387	0.0777*	1.0000		
Peer support in emergencies	0.1047*	-0.0070	0.0085	0.0191	0.1282*	0.0002	0.0787*	-0.0850*	0.1242*	0.2017*	1.0000	
Peer compassion	0.1343*	0.0319	-0.0156	0.0091	0.0535*	0.0065	0.0285	-0.0314	0.1564*	0.1117*	0.2989*	1.0000

*=p<0.05

Table 5.9A Summary of model fit indices for 1 to 6 latent classes

Number of latent classes	BIC	Adjusted BIC	AIC	CAIC	Entropy
1	4687.1585	4639.503	4603.4327	4702.1585	1
2	4312.1492	4213.6611	4139.1159	4343.1492	0.5626184
3	4124.642	3975.321	3862.301	4171.642	0.687854
4	4174.517	3974.3638	3822.8687	4237.517	0.67393704
5	4216.4506	3965.4648	3775.4947	4295.4506	0.6314835
6	4286.7608	3984.9425	3756.4975	4381.7608	0.62328219

BIC= Bayesian Information Criterion; AIC= Akaike Information Criterion; CAIC= Consistent AIC

Table 5.10A Socio-demographic characteristics of the latent classes

	LC1	**LC2**	**LC3**
Variables	RRR (95% CI)	RRR (95% CI)	Reference
Gender			
Male	1.00	1.00	
Female	0.68 (0.53; 0,89)*	0.92 (0.74; 1.15)	
Age (years)			
55-65	1.00	1.00	
65-75	2.11 (1.59; 2.80)**	1.21 (0.95; 1.53)	
75+	2.69 (1.90; 3.79)**	0.95 (0.68; 1.31)	
Education level			
Low	1.00	1.00	
Middle	0.51 (0.26; 1.01)	0.85 (0.41; 1.73)	
High	0.44 (0.21; 0.89)*	0.85 (0.41; 1.77)	
Physical activity guidelines (WHO)	0.70 (0.54; 0.91)*	0.74 (0.59; 0.93)*	
Smoking			
Never	1.00	1.00	
Former	0.93 (0.71; 1.22)	0.88 (0.70; 1.10)	
Current	1.22 (0.84; 1.78)	1.14 (0.83; 1.57)	
BMI	1.04 (1.01;1.07)*	1.00 (0.98; 1.03)	

Multinomial logistic regression
*RRR= Relative Risk Ratio; *= p<0.05; **=p<0.001*
Relative risk ratios are mutually adjusted for all variables included in the model as well as for study area
LC1=Retired, low values of social environment & low perception of built environment
LC2=Working full-time or retired, living with a partner, high perception of social- and perceived built- environment – distant to social places and sports facilities
LC3= Working full-time or retired, living with a partner, high perception of social- and perceived built- environment – proximate to social places
BMI= Body Mass Index

Table 5.11A Association of latent classes with health-related quality of life stratified by tertiles of noise annoyance

LCs	GH Coef (95% CI)	PF Coef (95% CI)	BP Coef (95% CI)	VT Coef(95% CI)	MH Coef (95% CI)
		Low noise annoyance (n=804)			
1	-2.78 (-6.22; 0.67)	0.13 (-1.54; 1.80)	-2.65 (-6.01; 0.72)	-1.36 (-5.30; 2.57)	-1.68 (-4.20; 0.84)
2	0.12 (-2.45; 2.69)	1.11 (0.20; 2.02)*	4.26 (1.34; 7.19)*	3.73 (1.17; 6.30)*	1.75 (0.12; 3.38)*
3	Reference				
		Mid noise annoyance (n=595)			
1	-0.24 (--4.15; 3.68)	-1.13 (-3.33; 1.07)	-0.25 (-7.80; 7.30)	-6.12 (-10.39; 1.86)*	-5.62 (-10.12; -1.11)*
2	1.67 (-0.63; 3.98)	1.09 (-0.45; 2.63)	4.13 (-0.95: 9.21)	-0.87 (-4.69; 2.95)	-0.71 (-3.02; 1-59)
3	Reference				
		High noise annoyance (n=563)			
1	-5.01 (-8.67; -1.35)*	-0.89 (-3.47; 1.69)	-5.07 (-11.61; 1.46)	-5.66 (-9.30; -2.02)*	-3.45 (-6.91; 0.02)
2	-3.88 (-7.13; -0.62)*	0.19 (-1.05; 1.43)	-0.28 (-5.13; 4.57)	1.98 (-1.27; 5.24)	3.10 (0.09; 6.12)*
3	Reference				

**p<0.05 **p<0.001*
Results were calculated using logistic regression model mutually adjusted for all exposure variables and confounders.
HRQoL was assessed using the SF-36: GH, General Health; PF, Physical functioning; BP, Bodily Pain; VT, Vitality; MH, Mental Health
Confounders: Sex, age, education, smoking status, study area, physical activity guidelines, BMI
LC1=Retired, low values of social environment & low perception of built environment
LC2= Working full-time or retired, living with a partner, high perception of social- and perceived built- environment – proximate to social places
LC3=Working full-time or retired, living with a partner, high perception of social- and perceived built- environment – distant to social places and sports facilities

Table 5.12A Association of latent classes with uses of medical services stratified by tertiles of noise annoyance

LCs	Physician visit OR (95% CI)	Hospital visit OR (95% CI)	Therapy visit OR (95% CI)	Combined (physician & hospital) OR (95% CI)
		Low noise annoyance (n=804)		
1	0.55 (0.34; 0.90)*	0.65 (0.38; 1.09)	1.14 (0.76; 1.71)	0.53 (0.32; 0.86)
2	0.91 (0.59; 1.41)	0.78 (0.50; 1.21)	0.95 (0.67; 1.35)	0.83 (0.53; 1.29)
3	Reference			
		Mid noise annoyance (n=595)		
1	0.72 (0.38; 1.37)	1.21 (0.62; 2.33)	1.40 (0.89; 2.21)	0.77 (0.41; 1.47)
2	1.20 (0.68; 2.12)	1.57 (0.90; 2.72)	1.13 (0.76; 1.67)	1.22 (0.68; 2.18)
3	Reference			
		High noise annoyance (n=563)		
1	1.85 (0.84; 4.06)	1.27 (0.66; 2.43)	1.00 (0.62; 1.60)	1.78 (0.81; 3.92)
2	1.36 (0.76; 2.44)	1.01 (0.57; 1.78)	0.86 (0.57; 1.29)	1.31 (0.73; 2.36)
3	Reference			

**p<0.05 **p<0.001*
Results were calculated using logistic regression model mutually adjusted for all exposure variables and confounders.
HRQoL was assessed using the SF-36.
Health service utilization was self-reported for the last 12 months
Confounders: Sex, age, education, smoking status, study area, physical activity guidelines, BMI
LC1=Retired, low values of social environment & low perception of built environment
LC2= Working full-time or retired, living with a partner, high perception of social- and perceived built-environment – proximate to social places
LC3=Working full-time or retired, living with a partner, high perception of social- and perceived built-environment – distant to social places and sports facilities

Table 5.13A Combined associations of variables defining the perceived built environment and social environment with health-related quality of life

Perceived built environment	General Health Coef (95% CI)	Physical Functioning Coef (95% CI)	Bodily Pain Coef (95% CI)	Vitality Coef (95% CI)	Mental Health Coef (95% CI)
Satisfaction with Apartment and Built Environment	1.53 (1.11; 1.96)**	0.50 (0.24;0.76)**	1.61 (0.83; 2.39)	1.29 (0.81; 1.76)**	1.03 (0.66; 1.41)**
Proximity to social places	-0.01 (-0.18; 0.17)	0.07 (-0.01; 0.15)	0.15 (-0.12; 0.42)	0.16 (-0.02; 0.34)	0.11 (-0.04; 0.26)
Proximity to public transportation	0.26 (-0.53; 1.05)	0.14 (-0.22; 0.50)	0.97 (-0.59; 2.52)	-0.11 (-1.03; 0.80)	-0.30 (-0.97; 0.36)
Proximity to sports facilities	-0.06 (-0.69; 0.57)	0.24 (-0.08; 0.56)	1.32 (0.32; 2.31)*	0.13 (-0.54; 0.78)	-0.05 (-0.59; 0.50)
Proximity to quite/green places	0.23 (-0.10; 0.57)	0.01 (-0.17; 0.19)	-0.04 (-0.61; 0.52)	0.11 (-0.27; 0.50)	0.25 (-0.05; 0.56)
Noise annoyance					
Low	Ref	Ref	Ref	Ref	
Middle	-2.06 (-2.56; -0.55)*	-0.51 (-1.25; 0.23)	-3.25 (-5.59; -0.91)*	-4.38 (-6.47; -2.30)**	-3.40 (-4.69; -2.11)**
High	-2.00 (-3.74; -0.27)*	-0.74 (-1.46; -0.01)*	-5.10 (-7.82; -2.37)**	-4.18 (-5.95; -2.42)**	-3.95 (-5.60; -2.31)**
Living alone vs. with Partner	0.76 (-0.86; 2.38)	0.70 (-0.08; 1.48)	4.31 (1.36; 7.25)*	2.86 (0.98; 4.74)*	2.68 (1.28; 4.07)**
Occupational status					
Working full-time	Ref	Ref	Ref	Ref	
Working part-time	0.56 (-1.31; 2.43)	0.24 (-0.59; 1-08)	2.10 (-0.57; 4.77)	-0.96 (-3.53; 1.61)	0.61 (-1.21; 2.42)
Retired	-1.81 (-4.12; 0.49)	-0.76 (-2.10: 0.57)	2.11 (-1.87; 6.09)	2.95 (0.32; 5.58)*	2.16 (0.12; 4.20)*
Retired but working	1.48 (-1.08; 4.04)	1.39 (-0.11; 2.89)	6.36 (2.20; 10.52)*	5.32 (3.85; 7.79)**	1.06 (-1.08; 3.20)
Social engagement					
Low	Ref	Ref	Ref	Ref	

Middle	0.43 (-1.20; 2.95)	0.30 (-0.49; 1.09)	-0.28 (-2.69; 2.64)	-0.11 (-1.94; 1.71)	0.14 (-1.20; 1.49)
High	0.22 (-1.39; 1.82)	0.20 (-0.65; 1.05)	0.20 (-2.49; 2.90)	1.16 (-0.91; 3.22)	-0.10 (-1.67; 1.27)
Daily Peer Support	0.87 (-1.15; 2.89)	0.87 (-0.08; 1.82)	-1.32 (-4.48; 1.84)	0.45 (-2.04; 2.95)	1.53 (-0.78; 3.84)
Peer support in emergencies	-0.85 (-2.39; 0.69)	-0.55 (-1.26; 0.17)	-1.17 (-3.38; 1.04)	0.66 (-1.25; 2.56)	0.53 (-0.73; 1.79)
Peer compassion					
Low	Ref	Ref	Ref	Ref	
Middle	1.23 (-1.26; 3.73)	-0.72 (-2.15; 0.70)	-1.56 (-7.17; 4.05)	3.09 (-0.62; 6.81)	3.52 (-0.29; 7.32)
High	2.75 (0.30; 5.20)*	-0.45 (-1.87; 0.96)	0.20 (-5.30; 5.17)	4.98 (1.34; 8.61)*	4.58 (0.81; 8.36)*

**p<0.05 **p<0.001*
Results were calculated using multivariate quantile regression model mutually adjusted for all exposure variables and confounders.
HRQoL was assessed using the SF-36.
Confounders: Sex, age, education, smoking status, study area, physical activity guidelines, BMI
Categorical variables represent tertiles

Table 5.14A Combined associations of variables defining the perceived built environment and social environment with health service utilization

Perceived built environment	Physician visit OR (95% CI)	Hospital visit OR (95% CI)	Therapy visit OR (95% CI)	Combined (physician & hospital) OR (95% CI)
Satisfaction with Apartment and Neighbourhood	1.01 (0.93; 1.09)	1.04 (0.96; 1.12)	0.91 (0.86; 0.97)*	1.00 (0.92; 1.09)
Proximity to social places	1.03 (0.99; 1.06)	1.01 (0.98; 1.04)	0.99 (0.97; 1.02)	1.02 (0.99; 1.06)
Proximity to public transportation	0.98 (0.84; 1.13)	1.09 (0.94; 1.27)	1.01 (0.91; 1.13)	0.94 (0.80; 1.09)
Proximity to sports facilities	0.95 (0.84; 1.08)	0.94 (0.84; 1.05)	1.05 (0.96; 1.15)	0.97 (0.86; 1.10)
Proximity to quite/green places	1.03 (0.98; 1.10)	0.98 (0.92; 1-05)	0.99 (0.94; 1.04)	1.03 (0.96; 1.09)
Noise annoyance				
Low	Ref			
Middle	1.44 (1.06; 1.95)*	1.02 (0.75; 1.39)	1.26 (1.00; 1.59)*	1.51 (1.11; 2.06)*
High	1.58 (1.13; 2.20)*	1.19 (0.86; 1.66)	1.41 (1.11; 1.79)*	1.52 (1.09; 2.12)*
Social environment				
Living alone vs. with Partner	1.26 (0.92; 1.72)	0.91 (0.67; 1.23)	1.08 (0.86; 1.36)	1.25 (0.91; 1.71)
Occupational status				
Full-time	Ref			
Part-time	1.30 (0.86; 1.96)	0.76 (0.47; 1.22)	1.08 (0.80; 1.47)	1.29 (0.85; 1.95)
Retired	1.17 (0.75; 1.82)	1.46 (0.92; 2.30)	0.82 (0.59; 1.15)	1.20 (0.77; 1.88)
Retired but working	0.96 (0.57; 1.62)	0.76 (0.45; 1.30)	0.72 (0.49; 1.06)	0.96 (0.56; 1.64)
Social engagement				
Low	Ref			
Middle	1.09 (0.81; 1.48)	0.95 (0.70; 1.30)	1.29 (1.03; 1.63)*	1.08 (0.79; 1.46)
High	1.14 (0.82; 1.59)	1.14 (0.82; 1.58)	1.31 (1.02; 1.67)*	1.15 (0.82; 1.61)
Daily Peer Support	0.97 (0.68; 1.38)	1.28 (0.86; 1.89)	1.05 (0.80; 1.39)	0.99 (0.69; 1.42)
Peer support in emergencies	1.20 (0.89; 1.60)	1.27 (0.95; 1.71)	0.99 (0.80; 1.15)	1.22 (0.91; 1.64)
Peer compassion				
Low	Ref			
Middle	1.42 (0.90; 2.23)	0.68 (0.42; 1.07)	0.78 (0.55; 1.11)	1.30 (0.81; 2.07)
High	1.19 (0.89; 1.60)	0.81 (0.52; 1.26)	0.81 (0.58; 1.15)	1.15 (0.72; 1.81)

**p<0.05 **p<0.001*
Results were calculated using two separate multivariate logistic regression model (1) perceived built environment; 2) perceived social environment) mutually adjusted for all variables in the respective group, and additionally for confounders.
Health service utilization was self-reported for the last 12 months
Confounders: Sex, age, education, smoking status, study area, physical activity guidelines, BMI
Categorical variables represent tertiles

6 MANUSCRIPT III

The independent association of source-specific transportation noise exposure, noise annoyance and noise sensitivity with health-related quality of life

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6.1 Abstract

Noise exposure is affecting health-related quality of life (HRQoL). There are many modelling approaches linking specific noise sources with single health-related outcomes. However, an integrated approach is missing taking into account measured levels as well as self-reported noise exposure (annoyance and sensitivity) and evaluating their independent association with HRQoL domains. Therefore, we investigated the predictive association of most common transportation noise sources (aircraft, railway and road traffic) as well as self-reported transportation noise annoyance and noise sensitivity with HRQoL using data from SAPALDIA (Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults).

We assessed 2035 subjects, who participated in the second and third wave of SAPALDIA (3&4) and had complete information on exposure, outcome and covariates. At SAPALDIA3, we calculated annual means (Lden) of source-specific transportation noise exposure at the most exposed facade of participant's dwelling floor height. Participants reported noise annoyance on the widely used 11-point ICBEN scale and answered to 10 questions evaluating individual noise sensitivity. To assess the potentially predictive effect of these noise exposures, HRQoL was assessed about 8 years later (SAPALDIA4) using the SF-36. We performed predictive multiple quantile regression models to elucidate associations of noise parameters measured at SAPALDIA3 with median SF-36 scores at SAPALDIA4.

Source-specific transportation noise exposures showed few yet not consistent associations with HRQoL scores. We observed statistically significant negative associations of transportation noise annoyance with HRQoL scores covering mental health components (adjusted difference in SF-36 mental health score between highest vs. lowest annoyance tertile: -2.54 (95%CI: -3.89; -1.20). Noise sensitivity showed strongest and most consistent associations with HRQoL scores covering both general and mental health components (adjusted difference in SF-36 scores between highest vs. lowest sensitivity tertile: Mental health -5.96 (-7.57; -4.36); general health -5.16 (-7.08; -3.24)).

Within all noise parameters, we predominantly observed negative associations of noise sensitivity with HRQoL attaining a magnitude of potential clinical relevance. This implies that factors other than transportation noise exposure may be relevant for this

exposure-outcome relation. Nonetheless, transportation noise annoyance showed relevant associations with mental health components, demonstrating a negative association of self-reported transportation noise exposure with HRQoL.

Key words: Noise, aircraft, railway, annoyance, sensitivity, health-related quality of life

6.2 Introduction

Noise has globally become one of the most common environmental exposures and has been included by the WHO in the first priority list of environmental stressors influencing public health (WHO, 2011). The rapid growth of populations is increasing the demand for aircraft, road and railway transportation while decreasing available space per citizen (Kotzeva and Brandmüller, 2016). Hence, minimizing excessive noise exposure has become a major aspect for urban development and planning policies (Jarosińska et al., 2018).

Exposure to noise - also referred as unwanted or harmful sound - shows adverse effects on physiological and psychological health outcomes (Hanninen et al., 2014b). Recent research has demonstrated that environmental noise exposure may increase the risk of hypertension, stroke and ischemic heart disease (Van Kempen et al., 2018), decrease physical activity (Foraster et al., 2016), promote obesity (Oftedal et al., 2015, Pyko et al., 2015, An et al., 2018, Foraster et al., 2018), increase the risk for type 2 diabetes (Eze et al., 2017, An et al., 2018, Sørensen et al., 2013), and possibly also relate to anxiety and depression (Clark and Paunovic, 2018, Dzhambov and Lercher, 2019).

Studies on the association of transportation noise exposure with HRQoL have found mixed results. A recent systematic review identified 20 studies on the association of transportation noise exposure with HRQoL in adults. Ninety percent of these studies were cross-sectional and only three studies looked at mutually adjusted co-exposures of noise sources (aircraft, railway and road traffic) (Clark and Paunovic, 2018). Most studies used LAeq noise metrics and less than half of the studies used Lden. Further, most studies tended to make poor adjustments for the individual perception and ability to cope with higher noise levels. These personal factors are captured in both noise annoyance (a measure of the grade of disturbance and dissatisfaction from noise exposure (Guski, 1999)), and in noise sensitivity (a measure of the individual variation in perception of noise effects (Smith, 2003)) making it difficult to disentangle the effects of noise on HRQoL. A further study elucidated the relationship of source-specific transportation noise and transportation noise annoyance with HRQoL, yet did not consider noise sensitivity (Héritier et al., 2014).

In addition to noise exposure itself, noise annoyance may be influenced by personal factors such as age and health status, the ability to cope with stress, the duration, frequency and source of exposure as well as noise sensitivity, which is probably the most important non-acoustic factor influencing noise annoyance (Figure 1) (Urban and Máca, 2013). Furthermore, it was shown that different sources of transportation noise (aircraft, railway or road traffic) were related to different noise annoyance ratings at the same decibel level (dB) (Brink et al., 2019). Although the correlation of noise sensitivity and noise annoyance is well-established (Okokon et al., 2015, Shepherd et al., 2010, Urban and Máca, 2013), noise sensitivity is invariant across noise exposure levels (Belojevic et al., 2003, Zimmer and Ellermeier, 1999). Noise sensitivity, a measure for the individual perception of a given level and quality of noise, is indicative of personality traits. The impact of noise sensitivity on annoyance ratings is fairly remarkable as it can lower thresholds of annoyance up to 10 dB. Higher noise annoyance and sensitivity ratings were generally associated with lower HRQoL scores, but these studies did not consider source-specific noise exposure (Shepherd et al., 2016, Shepherd et al., 2010, Welch et al., 2018, Dratva et al., 2010).

To the best of our knowledge, few studies have investigated the triangular relationship of source-specific noise levels, self-reported transportation noise annoyance and noise sensitivity (Fyhri and Aasvang, 2010, Fyhri and Klæboe, 2009), yet no study has investigated these parameters in independent and joint associations with HRQoL in the same population. A combined investigation of these factors will help minimize over-simplification of the relationship between transportation noise and HRQoL (Clark and Paunovic, 2018). Therefore, the objective of this study is to investigate the independent association of source-specific transportation noise levels (aircraft, railway and road traffic), self-reported noise annoyance and noise sensitivity with HRQoL in a predictive longitudinal manner (Figure 6.1).

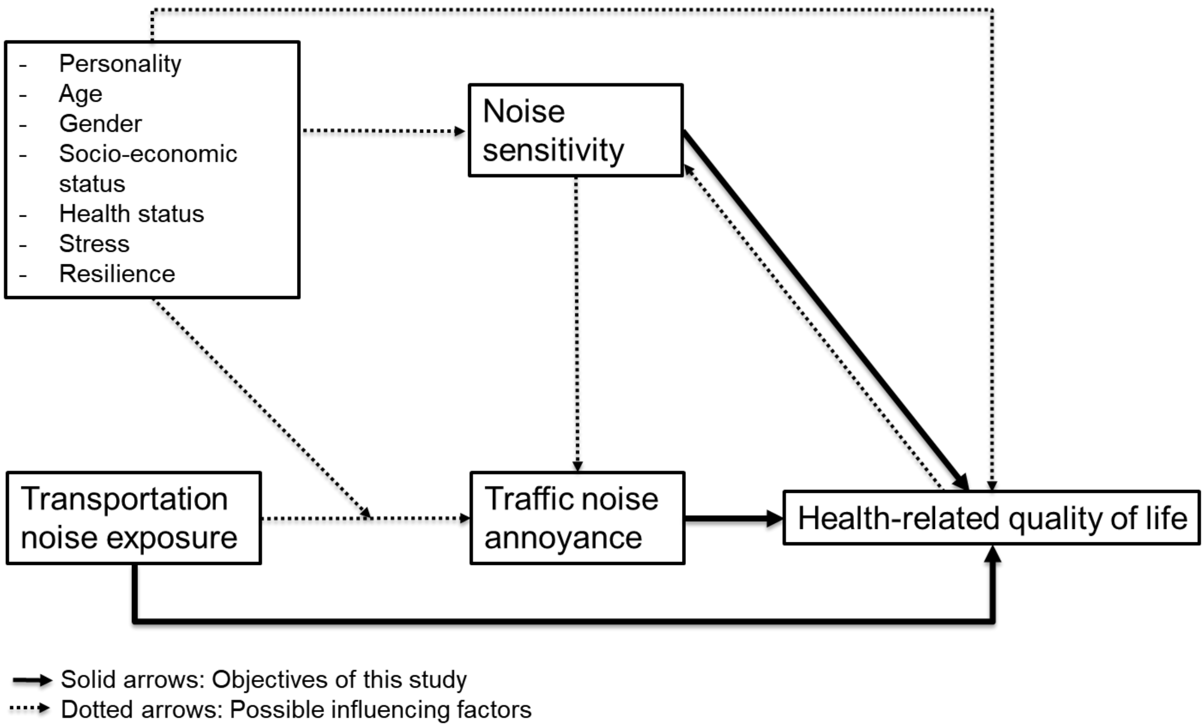

Figure 6.1 Hypothesized pathways of self-reported transportation noise, noise sensitivity and source-specific transportation noise exposure with health-related quality of life

6.3 Materials and Methods

6.3.1 Study Population

The current research used data from SAPALDIA (Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults), a population-based cohort with associated biobank initiated in 1991. In the baseline assessment SAPALDIA1, 9'651 adults (18-62 years) were randomly recruited from eight study areas in Switzerland representing the country's geographic and cultural diversity (Martin et al., 1997). So far, three follow-ups were carried out including 8'047 subjects in SAPALDIA2 (2001/2002) (Martin et al., 1997), 6'088 in SAPALDIA3 (2010/2011) (Endes et al., 2017) and 5'189 in SAPALDIA4 (2017/18). Assessments and information obtained comprised among others, transportation noise modelling at residential addresses, multiple self-administered questionnaires (including items on noise annoyance, noise sensitivity and HRQoL) and health examinations of extended phenotypes over time. High-quality noise data, predicted at address and floor of residence and covering residential history, was available for SAPALDIA2 and SAPALDIA3. Noise annoyance data was available for SAPALDIA1-4, while noise sensitivity data was available only for SAPALDIA3. HRQoL data was available for SAPALDIA2-4. For the present study, we included 2035 participants who had complete information on source-specific transportation noise levels, transportation noise annoyance, noise sensitivity, HRQoL and relevant covariates. This allowed the investigation of the predictive association of noise level, transportation noise annoyance, and noise sensitivity at SAPALDIA3 with HRQoL at SAPALDIA4 (main model). A subset of these participants who also participated in SAPALDIA2 (n = 1835) were used to assess stability of findings (for transportation noise levels and transportation noise annoyance) over a longer period (Robustness models, SAPALDIA2-4) (Figure 6.2).

The SAPALDIA cohort study complies with the Declaration of Helsinki. At each survey, the regional ethics committees granted ethics approval and participants provided written informed consent prior to participation.

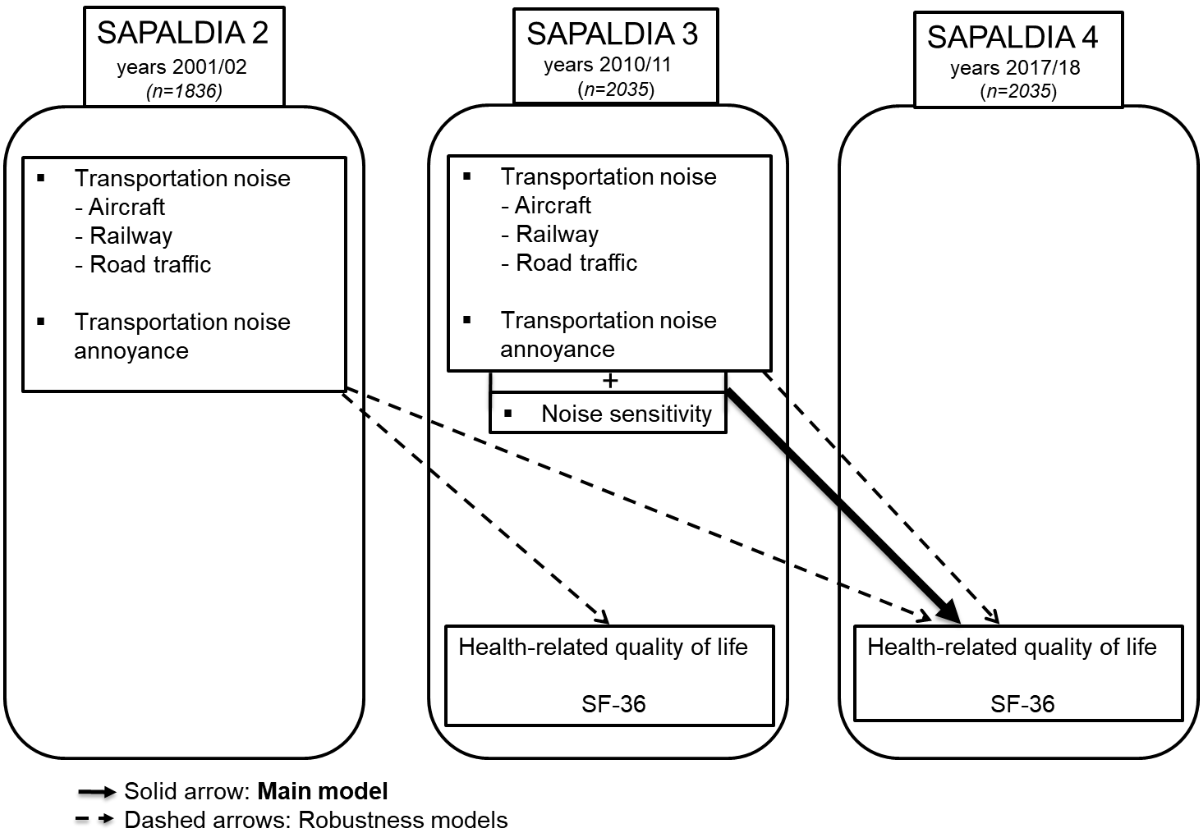

Figure 6.2 Investigated variables at each SAPALDIA survey. In the main model (solid arrow), the predictive association of noise (measured exposure; noise annoyance; noise sensitivity) at SAPALDIA3 on health-related quality of life at SAPALDIA4 was

tested. In the context of 3 separate robustness models (dashed arrows) the predictive association of noise (measured exposure; noise annoyance) with health-related quality of life was tested for SAPALDIA2 to SAPALDIA3; SAPALDIA3 to SAPALDIA4 and SAPALDIA2 to SAPALDIA4.

6.3.2 Outcome measure - Health-Related Quality Of Life (HRQoL)

HRQoL was assessed using the 36-Item Short-Form Health Survey (SF-36), a widely used HRQoL assessment tool, which was validated in large population-based surveys as well as in clinical settings (Hart et al., 2015, Keller et al., 1998). The questionnaire provides a summary of physical component scores (PCS) and mental component scores (MCS), based on eight domains. The PCS comprises physical functioning (PF), bodily pain (BP), role-physical (RP) and general health perception (GH). The MCS reflects vitality (VT), social role functioning (SF), role emotional (RE) and mental health perception (MH). Scores for each subscale range from 0-100, and higher scores indicate better HRQoL (Framework, 1992).

Three domains of the SF-36 (social role functioning, role-physical & role emotional) had only very few distinct values in our sample and the proportion of subjects with the perfect score 100 was between 72% and 83%. Therefore, these domains were not considered in our analyses. As these variables represent minor sub-scales of the SF-36, their exclusion will still allow us to assess MCS and PCS as HRQoL outcomes.

6.3.3 Transportation noise exposure measurements

Aircraft, road and railway noise exposure at the residential address was estimated as annual mean day-evening-night levels (Lden, with respective 5dB and 10dB penalties for evening and night) for 2001 and 2011 (equivalent to the time points of SAPALDIA 2 and 3) using standardized Swiss-wide noise models as previously described in detail (Karipidis et al., 2014). The estimates were made at the most exposed facades on the participant’s residential floors. Aircraft noise exposure was calculated using the FLULA2 model, which includes data on air traffic statistics and flight tracks based on radar data for the major Swiss airports (Thomann et al., 2005).

Road traffic noise was derived by combining the Swiss sonROAD emission model (Heutschi, 2004) with the sound propagation model of StL-86 (von Strassenlärm, 1987). The input data used for these models covered bridges, noise barriers as well as precise traffic statistics. Railway noise exposure was generated using the sonRAIL emission model (Thron and Hecht, 2010) and the propagation part of SEMIBEL (SEMIBEL, 1990). Input data considered railway tracks geometry, noise barriers, train type and data on rail traffic. The exposure modelling was validated with field measurements at 180 sleeping and/or living room windows with sound level meters for one week, at locations primarily exposed to road traffic noise. The comparison of measured vs. calculated exposure levels resulted in a mean difference of the Lden of 1.6 ± 5dB. The tendency to overestimate the exposure in the modelling was primarily caused by noise mitigation measures not considered in the modelling (Schlatter et al., 2017). As described by Vienneau et al. (2019) “prior to epidemiological analyses, noise levels for all exposure definitions were censored at 35 dB for road noise and at 30 dB for railway and aircraft noise. This was done to account for background noise from diffuse sources in this lower range of exposures.” Noise exposures were truncated to 30dB for aircraft and railway noise and 35dB for road traffic noise. Following our previous source-specific noise exposure studies (Eze et al., 2018, Foraster et al., 2018, Eze et al., 2017), these binary truncation indicators for aircraft and railway noise were added to the statistical models as covariates. Only a minor proportion of subjects (9%) were assigned truncated exposure, thus the truncation indicator for road traffic noise was not included in the models. The spearman correlation (Table 6.5A) shows that the source-specific transportation noise Lden are correlated with the night variables (Leq), which gave us reason just to consider the Lden variables for our models.

6.3.4 Self-reported noise sensitivity and transportation noise annoyance

Noise sensitivity was assessed at SAPALDIA3 using the 10-item Weinstein’s noise sensitivity scale, the psychometric properties of which have been previously reported (Weinstein, Weinstein, 1978). Transportation noise annoyance was assessed at SAPALDIA2 and SAPALDIA3 using the 11-point numeric rating scale recommended by ICBEN (Fields et al., 2001). The specific questions used to assess noise sensitivity and transportation noise annoyance are presented in Table 6.1. The distribution of noise sensitivity and noise annoyance in the included participants are shown in Figures 6.5A and 6.6A.

Table 6.1. Questions on transportation noise annoyance and noise sensitivity

Noise sensitivity Scale 10-60	On a scale from 1 to 6 state how much you disagree or agree with the following statements. (If you strongly disagree choose 1, if you strongly agree choose 6, if you are somewhere in between, choose a number between 1 and 6)
	No one should mind much if someone turns up his or her stereo full blast once in a while
	I am easily awakened by noise
	I get annoyed when my neighbours are noisy
	I get used to most noises without much difficulty
	Sometimes noises get on my nerves and irritate me
	Even music I normally like will bother me if I am trying to concentrate
	I find it hard to relax in a place that is noisy
	I am good at concentrating no matter what is going on around me
	I get angry with people who make noises that keep me from falling asleep or getting work done
	I am sensitive to noise
Noise annoyance 0-10 rating scale	How much are you annoyed by transportation noise in your home when the windows are open?

6.3.5 Covariates – confounders and effect modifiers

We selected individual and contextual potential confounders based on prior knowledge, for inclusion in our models. These included participants' age (years), sex (male/female), years of formal education (≤9/>9-12/>12), smoking status (never/former/current), alcohol consumption (≤1/>1 glass per day), moderate-to-vigorous physical activity (<150/≥150 minutes per week) and body mass index (BMI; kg/m^2). On the contextual level, we included study area, neighborhood socio-economic status (an index of socioeconomic position (SEP) based on the 2000 census data covering education and occupation of households members as well as room occupancy and rents of households in a neighborhood (Panczak et al., 2012)). We included greenness index (normalized differential vegetation index based on land surface reflectance) within a 500m buffer around participants' residences calculated for 2014 (Vienneau et al., 2017). Furthermore, we included participants' residential outdoor nitrogen dioxide (NO_2), a marker of traffic-related air pollution and potential confounder of traffic noise (Tétreault et al., 2013, Héritier et al., 2019). Annual mean levels of NO_2 were modelled at SAPALDIA2 by regressing NO_2 field measurements against covariates comprising dispersion model estimates, land-use, traffic, seasonal and climatic variables (adjusted R^2 of 0.8) (Sally Liu et al., 2012) and at SAPALDIA3 using area-specific land-use regression models (adjusted R^2 of 0.5-0.9) (Eeftens et al., 2016).

6.3.6 Statistical analyses

First, we described the characteristics of the study population, summarizing continuous variables as medians and interquartile ranges, and categorical variables as proportions. To elucidate possible descriptive differences of population characteristics to transportation noise annoyance and noise sensitivity we stratified the variables by interquartile range (low/high) of the mentioned noise parameters.

The approach for testing predictive associations of HRQoL with noise parameters is illustrated in Figure 6.2. In the main model we tested the predictive association of noise exposure, transportation noise annoyance and noise sensitivity measured at SAPALDIA3 with HRQoL measured at SAPALDIA4. In the robustness models, we tested the predictive associations of noise exposure and noise annoyance with HQRoL from SAPALDIA2 to SAPALDIA3; from SAPALDIA3 to SAPALDIA4; and from SAPALDIA2 to SAPALDIA4.

In our main model, we applied predictive multiple quantile regressions to assess associations of noise parameters measured at SAPALDIA3 with SF-36 scores measured at SAPALDIA4 given the left-skewed distribution of the HRQoL measures (Figure 6.4A). We adjusted for potential individual-level and contextual confounders measured at baseline, including sex, age, education, smoking status, alcohol consumption, study area, neighborhood socio-economic position, physical activity, BMI, NO_2 and greenness. In the main model, regression models of noise parameters on HRQoL were performed in separate and joint analyses. First, in a multi-exposure model, we assessed the independent association of all exposures with HRQoL. Second, we looked at the alteration of association between the noise parameters and HRQoL when adjusting for the co-exposure variables (transportation noise, transportation noise annoyance and noise sensitivity). Finally, in sensitivity analysis we assessed robustness of our findings on the association of HRQoL with source-specific Lden and transportation noise annoyance by benefitting from data obtained on additional time points and testing various modifications of variables and models (including categorized variables continuously and interaction terms).

In robustness analysis, we investigated the predictive association of noise exposure at SAPALDIA2 respectively with HRQoL at SAPALDIA3 and SAPALDIA4. As noise sensitivity data had not been obtained at SAPALDIA2 it was not possible to test the robustness of the HRQoL association with this parameter over time. Separate multi-exposure regression models were thus run for SAPALDIA 2–3, SAPALDIA 3-4 and SAPALDIA 2-4, each indicating baseline exposure time-points with predictive outcome time-points as illustrated in Figure 6.2, adjusting for covariates at the respective baseline time-points.

We performed all analyses using Stata 15 (Stata Corporation, College Station, Texas) and considered associations as statistically significant at an alpha-level of 0.05.

6.4 Results

Characteristics of the participants included in the main model of noise exposure at SAPALDIA3 with HRQoL at SAPALDIA4 are presented in Table 6.2. Women and men were equally distributed among the study participants and were on average 57 years old. Nearly two third of participants (62%) reported having completed secondary school, middle school or an apprenticeship. Most subjects either never smoked or stopped smoking, did not consume alcohol on a regular basis and met the physical activity guidelines of the WHO. The values of exposure, outcome and covariates of the smaller sample included in the robustness analysis and considering data from the earlier follow up (SAPALDIA2) can be found in Table 6.6A. Furthermore, the characteristics stratified by transportation noise annoyance (low/high) and noise sensitivity (low/high) can be found in Table 6.7A.

Table 6.2 Exposure, outcome and covariates values of the study population for the main model

Variables	SAPALDIA3 *(n=2035)*
SF-36 Score (0-100)	
General Health	72*
Physical Functioning	95*
Bodily Pain	84*
Vitality	65*
Mental Health	80*
Role-Physical	100*
Role-Emotional	100*
Social Functioning	100*
Transportation noise exposure	
Aircraft (dB)	35.2 (6.6)
Road (dB)	54.6 (7.6)
Railway (dB)	34.8 (8.3)
Self-reported noise exposure	
Noise annoyance (0-10)	1.9 (2.4)
Noise sensitivity (10-60)	32.92
Covariates	
Age (Mean, SD)	57 (10.5)
Female	1003 (49%)
Education	
Low	50 (2%)
Middle	1254 (62%)
High	731 (36%)
Smoking Status	
Never	898 (47%)
Former	725 (38%)
Current	282 (15%)
Alcohol	
Regularly	854 (42%)
Physical Activity Guidelines (WHO)	
Sufficiently active	1548 (76%)
BMI	25.9 (4.5)
SSEP	64.7 (9.5)
NO_2	18.7 (7.9)
Greenness	0.6 (0.1)

*Values of SAPALDIA 4
Data are median (interquartile range) for SF-36 variables, mean and number (percent) for continuous and categorical variables (SD).
Education: Low= Primary School (≤ 9years), Middle= Secondary school, middle school or apprenticeship (>9-≤12 years), High= Technical College or University (≥12 years);
Physical Activity Guidelines (WHO):
Inactive: <150 min of MPA and <75 VPA per week
Sufficient: >150 min of MPA or >75 VPA per week

6.4.1 Results from Main Model

6.4.1.1 Predictive associations of transportation noise exposure, self-reported transportation noise annoyance and noise sensitivity (SAPALDIA3) with HRQoL (SAPALDIA4)

The results on the independent association of noise exposure, transportation noise annoyance and noise sensitivity at SAPALDIA3 with HRQoL at SAPALDIA4 (Table 6.3), showed negative associations of railway noise exposure with GH by -1.45 (95%CI: -2.54; -0.36) and VT by -1.57 (95%CI: -2.71; -0.43) points in score per 10dB increase of Lden. We observed statistically significant negative associations of the highest tertile of noise annoyance with HRQoL, decreasing the scores of BP by -3.85 (95%CI: -7.03; -0.67), of VT by -2.84 (95% CI: -4.70; -0.67) and of MH by -2.54 (95%CI: -3.89; -1.20) points in scores. High noise sensitivity ratings constantly showed negative associations with all HRQoL domains demonstrating consistent dose-exposure trends.

Table 6.3 Independent predictive association of transportation noise, noise annoyance, and noise sensitivity at SAPALDIA3 with SF-36 derived HRQoL domains at SAPALDIA4

Noise parameters	GH Coef (95% CI)	PF Coef (95% CI)	BP Coef (95% CI)	VT Coef (95% CI)	MH Coef (95% CI)
Aircraft	0.17 (-2.14; 2.49)	-0.01 (-0.81; 0.80)	-2.77 (-6.22; 0.67)	0.78 (-1.46; 3.02)	0.89 (-0.71; 2.50)
Road	-0.07 (-1.18; 1.04)	0.27 (-0.27; 0.80)	0.89 (-0.84; 2.62)	-0.41 (-1.58; 0.76)	0.13 (-0.70; 0.97)
Railway	-1.45 (-2.54; -0.36)**	-0.37 (-1.07; 0.33)	-0.65 (-2.46; 1.16)	-1.57 (-2.71; -0.43)**	-0.76 (-1.88; 0.36)
Noise annoyance					
Low	Ref				
Medium	-1.37 (-3.12; 0.38)	0.19 (-0.56; 0.94)	-0.04 (-2.43; 2.35)	-0.83 (-2.79; 1.12)	-0.89 (-2.89; 0.53)
High	-0.73 (-2.55; 1.10)	0.03 (-1.06; 1.11)	-3.85 (-7.03; -0.67)**	-2.84 (-4.70; -0.98)**	-2.54 (-3.89; -1.20)***
Noise sensitivity					
Low	Ref				
Medium	-2.19 (-3.76; -0.62)**	-1.29 (-2.09; -0.50)**	-4.00 (-6.46; -1.54)**	-1.54 (-3.30; 0.23)*	-1.27 (-2.41; -0.14)**
High	-5.16 (-7.08; -3.24)***	-1.50 (-2.37; -0.62)**	-7.07 (-9.97; -4.17)***	-6.67 (-8.50; -4.83)***	-5.96 (-7.57; -4.36)***

*p<0.1 **p<0.05 ***p<0.001
Results were calculated by quantile regression model mutually adjusted for all exposure variables and adjusted for confounders and truncation measures for rail & aircraft noise exposure.
Associations of HRQoL with aircraft, road and railway are displayed per 10dB Lden
HRQoL at SAPALDIA 4: GH, General Health; PF, Physical functioning; BP, Bodily Pain; VT, Vitality; MH, Mental Health
Confounders (SAPALDIA3): Sex, age, education, smoking status, alcohol consumption, study area, neighborhood Swiss index of socioeconomic position, physical activity guidelines, BMI, NO2, greenness
Categorical variables represent tertiles

6.4.1.2 Change in association of HRQoL with noise parameters (noise sensitivity, transportation noise annoyance and noise exposure) when adjusting for co-exposures

The correlation between aircraft, road traffic and railway noise exposure with self-reported transportation noise annoyance and noise sensitivity is presented in Table 6.5A.

The association of noise sensitivity with GH and MH remained materially unaltered when adding transportation noise annoyance to the model, while for PF, BP and VT the associations slightly decreased, but remained statistically significant (Table 6.4). By adding the source-specific noise exposures, the association of noise sensitivity with HRQoL increased again for all domains except PF. Having all exposures in the model (Table 6.3) did not substantially change the effect of noise sensitivity on HRQoL.

The associations between noise annoyance and HRQoL were somewhat more sensitive to adjustment. After adjustment for noise sensitivity, the effect of noise annoyance on GH decreased. However, the effects on the other domains remained consistent. Noise annoyance associations remained stable for most HRQoL domains when adding the transportation noise exposures, except for a slight increase of the negative association with BP.

As for the transportation noise exposures, when adjusting for transportation noise annoyance the association with HRQoL remained quite stable. While there was a tendency for noise annoyance to attenuate the negative association of GH and VT with railway noise, adding noise sensitivity had the opposite effect.

Table 6.4. Change in predictive associations of noise sensitivity, transportation noise annoyance and noise exposures (SAPALDIA3) with HRQoL (SAPALDIA4), when adjusting for co-exposures

	GH Coef (95% CI)	PF Coef (95% CI)	BP Coef (95% CI)	VT Coef (95% CI)	MH Coef (95% CI)
Noise sensitivity					
Low	Ref				
Medium	-1.93 (-3.55; -0.30)**	-1.37 (-2.14; -0.59)**	-4.53 (-6.61; -2.44)***	-2.64 (-4.46; -0.81)**	-1.87 (-3.24; -0.49)**
High	-4.95 (-6.76; -3.15)***	-3.53 (-2.53; -0.86)***	-8.01 (-10.54; -5.48)***	-7.43 (-9.34; -5.51)***	-6.68 (-8.44 ; -4.92)***
Noise sensitivity		***+ transportation noise annoyance***			
Low	Ref				
Medium	-1.89 (-3.48; -2.29)**	-1.49 (-2.33; -0.66)***	-3.73 (-6.01; -1.44)**	-1.81 (-3.71; 0.10)*	-1.19 (-2.46; 0.08)*
High	-4.79 (-6.70; -2.88)***	-1.66 (-2.57; -0.75)***	-7.14 (-9.82; -4.46)***	-6.35 (-8.45; -4.25)***	-6.18 (-7.84 ; -4.51)***
Noise sensitivity		***+ modelled road, railway and aircraft noise exposure***			
Low	Ref				
Medium	-2.42 (-3.89; -0.95)**	-1.25 (-2.03; -0.48)**	-4.04 (-6.52; -1.56)**	-2.17 (-3.91; -0.42)**	-1.86 (-3.10; -0.62)**
High	-5.35 (-7.23; -3.48)***	-1.61 (-2.48; -0.74)***	-8.03 (-10.74; -5.33)***	-7.34 (-9.24; -5.45)***	-6.64 (-8.29; -4.98)***
Noise annoyance					
Low	Ref				
Medium	-1.60 (-3.55; 0.35)	0.13 (-0.54; 0.80)	-0.52 (-2.68; 1.63)	-0.87 (-2.70; 0.94)	-1.10 (-2.45; 0.25)
High	-1.66 (-3.30; -0.02)**	0.01 (-1.08; 1.10)	-4.80 (-7.83; -1.77)**	-4.14 (-5.99; -2.30)***	-2.92 (-4.32; -1.52)***
Noise annoyance		***+ noise sensitivity***			
Low	Ref				

Medium	-1.13 (-2.95; 0.68)	0.36 (-0.42; 1.14)	-0.56 (-2.88; 1.75)	-0.91 (-2.97; 1.14)	-1.38 (-2.87; 0.11)*
High	-0.83 (-2.57; 0.90)	0.16 (-0.95; 1.28)	-4.22 (-7.21; -1.24)**	-3.56 (-5.46; -1.58)***	-2.83 (-4.25; -1.42)***
Noise annoyance		***+ modelled road, railway and aircraft noise exposure***			
Low	Ref				
Medium	-1.25 (-3.17; 0.67)	0.12 (-0.58; 0.83)	-0.53 (-2.55; 1.49)	-1.14 (-2.93; 0.65)	-1.08 (-2.48; 0.31)
High	-1.79 (-3.56; -0.01)**	0.18 (-0.89; 1.26)	-5.37 (-7.97; -2.77)***	-4.25 (-6.20; -2.31)***	-2.89 (-4.45; -1.33)***
Noise exposures					
Aircraft	1.04 (-1.24; 3.32)	-0.14 (-0.70; 0.41)	-2.32 (-5.78; 1.14)	0.19 (-1.83; 2.21)	0.07 (-1.58; 1.73)
Road	-0.66 (-1.77; 0.44)	0.24 (-0.22; 0.71)	0.52 (-0.70; 1.75)	-0.25 (-1.45; 0.95)	-0.10 (-1.00; 0.80)
Railway	-1.40 (-2.46; -0.35)**	-0.31 (-0.82; 0.20)	-1.30 (-3.59; 0.99)	-1.39 (-2.71; -0.08)**	-0.61 (-1.75; 0.53)
		+ transportation noise annoyance			
Aircraft	0.77 (-1.50; 3.04)	-0.15 (-0.95; 0.65)	-2.33 (-4.85; 0.19)*	1.09 (-0.81; 2.99)	0.80 (-1.07; 2.67)
Road	-0.22 (-1.34; 0.91)	0.23 (-0.31; 0.78)	1.11 (-0.31; 2.52)	0.05 (-1.08; 1.18)	0.52 (-0.41; 1.44)
Railway	-1.23 (-2.31; -0.14)**	-0.34 (-0.94; 0.27)	-0.09 (-1.99; 1.81)	-1.32 (-2.61; -0.03)**	-0.11 (-1.20; 0.98)
		+ noise sensitivity			
Aircraft	0.27 (-1.91; 2.47)	0.02 (-0.79; 0.82)	-2.70 (-5.72; 0.32)*	0.24 (-2.18; 2.66)	0.18 (-1.51; 1.86)
Road	-0.26 (-1.277; 0.76)	0.32 (-0.23; 0.86)	0.42 (-1.09; 1.94)	-0.99 (-2.10; 0.11)*	-0.24 (-1.12; 0.64)
Railway	-1.67 (-2.71; -0.63)**	-0.39 (-0.98; 0.20)	-1.22 (-3.06; 0.62)	-1.66 (-2.67; -0.65)**	-0.86 (-1.95; 0.22)

*p<0.1 **p<0.05 ***p<0.001
Results were calculated by quantile regression model adjusted for confounders and truncation measures for rail & aircraft noise exposure
Associations of HRQoL with aircraft, road and railway are displayed per 10dB Lden
HRQoL was assessed using the SF-36 at SAPALDIA 4: GH, General Health; PF, Physical functioning; BP, Bodily Pain; VT, Vitality; MH, Mental Health
Confounders (SAPALDIA3): Sex, age, education, smoking status, alcohol consumption, study area, neighborhood Swiss index of socioeconomic position, physical activity guidelines, BMI, NO2, greenness
Categorical variables represent tertiles

6.4.1.3 Association of HRQoL with noise sensitivity, transportation noise annoyance and transportation noise exposure measured as continuous variables, additionally adjusted for HRQoL, and considering effect modification

The associations of noise sensitivity, transportation noise annoyance, and source-specific transportation noise exposure measured at SAPAPLDIA3 with HRQoL at SAPALDIA4 were confirmed when applying the variables continuously (Table 6.8A), and were not substantially altered by additionally adjusting analyses for HRQoL at SAPALDIA3 (Table 6.9A). Single pollutant models for each noise source in relation to HRQoL were similar to the mutually adjusted models (Table 6.10A). Additionally, by adding interaction terms of the noise parameters with age, gender and education we observed no relevant effect modifications in the association of the noise parameters with HRQoL.

6.4.2 Results from Robustness Models

6.4.2.1 Consistency in the association of HRQoL with transportation noise exposure and transportation noise annoyance across three follow-ups (SAPALDIA2 2001 – SAPALDIA3 2011 – SAPALDIA4 2017)

In this somewhat smaller sample consisting of subjects participating in all three SAPALDIA follow-up examinations, we illustrated the mutually adjusted association of transportation noise exposure and transportation noise annoyance across three follow-up time-points of SAPALDIA in Figure 6.3.

Aircraft noise showed a statistically not significant trend for a negative association with BP over the three follow-ups. Railway noise exposure showed little consistency in its association with domains of HRQoL when compared to the larger sample of the main model and across the different time points. In the smaller sample, there was a tendency for a consistent direction of association with PF and BP. The statistically significant negative associations with GH and VT were only observed in SAPALDIA3 – 4 and SAPALDIA 2 – 4, while the results of SAPALDIA 2 – 3 displayed the opposite. These differences across time points are not explained by differences in sample size, as the negative association of railway noise with GH and VT was observed in the reduced sample irrespective of adjustment for self-reported noise parameters.

The negative association of transportation noise annoyance with HRQoL was observed to be stable in direction over the three follow-ups.

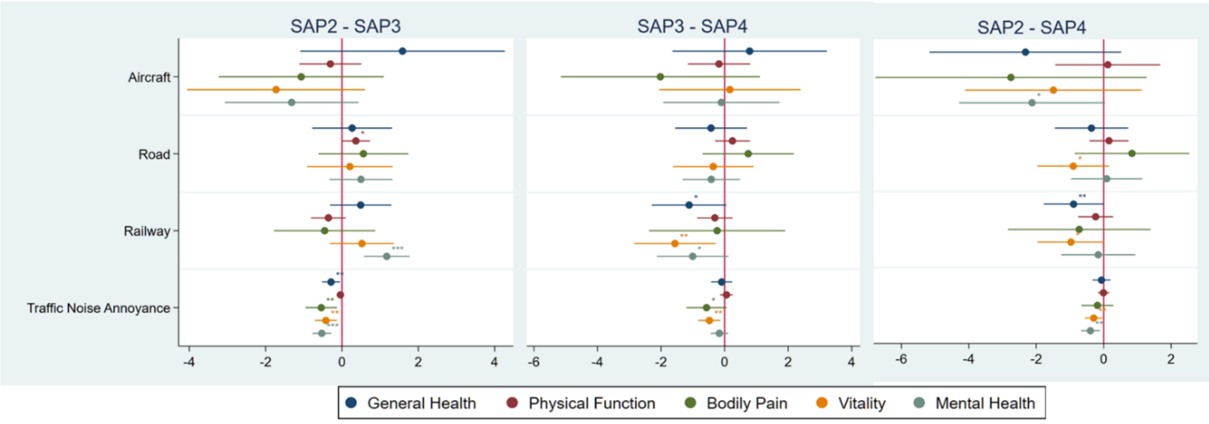

Figure 6.3 Change in outcome, for the independent association of transportation noise exposure with HRQoL domains at different time points, including transportation noise annoyance

6.5 Discussion

This study examined the independent association of source-specific measured noise exposure, self-reported transportation noise annoyance and noise sensitivity with HRQoL in a predictive longitudinal setting. Among all the considered noise parameters, noise sensitivity exhibited the most consistent association with HRQoL and a clear dose-response trend. We also thoroughly investigated this association in joint and independent analysis and thereby addressed interrelations between the co-exposures.

Noise sensitivity

The predictive association of noise sensitivity was notable for both the PCS and MCS domains of the SF-36, and was insensitive to adjustments, categorization and adjustment for HRQoL at baseline (Table 6.9A). The coefficients on the sub-scales GH, BP, VT and MH even surpassed 5 points in effect scores, pointing to the clinical relevance of the observed associations (Maruish, 2011). The values of noise sensitivity followed a Gaussian distribution, which indicate no clear cut-offs for individuals being sensitive or not (Figure 6.5A). The same distribution and data characteristics were found by studies in different settings (Okokon et al., 2015, Shepherd et al., 2010). Thus, the results suggest that at each level of noise sensitivity in the distribution, an increase in one score point increases the percentage of the population with a relevant reduction in HRQoL. Our results also add further evidence that noise sensitivity is invariant across noise exposure and annoyance levels as displayed in Table 6.5A.

The study of Schreckenberg et al. (2010) only found an association of noise sensitivity and HRQoL domains covering physical health, while the study of Shepherd et al. (2010) and Stansfeld and Shipley (2015) only found associations with mental health components. Our study found strong associations with both the PCS and MCS. We demonstrated that noise sensitivity seems to capture aspects related to future HRQoL that are independent of transportation noise annoyance and transportation noise exposure. Furthermore, our results are consistent with findings from Shepherd et al. (2010) and Stansfeld and Shipley (2015) explaining that noise sensitivity seems being a relevant predictor of noise annoyance.

Transportation noise annoyance

Transportation noise annoyance was mainly related to MCS. Several studies share these results (Dratva et al., 2010, Shepherd et al., 2016, Urban and Máca, 2013). This association proved to be robust throughout the three studied time-points (SAPALDIA2 -1991; SAPALDIA3 - 2001; SAPALDIA4 - 2017). Yet, after adjustment for the co-exposures - noise sensitivity and source-specific transportation noise exposures - the association slightly decreased and was less consistent than for noise sensitivity. Compared to noise sensitivity the values of transportation noise annoyance did not show a Gaussian distribution but instead were very right-skewed (Figure 6.6A). This indicates that most subjects reported not being annoyed by transportation noise. Furthermore, these findings underline that noise annoyance and noise sensitivity are capturing different concepts, despite the fact that the spearman's correlation revealed that transportation noise annoyance was correlated with railway noise and road traffic noise. This correlation has also been shown in other studies (Urban and Máca, 2013).

We can only speculate on the potential reasons for a less consistent association of noise annoyance with HRQoL compared to noise sensitivity. This may either point to the additional relevance of non-transportation noise (Shepherd et al., 2019, Park et al., 2018, Dzhambov et al., 2017) or to noise sensitivity reflecting non-noise related characteristics of participants, such as state of health (Shepherd et al., 2015a, Park et al., 2017, Shepherd et al., 2015b) or personality given that the questions on noise sensitivity were not restricted to transportation noise.

Considering that both noise sensitivity and transportation noise annoyance showed negative associations with HRQoL implies that these self-reported measures may truly have significant impact on people's HRQoL and seem to investigate different domains of the reaction to noise on health outcomes.

Source-specific transportation noise (aircraft, railway and road traffic)

Among the source-specific noise exposures, we did not find any consistent association with HRQoL. It was only when predicting exposure at SAPALDIA3 to outcome at SAPALDIA4 that we found associations of railway noise exposure with the domains GH and VT. These associations were not confirmed at other time points. Nevertheless, the direction of our findings is in line with the recent systematic review of the WHO, stating that there could be a negative association of railway noise on QoL but that further investigations are needed to confirm this association (Clark and Paunovic, 2018). Consequently, we should adapt Figure 6.1 and consider removing the line from transportation noise exposure to HRQoL, as this association remains unclear. However, most likely the absence of consistent associations of HRQoL with measured transportation noise, after adjustment for noise sensitivity and annoyance, rather suggests that noise exposure impacts HRQoL if combined with personality traits vulnerable towards the perception of noise and possibly other environmental stressors.

Among the hypothesized mechanisms underlying transportation noise annoyance and sensitivity with HRQoL, it is likely that an increase in stress hormones, like catecholamine and cortisol, is of relevance. Such an increase may subsequently lead to adverse health effects (Clark and Paunovic, 2018). It is also conceivable that noise annoyance and sensitivity are further influenced by poor health state itself. This bi-directional hypothesis is based on the fact that a degraded health state inhibits the individual response to life stressors, such as transportation noise (Schmidt and Klokker, 2014). This implies that unhealthy individuals may report higher rates of noise annoyance and sensitivity compared to healthy people. Nonetheless, even though there could be reverse causality, the need remains high or even increases for considering transportation and possibly other noise sources as a major risk to well-being.

Strengths and limitations

Strengths of the current study comprise the longitudinal nature of the data, reaching a maximum of 20 years from exposure to outcome. Due to the rich data of this long lasting cohort, most known possible confounders and effect modifiers could be included in the models leading to minimization of biases. SAPALDIA is a general population sample for Switzerland, thus our findings are generalizable to the Swiss adult population. This study is the first to consider transportation noise exposure, transportation noise annoyance and noise sensitivity at the same time in analysis with HRQoL outcomes. The individually assigned noise exposure data covered all major transportation noise sources, and the included SAPALDIA participants are broadly distributed across the country in a mix of urban, suburban and rural areas. Information on transportation noise annoyance was asked in the same manner over the three follow-ups, while questions on noise sensitivity were added at the third follow-up.

Limitations of the study include the fact that information on noise sensitivity was only obtained at one time point of the follow-up. In addition, no information on exposure to noise sources other than transport was available to differentiate between effects of noise annoyance and sensitivity from transport versus other sources. However, this might be a specific issue to the notion of noise sensitivity as it is not specific to transportation noise. More sophisticated statistical analysis could be used (i.e. structural equation models) yet we wanted to focus on a holistic perspective of five HRQoL outcomes and numerous co-exposures and confounders rather than answer the question of directionality. Nonetheless, for future research it would be important to elucidate these aspects to further understand the underlying mechanisms of this triangular relationship and its association with HRQoL

Conclusion

Our novel research findings point to noise sensitivity being inversely associated with physical and mental components of HRQoL in the general population. The observed size of associations are in a clinically relevant range. The more consistent associations with noise sensitivity compared to transportation noise annoyance suggest that sources other than transportation are relevant. We nevertheless also found transportation noise annoyance to be linked to lower scores of HRQoL covering mental health components. The inconsistency of independent associations with source-specific transportation noise suggest, from a HRQoL perspective that noise only if combined with personality traits vulnerable towards the perception of this environmental stressor, shows negative relations to HRQoL domains.

The strong independent association of noise sensitivity and HRQoL should shape public health and clinical interventions to decrease noise exposure from all sources.

Competing interests

The authors declare no conflict of interest.

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Appendix A. Supplementary information

6.6 Supplementary Information

Table 6.5A Spearman's correlation of all exposure variables Lden and Leq at SAPALDIA3 (n=2035*)*

	Noise sensitivity	**Transportation noise annoyance**	**Aircraft (Lden)**	**Road (Lden)**	**Rail (Lden)**	**Aircraft Night (Leq)**	**Road Night (Leq)**	**Rail Night (Leq)**
Noise sensitivity	1							
Transportation noise annoyance	0.1588*	1						
Aircraft 24h (Lden)	-0.0207	-0.0249	1					
Road 24h (Lden)	-0.0065	-0.0480*	0.1751*	1				
Rail 24h (Lden)	0.0199	-0.0559*	0.0223	0.0360	1			
Aircraft Night (Leq)	0.0377	0.0367	-0.7389*	0.0034	-0.0043	1		
Road Night (Leq)	0.0011	0.0599*	-0.1642*	-0.9283*	-0.0167	-0.0044	1	
Rail Night (Leq)	-0.0158	0.3774*	0.0007	-0.0706*	-0.1084*	0.0578*	0.0024	1

* p<0.05

Table 6.6A Characteristics of study participants for the main model and the subsample of earlier SAPALDIA follow-ups

Variables	SAPALDIA 2	SAPALDIA 3
SF-36 (0-100)	*(n=1836)*	*(n=2035)*
General Health	77**	72*
Physical Functioning	95**	95*
Bodily Pain	84**	84*
Vitality	70**	65*
Mental Health	80**	80*
Role-Physical	100**	100*
Role-Emotional	100**	100*
Social Functioning	100**	100*
Transportation noise exposure		
Aircraft	35.0 (8.4)	35.2 (6.6)
Road	54.6 (7.7)	54.6 (7.6)
Railway	36.3 (9.1)	34.8 (8.3)
Self-reported noise exposure		
Noise annoyance (0-10)	2.5 (2.9)	1.9 (2.4)
Noise sensitivity (10-60)	n.a.	32.92
Covariates		
Age (Mean, SD)	49 (10.5)	57 (10.5)
Female	896 (49%)	1003 (49%)
Education		
Low	37 (2%)	50 (2%)
Middle	1121 (61%)	1254 (62%)
High	678 (37%)	731 (36%)
Smoking Status		
Never	885 (48%)	898 (47%)
Former	572 (31%)	725 (38%)
Current	379 (21%)	282 (15%)
Alcohol		
Regularly	729 (40%)	854 (42%)
Physical Activity Guidelines (WHO)		
Sufficiently active	1361 (74%)	1548 (76%)
BMI	25.1 (4.0)	25.9 (4.5)
SSEP	64.6 (9.6)	64.7 (9.5)
NO_2	22.4 (9.7)	18.7 (7.9)
Greenness	0.57 (0.12)	0.6 (0.1)

*Values of SAPALDIA4
**Values of SAPALDIA3
Data are median (interquartile range) for SF-36 variables, mean and number (percent) for continuous and categorical variables (SD).

Table 6.7A Characteristics of study participants for the main model stratified by transportation noise annoyance (low/high) and noise sensitivity (low/high)

Variables	SAPALDIA3	Transportation noise annoyance		Noise sensitivity	
	Entire sample (n=2035)	Low *(n=1159)*	High *(n=876)*	Low *(n=1023)*	High *(n=1012)*
SF-36 Score (0-100)					
General Health	72*	72*	72*	72*	72*
Physical Functioning	95*	95*	95*	95*	95*
Bodily Pain	84*	84*	84*	84*	84*
Vitality	65*	65*	65*	70*	65*
Mental Health	80*	80*	80*	84*	76*
Role-Physical	100*	100*	100*	100*	100*
Role-Emotional	100*	100*	100*	100*	100*
Social Functioning	100*	100*	100*	100*	100*
Transportation noise exposure					
Aircraft	35.2 (6.6)	35.0 (6.5)	35.6 (6.7)	35.4 (6.8)	35.1 (6.3)
Road	54.6 (7.6)	52.4 (7.3)	57.6 (7.0)	54.7 (7.7)	54.5 (7.6)
Railway	34.8 (8.3)	34.3 (7.4)	35.5 (9.3)	35.0 (8.4)	34.6 (8.2)
Self-reported noise exposure					
Noise annoyance (0-10)	1.9 (2.4)	0.2 (0.4)	4.1 (2.2)	1.6 (2.2)	2.2 (2.5)
Noise sensitivity (10-60)	32.9	31.6 (10.9)	34.6 (10.7)	23.9 (5.8)	(41.9 (6.6)
Covariates					
Age (Mean, SD)	57 (10.5)	57 (10.6)	58 (10.4)	58 (10.3)	57 (10.7)
Female	1003 (49%)	551 (48%)	452 (52%)	447 (44%)	556 (55%)
Education					
Low	50 (2%)	23 (2%)	27 (3%)	28 (3%)	22 (2%)
Middle	1254 (62%)	716 (62%)	538 (61%)	664 (65%)	590 (58%)
High	731 (36%)	420 (36%)	311 (36%)	331 (32%)	400 (40%)
Smoking Status					
Never	898 (47%)	546 (47%)	406 (46%)	470 (46%)	482 (48%)
Former	725 (38%)	428 (37%)	339 (39%)	367 (36%)	400 (40%)
Current	282 (15%)	185 (16%)	131 (15%)	186 (18%)	130 (13%)
Alcohol					
Regularly	854 (42%)	478 (41%)	367 (42%)	422 (41%)	423 (42%)
Physical Activity Guidelines (WHO)					
Sufficiently active	1548 (76%)	892 (77%)	656 (75%)	763 (75%)	785 (78%)
BMI	25.9 (4.5)	26.0 (4.6)	25.7 (4.2)	26.6 (4.6)	25. 1 (4.2)
SSEP	64.7 (9.5)	65.7 (9.4)	63.5 (9.5)	64.2 (9.7)	65.2 (9.4)
NO_2	18.7 (7.9)	16.9 (6.9)	21.2 (8.5)	18.5 (7.9)	19.0 (8.0)
Greenness	0.6 (0.1)	0.6 (0.1)	0.5 (0.1)	0.6 (0.1)	0.6 (0.1)

*Values of SAPALDIA 4
Transportation noise annoyance and noise sensitivity were dichotomized at the median to form low and high groups
Data are median (interquartile range) for SF-36 variables, mean and number (percent) for continuous and categorical variables (SD).
Education: Low= Primary School (≤ 9years), Middle= Secondary school, middle school or apprenticeship (>9-≤12 years), High= Technical College or University (≥12 years);
Physical Activity Guidelines (WHO):
Inactive: <150 min of MPA and <75 VPA per week
Sufficient: >150 min of MPA or >75 VPA per week

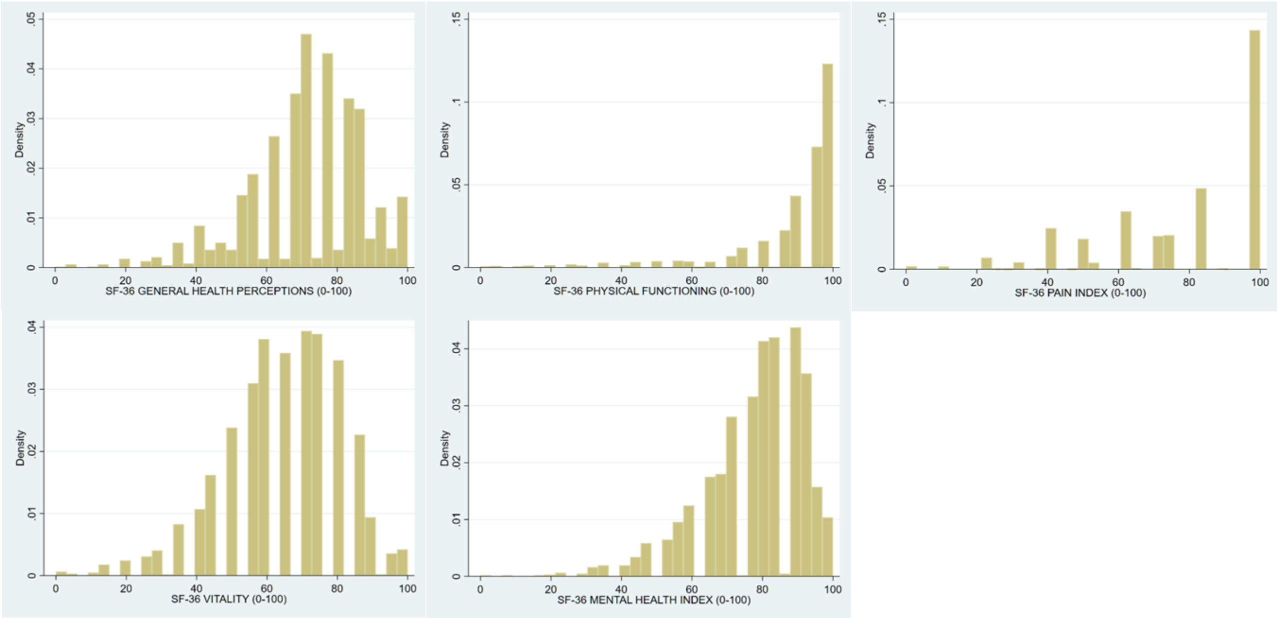

Figure 6.4A Histograms of SF-36 outcomes showing left-skewed distribution

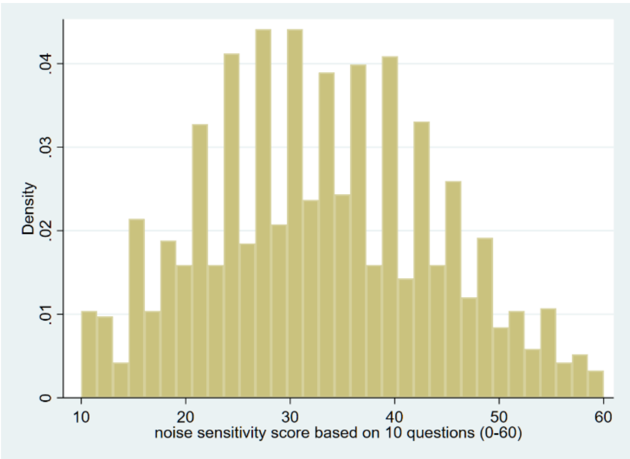

Figure 6.5A Histogram of noise sensitivity showing Gaussian distribution

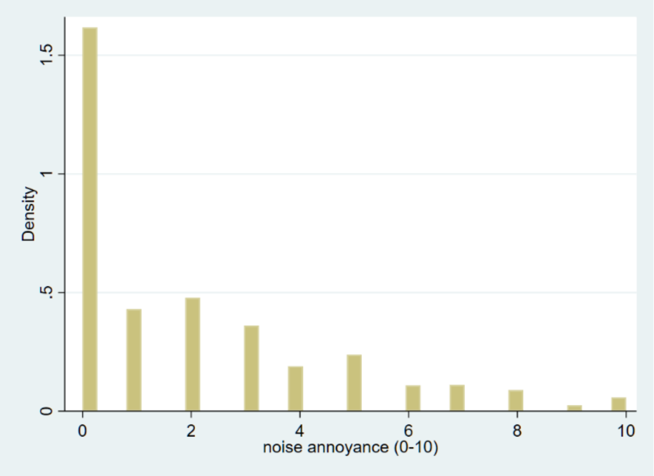

Figure 6.6A Histogram of transportation noise annoyance showing right-skewed distribution

Table 6.8A Independent association of predictive transportation noise, noise annoyance (continuous), and noise sensitivity (continuous) at SAPALDIA3 with SF-36 derived HRQoL domains at SAPALDIA4

	GH Coef (95% CI)	PF Coef (95% CI)	BP Coef (95% CI)	VT Coef (95% CI)	MH Coef (95% CI)
Aircraft	0.03 (-2.18; 2.25)	-0.03 (-0.75; 0.69)	-2.48 (-5.74; 0.79)	-0.11 (-2.21; 2.00)	-0.09 (-1.84; 1.66)
Road	-0.41 (-1.48; 0.66)	0.15 (-0.34; 0.63)	0.74 (-0.90: 2.39)	-0.65 (-1.90; 0.60)	0.19 (-0.72; 1.10)
Railway	-1.34 (-2.40; -0.28)**	-0.35 (-0.95; 0.24)	-0.54 (-2.12; 1.05)	-1.51 (-2.75; -0.27)**	-1.32 (-2.52; -0.11)**
Noise annoyance	-0.04 (-0.33; 0.24)	0.09 (-0.09 (0.26)	-0.57 (-1.14; -0.01)**	-0.35 (-0.69; 0.01)*	-0.20 (-0.45; 0.05)
Noise sensitivity	-1.75 (-2.42; -1.09)***	-0.54 (-0.83; -0.25)***	-2.89 (-3.93; -1.86)***	-2.29 (-3.05; -1.53)***	-2.45 (-3.01; -1.90)***

*p<0.1 **p<0.05 ***p<0.001
Results were calculated by quantile regression model mutually adjusted for all exposure variables and adjusted for confounders and truncation measures for rail & aircraft noise exposure
Associations of HRQoL with aircraft, road and railway are displayed per 10dB Lden
HRQoL at SAPALDIA 4: GH, General Health; PF, Physical functioning; BP, Bodily Pain; VT, Vitality; MH, Mental Health
Confounders (SAPALDIA3): Sex, age, education, smoking status, alcohol consumption, study area, neighborhood Swiss index of socioeconomic position, physical activity guidelines, BMI, NO2, greenness

*Table 6.9A Independent association of predictive transportation noise, noise annoyance, and noise sensitivity at SAPALDIA3 with SF-36 derived HRQoL domains at SAPALDIA4, additionally adjusted for HRQoL at baseline at SAPALDIA3 (*n=1836*)*

	GH Coef (95% CI)	PF Coef (95% CI)	BP Coef (95% CI)	VT Coef (95% CI)	MH Coef (95% CI)
Aircraft	-0.28 (-1.75 – 1.20)	0.70 (0.22 – 1.18)**	-1.37 (-3.46 – 0.72)	0.66 (-0.93 – 2.25)	1.19 (0.03 – 2.35)*
Road	-0.58 (-1.42 – 0.27)	0.04 (-0.33 – 0.42)	0.43 (-0.70 . 1,57)	-0.20 (-1.06 – 0.65)	-0.14 (-0.74 – 0.46)
Railway	-0.71 (-1.37 - -0.05)**	-0.09 (-0.50 – 0.32)	-0.14 (-1.04 – 0.75)	-0.68 (-1.43 – 0.06)*	-0.31 (-1.25 – 0.62)
Noise annoyance					
Low	Ref				
Medium	-0.56 (-1.90 – 0.78)	0.11 (-0.50 – 0.71)	-0.10 (-1.49 – 1.29)	-0.29 (-1.69 – 1.11)	-0.66 (-1.63 – 0.31)
High	0.17 (-1.17 -1.51)	-0.08 (-0.73 – 0.57)	-0.05 (-1.88 – 1.78)	-1.19 (-2.57 – 0.19)*	-1.74 (-3.01 - -0.45)**
Noise sensitivity					
Low	Ref				
Medium	-0.27 (-1.47 – 0.93)	-0.89 (-1.49 - -0.29)**	-0.59 (-1.96 – 0.78)	0.13 (-1.20 – 1.47)	0.12 (-0.83 – 1.06)
High	-2.64 (-4.30 - -0.98)**	-0.62 (-1.22 - -0.01)*	-1.82 (-3.80 – 0.16)*	-2.39 (-3.84 - -0.93)**	-2.05 (-3.55 - -0.55)**

*p<0.1 **p<0.05 ***p<0.001
Results were calculated by quantile regression model mutually adjusted for all exposure variables and adjusted for confounders and truncation measures for rail & aircraft noise exposure
Associations of HRQoL with aircraft, road and railway are displayed per 10dB Lden
HRQoL at SAPALDIA 4: GH, General Health; PF, Physical functioning; BP, Bodily Pain; VT, Vitality; MH, Mental Health
Confounders (SAPALDIA3): Sex, age, education, smoking status, alcohol consumption, study area, neighborhood Swiss index of socioeconomic position, physical activity guidelines, BMI, NO2, greenness
Categorical variables represent tertiles

Table 6.10A Predictive single source-specific transportation noise model not mutually adjusted for co-exposures at SAPALDIA3 with SF-36 derived HRQoL domains at SAPALDIA4 (n=2035)

	GH Coef (95% CI)	PF Coef (95% CI)	BP Coef (95% CI)	VT Coef (95% CI)	MH Coef (95% CI)
Aircraft	-0.01 (-2.08; 2.07)	-0.06 (-0.92; 0.80)	-2.45 (-5.81; 0.91)	0.39 (-1.99; 2.77)	0.99 (-0.62; 2.60)
Road	0.04 (-1.09; 1.16)	0.34 (-1.74; 0.86)	0.69 (-0.72; 2.10)	-0.48 (-1.73; 0.78)	0.04 (-0.86; 0.94)
Railway	-1.25 (-2.36; -0.15)**	-0.47 (-1.21; 0.19)	0.12 (-2.14; 2.38)	-1.50 (-2.73; -0.27)**	-0.98 (-2.21; 0.25)

*p<0.1 **p<0.05 ***p<0.001
Results were calculated by quantile regression model adjusted for transportation noise annoyance, noise sensitivity and confounders
Railway and aircraft noise models additionally adjusted for truncation measures
Associations of HRQoL with aircraft, road and railway are displayed per 10dB Lden
HRQoL SAPALDIA 4: GH, General Health; PF, Physical functioning; BP, Bodily Pain; VT, Vitality; MH, Mental Health
Confounders (SAPALDIA3): Sex, age, education, smoking status, alcohol consumption, study area, neighborhood Swiss index of socioeconomic position, physical activity guidelines, BMI, NO2, greenness

7 DISCUSSION

The aim of this PhD thesis was to stepwise elucidate associations of lifestyle, physiological functioning and the social and built environment with health-related quality of life in an aging population.

7.1 Summary of the main findings

By investigating the association of combined lifestyle and physiological functioning with HRQoL we established three latent classes using LCA. We labeled the classes “Healthy”, “Overweight at risk” and “Obese and unhealthy”. The labeling of the classes already showed that a high BMI or percentage body fat was critical for the assignment of a class. The Obese and unhealthy class reached lowest scores in all HRQoL domains except in the mental health and role-emotional domains compared to both other classes. The difference between the Healthy and the Overweight at risk class was only substantial for physical function and vitality. The probability of belonging to the Healthy class was higher for females, younger participants and higher educated subjects (Manuscript I).

In the analysis of the social and perceived built environment with HRQoL (Manuscript II), we found major associations of living alone versus in partnership as well as higher ratings of noise annoyance with decreased HRQoL. Compared to our prior manuscript the latent classes were not as heterogeneous, but still showed different cluster characteristics pointing towards relevant joint associations when considering HRQoL. In this manuscript, we moreover investigated the associations of the environmental parameters and the latent classes with differences in health service utilization. We found strong associations of the same variables (living alone versus in partnership and transportation noise annoyance) with enhanced use of medical services in the previous 12 months. However, we hypothesized that these results indicate two different directions, as higher noise annoyance ratings may promote an increased use of medical services due to adverse impacts on health, while living with a partner may help overcoming barriers to visit physicians or hospitals.

When we investigated the triangular relationship of source-specific transportation noise (aircraft, road traffic and railway), transportation noise annoyance and noise sensitivity, and its associations with HRQoL we found that noise sensitivity showed strongest and most stable associations with HRQoL domains amongst all measured noise parameters. This association attained a magnitude of potential clinical relevance (surpassing 5 points in effect scores). We further observed relevant inverse associations of transportation noise annoyance with mental health components of HRQoL. Source-specific transportation noise exposures showed no consistent associations with HRQoL scores (Manuscript III).

7.2 BMI and percentage body fat as central lifestyle and physiological functioning parameter related to health-related quality of life

In agreement with evidence in the literature (Gouveia et al., 2017, Knox and Muros, 2017, Dey et al., 2013, Kolotkin and Andersen, 2017, Corica et al., 2015), we observed a particularly strong association of obesity and overweight, measured in BMI and percentage body fat with HRQoL. This variable was most dominant also when considering other prominent health-risk behaviors, such as smoking, alcohol consumption and nutrition. It is widely deemed that obesity acts not as singular risk factor on morbidities or HRQoL, because several lifestyle behaviors, physiological parameters and genetic predispositions lead to obesity as shown in Figure 7.1. Hence, many lifestyle behaviors may lead to obesity or act as protective factor, yet causal inference around these factors is still lacking. This is mostly due to the fact that evidence on associations of lifestyle factors and obesity comes from observational studies, which rarely can allow conclusions around causality. Likewise, data from randomized control trials investigating protective effects of weight loss are prone to bias and confounding as lifestyle interventions are very different compared to treatment or medication interventions in terms of controlling and blinding (Franks and Atabaki-Pasdar, 2017). Nonetheless, what can be concluded from the large amount of evidence is that obesity is a consequence of many unhealthy lifestyle behaviors, even though exact causalities are still missing (Apovian, 2016). From a prevention perspective, it is therefore crucial to target overweight and obese populations, with interventions on all lifestyle domains, as it seems that these populations are affected by many risk factors simultaneously (Volpe et al., 2016).

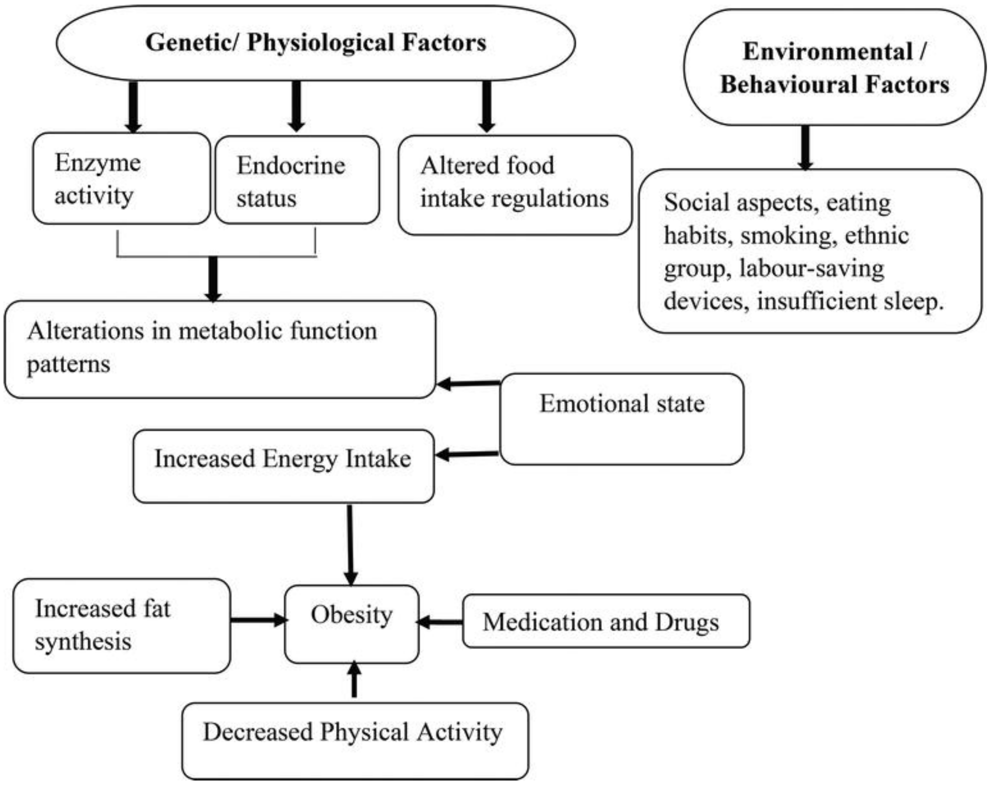

Figure 7.1 Interplay of physiological, lifestyle and environmental factors and effects on obesity (La Berge and Sciences, 2008)

We showed in our first manuscript that being classified into a cluster characterized by overweight or obesity in combination with poor lifestyle and nutrition showed similar risk factors as the ones defining the metabolic syndrome. Furthermore, these interrelations of risk factors can influence many exposure-outcome associations. For instance, aging in combination with overweight or obesity contributes to higher impairments of HRQoL (Zabelina et al., 2009).

Moreover, with aging, substantial losses in muscle mass and muscle quality occur. These aging-induced losses lead in many cases to sarcopenia (Rolland et al., 2008). Especially in obese people, the consequences of sarcopenia are detrimental, often leading to increased risk of falls and fractures, impaired ability to perform activities of daily living, loss of independence and increased risk of death, which all in the end contribute to decreased HRQoL (Batsis and Villareal, 2018). 'Sarcopenic obesity' should therefore be recognized by clinicians and researches as a clinical and scientific priority (Barazzoni et al., 2018).

A quite obvious central association of obesity – as well as sarcopenic obesity - is physical activity. Primarily in individuals aged 55 years and older physical activity can have major benefits for HRQoL (Bouaziz et al., 2017, Abdelbasset et al., 2019). The value of physical activity shows also benefits on related risks of obesity such as hypertension, as it can lower the use of medical treatment and therefore counteract the side effects of the drug often affecting HRQoL (Setters and Holmes, 2017). Due to the quickly aging population and consequent increases of non-communicable chronic diseases, physical inactivity is becoming a major risk factor among older adults. Worldwide figures show that physical inactivity is responsible for 6% of cardiovascular diseases, 7% of type II diabetes mellitus, 10% of breast cancers, and 10% of bowel cancers, which all contribute to 9% of premature deaths (Lee et al., 2012). These numbers show that the above-mentioned lifestyle factors, physiological functioning variables and predominantly obesity create a tremendous burden on the health system.

Finally, obesity is often linked to the presence of many possible comorbidities, which clearly have adverse effects on HRQoL (Ul-Haq et al., 2012, Doll et al., 2000). Obesity was also associated to premature death, yet causal relationships are still to be elucidated (Probst-Hensch, 2010).

7.3 Satisfaction with the built environment and living in partnership as major contributor for enhanced health-related quality of life

The perception of residents’ built environment seems to be crucial for maintaining HRQoL especially in older age. Most probably, it is indeed the perception and the individual satisfaction that is of importance, rather than the objective built environment itself. A recent systematic review (Moore et al., 2018) could not identify major associations of the built environment with HRQoL domains. However, this is not to say that a well-structured neighborhood does not affect HRQoL, but that the perspective of the individual is a key factor, as we were able to show in our second manuscript. This implies, as in many fields today, a so-called participatory approach should be promoted. By considering residents’ opinions when planning built environments, one may ultimately ensure better QoL. However, it has to be mentioned that the questionnaires used for our manuscripts did heavily focus on urban built environments and perhaps, especially for the Swiss context, where we still have large parts of the country in semi-urban or natural environments, these questions should may have been slightly adapted to validly represent the environmental characteristics of Switzerland.

The importance of residents' well-being becomes also noticeable when looking at social isolation or loneliness. A promising solution to tackle this challenge affecting many older adults is deemed to be community-engaged programs (Poscia et al., 2018). This is where the connection of the living (built) environment and the social environment gains importance. Loneliness is a multifaceted issue among older adults, which includes pertinent factors such as socio-demographic attributes or emotional life events. Having high peer support should incline personality traits towards better resilience for these life events; therefore, it is believed that maintaining social relationship throughout aging is pivotal for social well-being. The prevalence of loneliness among older adults is well documented (Luanaigh and Lawlor, 2008), therefore it is a highly relevant issue for public health. Loneliness is an issue that is hard to mitigate, as it is usually difficult to monitor.

Chalise et al. (2010) found that low social support and especially loneliness could predict low QoL values in older adults. Cohen-Mansfield et al. (2016) were able to show a relevant connection between living alone and neighborhood characteristics. Our research identified similar connections of the perceived built and social environment, expressed in latent classes that were clustered according to the above-mentioned characteristics (Manuscript II). Therefore, personalized interventions should be shaped according to neighborhood characteristics and correlates of loneliness, to ensure highest efficacy (Cohen-Mansfield et al., 2016).

7.4 Noise annoyance and noise sensitivity attain a magnitude of clinical relevance for health-related quality of life

By diving deeper into the association of environmental correlates of HRQoL and investigating one of the major environmental stressor (noise), we found remarkable persistent associations of transportation noise annoyance and noise sensitivity with HRQoL. This implies a significant importance of personality traits in the association of noise exposure and HRQoL. Similar to the previously described risk factors in this thesis, high noise sensitivity has been shown to be more prevalent in older adults (Clark et al., 2014). A possible explanation of noise sensitivity having such a significant impact on HRQoL could be the predictive nature of this parameter. It has been shown that noise sensitivity enhances the adverse effects with aging. Hence, the longer an individual shows high noise sensitivity values, the stronger will the impairments be.

Furthermore, it has been found that noise sensitivity could be an indicator of future adverse health effects (Stansfeld and Shipley, 2015), which underlines this hypothesis. It would be particularly valuable when considering environments for aging adults to be able to use the predictive elements of this parameter to minimize its impact on their HRQoL. The magnitude of associations we found in our studies, surpassed several times the clinical cut-off value of 5 points in effect scores of the SF-36, revealing a clinical relevance. These findings are novel and should be well considered. Especially, it should be transmitted to clinicians as this may have implications on treatment and recovery rate. Potentially, it is mostly connected to mental health impairments (Clark et al., 2014, Dzhambov and Lercher, 2019, Shepherd et al., 2010, Stansfeld and Shipley, 2015). A solution could be to include questions on transportation noise annoyance and noise sensitivity in anamnesis of psychiatrists and psychologists, to ensure capturing and considering this environmental stressor.

7.5 The danger of over-simplification – Occam's razor versus Hickam's dictum

One key-shared issue of the three presented manuscripts in this thesis is that we tried to investigate the problems from a holistic perspective to counteract over-simplification, which we believe is often at risk in HRQoL research. Many public health relevant topics are highly multi-dimensional with many internal and external influences leading to multiple diverse outcomes. Primarily, in medical sciences, this problem was recognized early and popularized by the opposing theories of Occam's razor and Hickam's dictum. They are often referenced as contradicting diagnoses meaning that Ockham (right spelled name) was fond of the theory "the simplest solution is most likely the right one" and Hickam contradicted "A man can have as many diseases as he damn well pleases" asserting that multiple causes can result in multiple outcomes (Miller, 1998). It is believed that for many problems, whether in medical sciences or public health Ockham is still right. Yet, especially in epidemiology where many outcomes, such as HRQoL are multifaceted we must realize that there might be a significant bias when making broad assumptions as "one risk factor causes one adverse health outcome". In addition, it seems that sometimes there are major exterior barriers (funding, publication biases, response rate in cohort studies etc.), which inhibit the investigation of such complex phenomena. Nonetheless, with today's advances in technology, especially favoring data capture and analysis in epidemiology, as well as productive international collaborations to combine resources, these barriers should be overcome.

To address this issue we specifically tried to consider an entire view of the underlying problems. For instance in the first manuscript we tried to look at clusters of lifestyle behavior and physiological functioning, as complete as possible within the given circumstances. Many challenges arose when trying to combine risk factors, predictors, confounders and effect modifiers (for example, technical challenges in quantifying these aspects). Moreover, most of the time it comes with a price of losing sensitivity of the results. In our second and third manuscripts, we also aimed at finding holistic solutions for the specific problems. That is why we thoroughly investigated the triangular relationship of source-specific transportation noise, transportation noise annoyance and noise sensitivity and its association with HRQoL, as we believed to contribute significantly to the existing literature, which most of the time considered just one or two of these parameters. In addition, considering the perceived built environment and the social environment in joint analysis helped us to identify how these central aspects of the environment are connected together and relate to HRQoL.

This thesis shows the benefit of considering more complex approaches, even though we recognize the huge public health importance of deep diving into specific singular factors, which was previously more common. However, the importance of considering complexity in public health is arising and deeply relevant as stated by Galea and Vaughan (2017) “First, and centrally, we have a core responsibility to produce science that cuts through the noise, that sheds light on the production of population health around issues of contemporary concern in ways that are useful and can illuminate potential solutions. We suggest that this can be done, even as we recognize and embrace complexity, and that it remains the central responsibility of population health scientists. Second, all science is a metaphor, providing us lenses through which we can see and understand the world better. That understanding stands, in turn, to help us clarify what matters, or what should matter, nudging the broader public conversation toward action. Third, science has a responsibility to bear witness, to provide the documentation to the complexity of population health challenges, even if they fall out of the dominant public din.”

7.6 Relevance of quality of life research

In the following chapter, the relevance of quality of life research will be discussed contemplating different perspectives.

7.6.1 Public health perspective

As already touched on at the beginning of this thesis, probably the most remarkable achievement of the 20th century was to gain about 30 years in life expectancy (Christensen et al., 2009). The large increase in percentage of older adults is a central challenge for public health as this group is also the most vulnerable to emerging health threats (as presently demonstrated by the COVID-19 pandemic). Living longer with increased vulnerability makes it even more important to age in good health (Steptoe and Wardle, 2012). We demonstrated this in our first manuscript and showed how poor lifestyle can adversely be associated with HRQoL. Urbanization as a further evolutionary success of humankind is, from a public health perspective, threatening as it increases vulnerability for psychiatric illnesses (Lambert et al., 2015) and mental health components of HRQoL (Manuscript II).

Another central aspect of the relevance of QoL research for public health is that it serves as prognostic measure for subsequent disability and frailty, as already shown one decade ago (Chida and Steptoe, 2008). By prospectively investigating disease-onsets, QoL can be an intermediate indication for initiations and progressions of morbidities. Due to demographic aging and decreased institutional capacity, the need for care services at older adults' homes is increasing. Many of them suffering from multimorbidity. As a cure is not always foreseeable, managed care at home and assistance for daily tasks are needed. This nursing at home increases the necessity of educated personnel (Verver et al., 2018, van Oostrom et al., 2014). The most important outcome for care services in this case – if a cure is not possible – is maintenance or improvement of QoL (van Leeuwen et al., 2019). To draw this further, the best-proven practices to maintain QoL, is early detection of health adversities through prevention. This is not a novel insight as stated by Rose (1992) "common diseases have their roots in lifestyle, social factors and the environment, and successful health promotion depends upon a population based strategy of prevention". Particularly investing into primary prevention of non-communicable chronic diseases, bears great potentials to the maintenance of well-being and additionally would help relieve the burden on healthcare systems especially in low- and middle-income countries (Probst-Hensch, 2017). Yet even in an economic strong country as Switzerland, we still lack of sufficient investments into primary and secondary prevention, which would certainly support individuals in the second half of their life to maintain adequate QoL levels. However, if the opposite is the case, it most probably leads to higher treatment costs and loss in active workforce (Goettler et al., 2017, Hämmig and Bauer, 2013). As evidence clearly shows that QoL is pivotal for a prolonged healthy life it is a major driver for the argument of the high relevance of prevention and can help shape strategies towards efficient prevention (Bartels, 2015, Martin et al., 2015).

7.6.2 Clinical perspective

Is it relevant for clinicians to measure HRQoL? Apart from the above-mentioned reasons to prevent a disease-onset, the primary relevance is that it is of major importance for the patient. Physicians often misperceive the HRQoL of patients, which has twofold consequences. It can hinder exact diagnosis and hamper determining the optimal treatment (Carter et al., 2006).

To ensure making right medical decisions, it is imperative to have a reference-basis. This reference data can only be gathered in population-based settings to ensure good comparability with exact cut-off reference points. Due to this, it is crucial to connect population-based projects with patient-based settings. Recent developments in medical sciences offered new possibilities of individualized targeted treatments, known as personalized health or precision medicine. These developments resulted in large-scale projects. Exactly in these projects, the linking to public health and population-based studies – usually cohort studies - is crucial, as shown in the large flagship cohort of the US, namely “All of US”, where major investments in personalized health are used to grow this cohort with associated biobank (Sankar and Parker, 2017). It is only through this connection that we can identify what external factors are contributing to pre-morbid and morbid states. We gain highly valuable data and information when combining these settings and it would endorse a step towards closing the gap in bench-to-bedside research. It builds the basis for the possibility to combine routinely collected health data with data of healthy citizens (from a population-based setting) that in best-case scenario has an associated biobank of prospective bio specimen helping the retrieval of new biomarkers that were unknown at the time of collection (Probst-Hensch, 2019). As stated by Probst-Hensch (2019) “one reason for this is that the health status of an individual is governed by long-term exposure to multiple factors that are not adequately and prospectively captured via encounters in the routine healthcare setting.” Hence, this combination would be beneficial for clinicians, researchers, policy makers and lastly but most importantly patients. By capturing all relevant entities, a solid basis is created to ensure multi-faceted evidence-based decision-making. In this way, there is the possibility to greatly enhance the efficacy of HRQoL tools that are currently already well embedded in medical decision-making. This basis could be additionally used to expand endpoints of randomized clinical trials as well as requirements for drug approvals by regulatory agencies (Crosby et al., 2003).

7.6.3 Socio-economic gradient of health-related quality of life

It is well documented that socio-economic differences affect HRQoL (Choi et al., 2015, Read et al., 2016, Stojanović et al., 2018). We aimed in every manuscript at identifying socio-economic differences of participants, which could be relevant for the investigated associations with HRQoL. In our first manuscript, we observed a clear socio-economic gradient across the three latent classes (Healthy, Overweight at risk & Obesity and unhealthy), agreeing with large amounts of literature showing a connection of metabolic syndrome to socio-economic differences (Alkerwi et al., 2012, Pucci et al., 2017, Santos et al., 2008). Participants reporting low educational levels were over-represented in the class scoring lowest HRQoL scores (“Obese and unhealthy”). Individuals with poor lifestyle and physiological functioning characterized this class, as the label is indicating. The well-studied strong association of lifestyle behavior with socio-economic status (Ball et al., 2015, Bonaccio et al., 2012, Livingston and review, 2014, Newton et al., 2017, Prince et al., 2017, Thebault et al., 2018, Volaco et al., 2018) shows the persisting importance of investing in improvements of lifestyles and invaluable promotion of physical activity. It seems that this topic is over-investigated yet still not translated sufficiently into decision-making entities, as obviously shown by the high rates of obesity (WHO, 2020), where physical activity plays a pivotal role. However, again – even though physical activity is recognized as major contributor – this negative impact of socio-economic status is multifaceted.

Factors like the understanding of healthy habits, access to sports facilities, green spaces and further built environmental characteristics play a relevant part in this context. Similarly relevant is access to medical services to undergo screenings (i.e. regular precautious testing of biomarkers as blood pressure, glycemia, lipids) or to control and monitor disease risks and treatments (i.e. blood pressure medication) (Ball et al., 2015, Livingston and review, 2014, Bonaccio et al., 2012). We found a same socio-economic gradient in our second paper for the latent class describing bad perceptions of the built environment and low social support.

It is therefore pertinent that researchers, policy-makers and care-giving entities support policies and frameworks with the goal of achieving health equity as in the example of the “Health in All initiative” introduced by the WHO (2014), which states: “Health in All Policies is an approach to public policies across sectors that systematically takes into account the health implications of decisions, seeks synergies, and avoids harmful health impacts in order to improve population health and health equity. It improves accountability of policymakers for health impacts at all levels of policy-making. It includes an emphasis on the consequences of public policies on health systems, determinants of health and well-being.”

A further pivotal factor, from a socio-economic perspective, seems to be active employment. It is hypothesized that the encompassed economic security and social status are major sources contributing to high HRQoL values (Huang and Hung, 2007, Kiadaliri et al., 2013). Financial security through relative income levels is strongly correlated to health outcomes. Major diseases, ranging from ulcers to cardiovascular diseases and depression are much more prevalent in low-income households (Pickett et al., 2015). Moreover, the topic of financial insecurity not only affects the aging generation but is impacting negatively on young adults as well (Weinstein and Stone, 2018). Tracking this problem seems then of major importance, yet tremendously complex and risky. Sircar and Friedman (2018) point out several possible solutions to this problem consisting of basic income guarantee (BIG), conditional cash transfers, or unconditional cash transfers. They conclude “All else held equal, BIG might provide the greatest health gains by providing the most financial security, reaching all people who might benefit, and providing the greatest boon to public health within one or two generations. However, if raising funds to provide BIG entails new, highly regressive revenue streams, or eliminating social welfare programs that provide qualifying households significant levels of resources (such as for health care, housing or social security), BIG risks harming some of the most vulnerable populations. BIG may be particularly promising in countries (or localities) with widespread poverty and no substantial welfare system, where the broad reach of BIG rather than a more targeted approach could be particularly pertinent."

The current COVID-19 pandemic brings as well many socio-economic implications, which will be bound to QoL outcomes, even if yet not discussed. During these pandemic times, it becomes very evident again that vulnerable populations (socio-economically underprivileged people) suffer more from indirect effects as increase of domestic violence, substance abuse and no access to appropriate treatment (Nicola et al., 2020). However, increases in mental health problems and decreases in QoL, following the pandemic and the above-mentioned indirect effects are expected in all populations. As until today most investments in research have been made on the prevention, pathogenesis and therapy of COVID-19, the need to start gathering high-quality data and research to address mental health consequences and provide mitigation plans is imperative (Holmes et al., 2020). Tackling this challenge will need a close collaboration across disciplines, sectors and policies to balance out the mortality of mostly elderly and the potential increases in mental health and losses of QoL in all populations.

7.7 Strengths and limitations

This thesis is based on data of the long-lasting cohort SAPALDIA (1991-present). The longtime observational study experience, added precious value to all manuscripts, which resulted in many advantageous. We were able to include most known possible confounders and effect modifiers from the literature in all models, which helped in discovering precise associations of studied exposure-outcome relationships. In many analyses, we could benefit from the longitudinal nature of the data, mostly expressed in our third manuscript, where we applied a time horizon of 20 years. We strived in all three manuscripts to overcome over-simplification and capture the complexity of theses multifaceted phenomena. Therefore, we performed exhaustive analysis to consider multiple exposure with multiple outcome possibilities. From a methodological point of view, we were able to model patterns into clusters, with the help of LCA. We succeeded in our first manuscript to distinguish poor and healthy lifestyles combined with physiological functioning parameters. Yet, in our second manuscript, we could not totally identify patterns of social and perceived built environments, while this indicates that these stressors are not highly co-occurring in the population yet may interact and influence on the biological level. Overall, this thesis aimed at displaying the holistic notion of HRQoL correlates, considering and focusing on individual and environmental determinants. The population-based design of our studies favors generalizability in Swiss settings. Yet, this point brings us also to a major limiting factor.

The Swiss population seems not to be representative of the global population. Hence, the findings of this thesis will be difficult to replicate in low- and middle-income countries. Especially findings from the second and third manuscript are expected to be difficult to transfer to settings with major differences in population size (density) and income level. On the other hand, the first manuscript might be replicated also in different settings. As most observational research, also this thesis, cannot allow inferences around causality. For some analysis we had a restricted sample size (<2000) and therefore could have missed some relevant associations. Especially in our third manuscript, many individuals were not exposed to noise, which could lead to some biases.

A further limiting factor is the outcome measure. The SF-36 is widely used and is highly important for many medical fields. However, three of the eight domains showed only minimal differences in the study population and had to be excluded most of the time for analysis.

7.8 Outlook and future work

As indicated in prior sections there is a need to translate the large amounts of evidence on the advantageous of early prevention. Therefore, a suggestion is to conduct health economic evaluations pointing towards comparing cost-effectiveness of several programs targeting individual and environmental risk factors. Precisely, seeing budget impact analysis of certain prevention programs would be interesting and has the benefit to compete with state-of-the-art analysis (mostly done by governments and industries) to evaluate treatments.

Furthermore, few studies have investigated genetic predispositions or gene-environment interactions and their associations with HRQoL. Applying an approach to investigate these mechanism and stepwise combine them with lifestyle behaviors and environmental variables would add most important information to understand the complex concept of HRQoL.

Additionally, work could be done in improving HRQoL measures, focusing on conceptualizing what exact data wants to be captured with this measurement and enhancing face validity. There would probably be good funding opportunities for these projects as HRQoL measures are nowadays frequently used in many different sectors.

Lastly and most important, this work should be translated and replicated in low- and middle-income countries where the need remains highest to improve health-related outcomes. It would be highly interesting to see how noise sensitivity and transportation noise annoyance are associated to HRQoL in such different settings of low- and middle income countries, as this analysis was the only one, where we did not find relevant socio-economic gradients. A general lack in this research area is how neighborhood noise or noise from other sources than transportation are interrelated to noise sensitivity, especially considering different settings, as they could vary significantly in exposure and have relevant implications on the studied noise and HRQoL associations in this thesis.

7.9 Conclusion

This PhD thesis primarily adds knowledge to the understanding of major correlates of health-related quality of life in aging populations. By jointly investigating lifestyle behaviors and physiological functioning, we could identify clusters of a heterogeneous population, which resulted in relevant differences of health-related quality of life scores. Clusters characterized by poor lifestyle and with high cardio-metabolic risk values showed lowest scores. We further identified major differences of health-related quality of life between older adults that lived alone or lived with a partner. With regard to environmental health hazards, transportation noise annoyance and noise sensitivity resulted in major correlates of health-related quality of life, in many cases attaining a negative effect magnitude that potentially is of clinical relevance and influences health service utilization and associated costs.

Furthermore, this thesis aimed at displaying how pivotal information on health-related quality of life is, for a wide array of medical and public health topics. The findings of this thesis in addition to many studies investigating health-related quality of life should shape public health interventions for older adults. Aiming especially towards increasing funds for prevention programs and targeted interventions to support socio-economic underprivileged populations in improving health-related quality of life and ultimately achieve health equity in all populations, as this inequality remains the major predictor of adverse health-related outcomes.

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9 APPENDICES

9.1 Appendix 1. Protocol - Harmonization of bio-electrical impedance analysis in standing and lying position for the SAPALDIA cohort

Harmonization of bio-electrical impedance analysis in standing and lying position for the SAPALDIA cohort

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Introduction

Bio-electrical impedance analysis (BIA) is a method to estimate body composition. In both epidemiological and clinical settings BIA is considered a useful tool to predict percentage body fat (Böhm and Heitmann, 2013). The results are based on equations from the resistance of the electrical signals to different tissue cells. Hydrated muscle cells encounter a smaller resistance than fat cells, which have lower water content. Therefore, the water distribution determines the results of the BIA (Nichols et al., 2006).

As water distribution is much different in standing position compared to lying position, outcome measures can be substantially dissimilar – standing BIAs show mostly lower values. Therefore, it is necessary to develop methods to compare measurements across devices and positions (Rush et al., 2006).

In the 4th follow-up of SAPALDIA (Swiss Study on Air Pollution and Lung and Heart Diseases) two different BIA devices were used. In two study centers of SAPALDIA (Aarau & Geneva) both a standing (Tanita MC780) and a lying (Helios) BIA device was used. In the other six centers only lying BIAs where performed.

The major difference of these two devices – apart from the measurement position – is that they use different electrical frequencies and the Helios devices computes no direct outcome measure, such as percent body fat. Hence, there was a need to harmonize the data of these devices to generate comparable results.

The first objective of this study was to harmonize all BIA data (Helios and Tanita) of SAPALDIA4 and the second objective was to validate measurements across devices of the same and of different types in a test sample.

Methods

Study setting

This study was conducted as a nested project of the SAPALDIA4 follow-up. SAPALDIA started in 1991 as a population-based cohort. Initially (SAPALDIA 1) 9’651 adults (18-62 years) were recruited for the cohort, from eight different study areas in Switzerland (Ackermann-Liebrich et al., 2005). The two coming follow-ups were in 2001/2002 (SAPALDIA 2) and 2010/2011 (SAPALDIA 3). SAPALDIA4 was carried out in 2017/2018 and involved 5’148 participants. Participants aged above 55 years (n=1’752) participated in health examinations. Since SAPALDIA3 the BIA is a fundamental part of the health examination and was carried out in all eight study centers.

Subjects

46 SAPALDIA participants were measured in Aarau and Geneva on both device types: Aarau: Tanita1 and Helios BIA08, Geneva: Tanita2 and Helios BIA08. 32 healthy volunteers employed at Swiss TPH were tested on all 7 Helios devices (while the 8th (BIA06) was no longer working) and both Tanita devices.

Measurements

This study tested 7 lying (Helios) and 2 standing BIAs (Tanita MC780). All participants had to empty the bladder before the measurement and it was communicated that no physical activity should be performed prior to the measurement. Furthermore, it was emphasized to only have smallest meals possible 3-4 hours prior the measurement. Participants were advised to lie down for 5 minutes before the BIA started. The outcome values of the Tanita were saved in the respective software (Health Monitor) and were exported via SQL to Excel. The Helios results (resistance and reactance of frequencies) where manually noted in Excel.

Determination of outcome measures for Helios by Kyle et al.

The Helios devices used in SAPALDIA4 give only information on the resistance and reactance of the different electrical frequencies. Therefore, reference equations, such as the one validated by Kyle et al. have to be applied to get outcome values, such as percentage body fat, fat free mass etc. (Kyle et al., 2004).

Kyle formula:

FFM (fat free mass) = -4.104 +0.518*(height in cm)2/resistance50kHz +0.231*weight
+0.130*reactance50kHz +4.229*(1-female)
FM (Fat mass)=weight-FFM
PBF (%Body Fat)=(weight-FFM)/weight*100
(female is a dummy-variable)

Statistical analysis

In order to derive a reference equation for imputing Helios percent body fat (PBF) Kyle definition from Tanita values the SAPALDIA4-sample (consisting of N=46 subjects having measured both) was merged with the Swiss TPH-test sample (N=32 subjects). As in Aarau and Geneva only the Helios device BIA08 was used, just the data of this device from the Swiss TPH-test were used. As Swiss TPH-subjects were measured on both Tanita devices, each of these subjects was entered twice into the data set.

A mixed model with repeated effects for subject was then carried out to derive a reference equation for predicting percent body fat calculated with the Kyle formula using output from Tanita. It was only adjusted for Tanita device, age and BMI (and not for sex, height, and weight which are used later to define %BF Kyle). Although BMI is calculated from height and weight, it is included in the models since it is known to sometimes yield an additional effect. Unfortunately, it is also not possible to adjust for sample (SAPALDIA4 resp. Swiss TPH) because the imputation for of the Helios value is just for the SAPALDIA4 sample.

After imputing the lying measurement values for subjects that only measured standing BIA the Kyle formula was applied to get percent body fat for the entire SAPALDIA sample.

Results

Table 1 shows the characteristics of the study population. 47 SAPALDIA4 subjects completed the measurements on both devices. The gender was equally distributed throughout the study population, while the majority was either having a normal BMI or was overweight. The mean age was 64.7. The Swiss TPH study sample rounded up the SAPALDIA 4 sample in adding younger and leaner subjects.

Table 1. Characteristics of the study population

		SAPALDIA 4	Swiss TPH
Subjects		n=47	n=32
Sex	Female	53.2%	59.4%
BMI	Underweight	0%	3.1%
	Normal	38.3%	68.8%
	Overweight	40.4%	28.1%
	Obese	21.3%	0%
Age	Median (Q1;Q3)	64.7 (60.6; 69.9)	31.0 (27.5; 44.5)
Resistance 50 kHz Helios (lying)	Median (Q1;Q3)	562 (496; 613)	607 (580; 675)
Resistance 50 kHz Tanita (standing)	Median (Q1;Q3)	582 (530; 621)	644 (596; 698)
Reactance 50 kHz Helios (lying)	Median (Q1;Q3)	48 (44; 54)	62 (56; 70)
Reactance 50 kHz Tanita (standing)	Median (Q1;Q3)	56 (53; 63)	69 (64; 76)

1. Comparing original measurements

In a first step, resistance and reactance at 50 kHz (the input parameters of the Kyle-formula) were compared between Helios and Tanita devices. Figures 1 and 2 show scatter plots of the measurements of resistance and reactance at 50 kHz between devices with N=47 SAPALDIA and N=32 Swiss TPH subjects (each Swiss TPH – subjects appears twice). It can be seen in Figure 1 that the measurements for resistance 50 kHz agree quite well between devices. Although the measurements for reactance 50 kHz are substantially higher, the values from both devices are also quite well linearly related. Unlike for resistance 50 kHz the slope of the regression lines seem to differ for reactance 50 kHz.

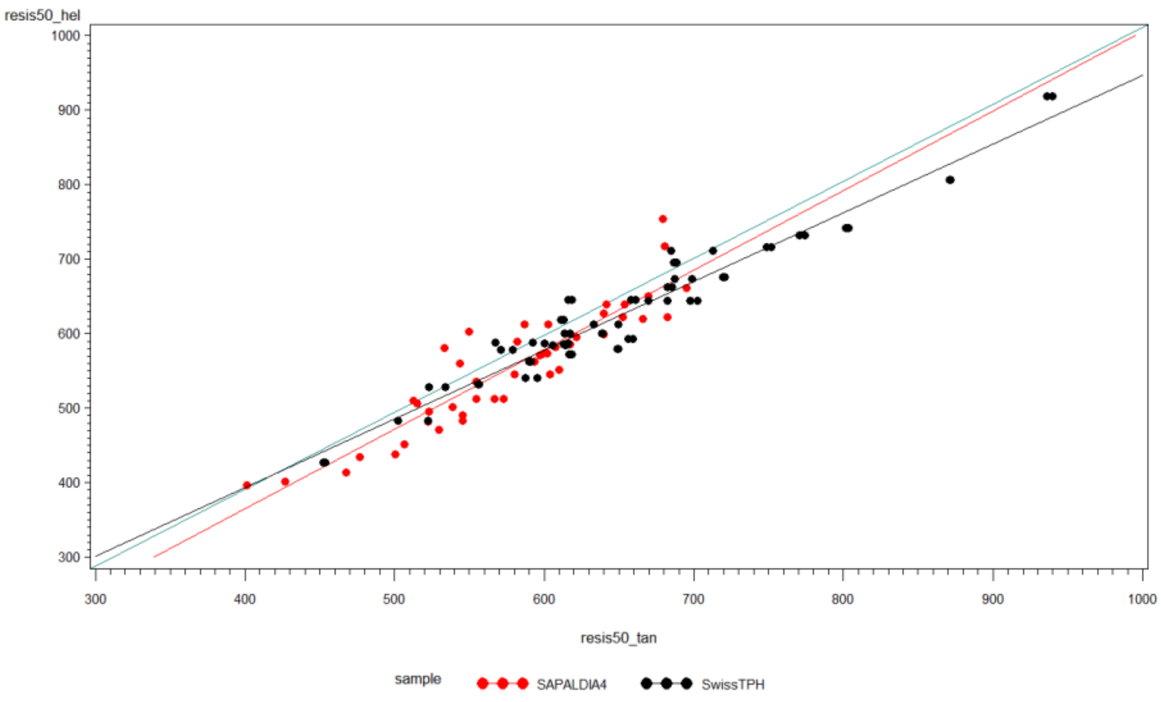

Figure 1: Scatter plot of resistance 50 kHz measurements of both devices including regression lines and 1:1 - line

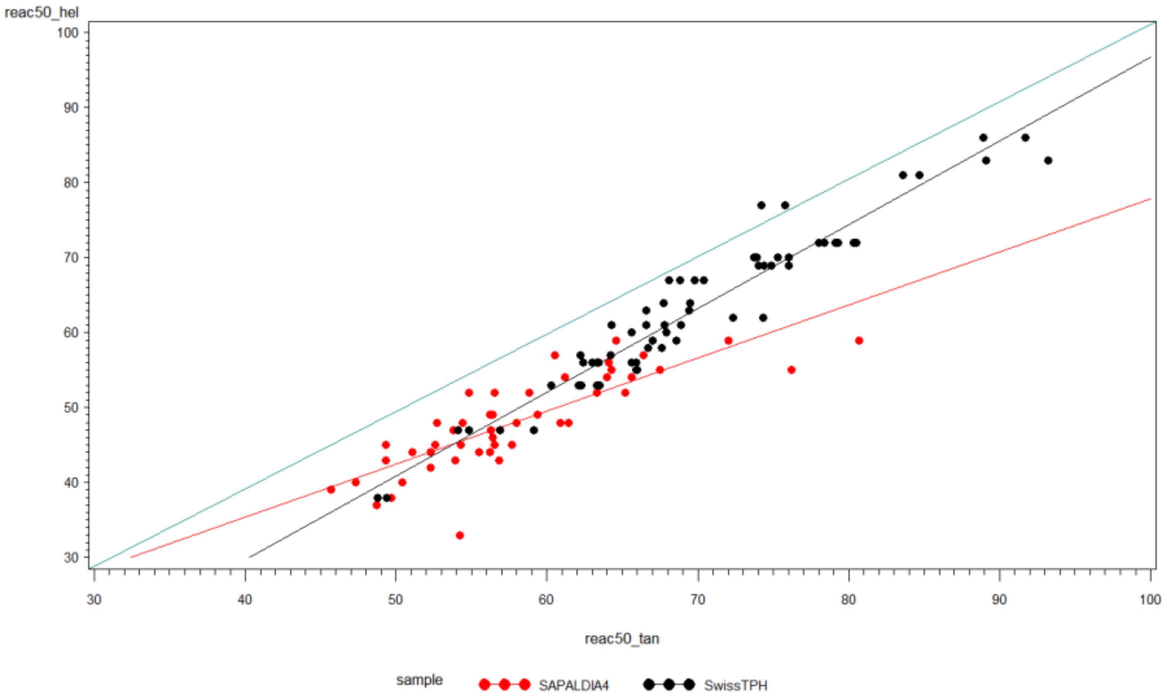

Figure 2: Scatter plot of reactance 50 kHz measurements of both devices including regression lines and 1:1 – line

2. *Predicting %BF Kyle from %BF Tanita and other co-variates*

A mixed model was applied to predict % Body Fat (Kyle definition) from % Body Fat (Tanita) and other input variables as shown in the following table (the variable resistance 50 kHz (Tanita) and the categorical variable for Tanita devices 1 and 2) were not contributing to the model).

Table 2: Prediction % Body Fat (Kyle definition) from % Body Fat (Tanita)

Effect	Estimate	SE	DF	t Value	Pr > |t|
Intercept	114.59	21.8995	98	5.23	<.0001
Tanita (%BF)	0.6775	0.04344	98	15.60	<.0001
Tanita (reac50)	0.4743	0.1494	98	3.17	0.0020
Tanita (reac502)	-0.00433	0.001087	98	-3.98	0.0001
Age	0.02123	0.01894	98	1.12	0.2651
Female	4.2936	0.7768	98	5.53	<.0001
Height	-0.6899	0.1342	98	-5.14	<.0001
Weight	0.8372	0.1561	98	5.36	<.0001
BMI	-2.2985	0.4409	98	-5.21	<.0001
reac50tan_sample	0.03451	0.01146	98	3.01	0.0033
female_sample	-2.5873	0.6540	98	-3.96	0.0001

%BF: Percentage body fat; reac50: Reactance at 50 kHz; reac502: Reactance at 50 kHz squared; BMI: Body Mass Index; reac50_tan_sample: interaction of reactance at 50 kHz with study sample (Swiss TPH vs. SAPALDIA); female_sample: interaction of sex and study sample

The model was then applied to subjects who only measured Tanita by creating the variable PBF. The results from the regression model on % Body Fat (defined by Helios) including the co-variates sex, age, height, weight, BMI, study area are shown in Table 3. The variable impute has the values “Helios only” for subjects being examined on Helios only, “imputed (Tanita only)” for subjects being examined on Tanita only and “Model sample (Tanita and Helios)” for subjects being measured on both devices.

Table 3: Association of imputation sample and % Body Fat

Imputation samples	Estimate	Standard Error	DF	t Value	Pr > |t|
Model sample (Tanita and Helios)	0.8403	0.6611	1399	1.27	0.2039
imputed (Tanita only)	0.5073	0.4590	1399	1.11	0.2692
Helios only	0	.	.	.	.

Type 3 Tests of Fixed Effects				
Effect	Num DF	Den DF	F Value	Pr > F
impute	2	1399	0.91	0.4036

It seems that after imputation of the percent body fat values for Aarau and Geneva, both the model sample and the imputed sample do not differ from the other SAPALDIA subjects.

3 Results from the Device comparison test at Swiss TPH

The results from the device comparison showed a clear difference in PBF of the Helios devices compared to the Tanita devices (Figure 3).

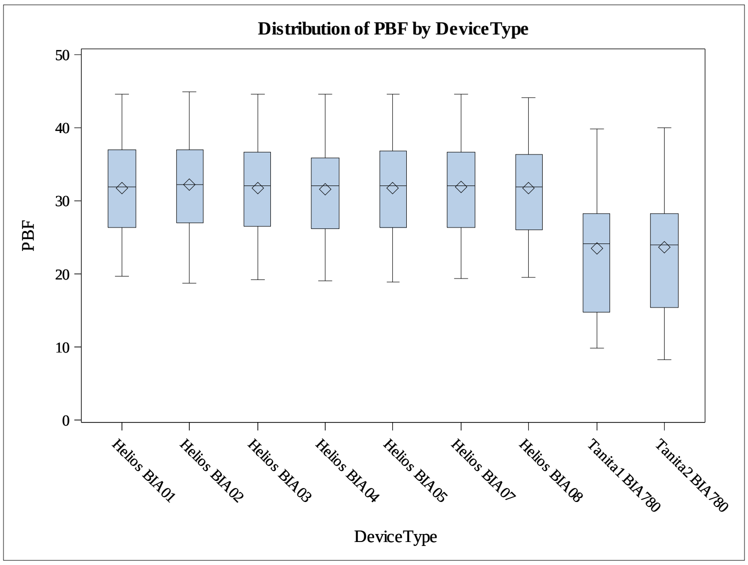

Figure 3: % Body Fat by Type and Device (N=32) (Kyle formula for Helios and reported output for Tanita)

After imputing the kyle formula for Tanita values there was no visible difference between devices and device types (Helios – Tanita) as illustrated in Figure 4.

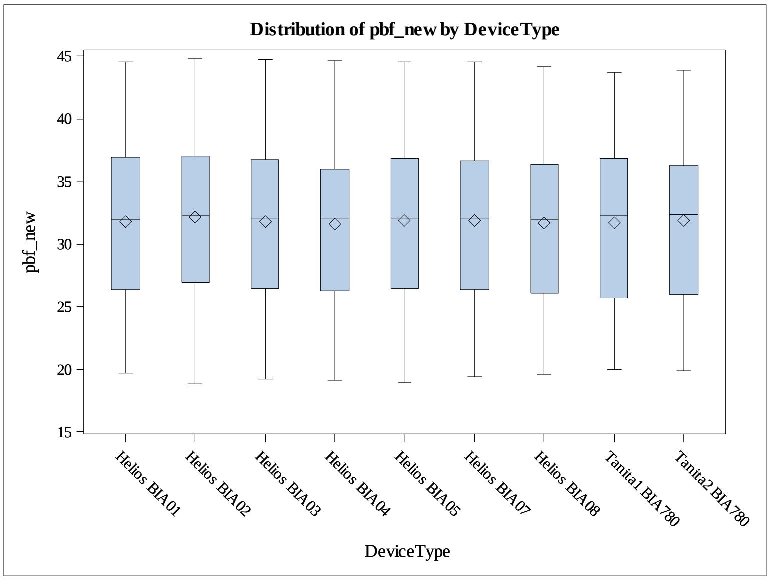

Figure 4: % Body Fat by Type and Device (N=32) (Kyle formula: using measurement values for Helios and modeled measurement values for Tanita).

The results of the between and within device variability (Table 4) suggest that percentage Body Fat Helios (calculated with the Kyle formula) shows only very little variability between devices (i.e. the variability is virtually only from with-in devices, which should be the variability between subjects).

Table 4: Intra-class correlation coefficient (ICC) as a measure of between and within device variability

Outcome	ICC (all devices)	ICC (Helios)	ICC (Tanita)
%BF (Helios) resp. Tanita (%BF)	0.90	0.22	0.38
PBF (calculated with Kyle formula)	0.06	0.22	0.38

Discussion and conclusion

This protocol aimed at harmonizing different BIA devices for the SAPALDIA cohort. We successfully derived consistent data from the two devices to provide a harmonized variable. By producing this variable, we ensure consistency in BIA data across all study areas of SAPALDIA, which will be of critical use for future research projects.

10 CURRICULUM VITAE

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EDUCATION

Expected 09/2020	**PhD.: Epidemiology and Public Health** Swiss Tropical and Public Health Institute (Swiss TPH)
10/2014 - 10/2016	**MSc.: European Master of Public Health and Physical Activity** • Jointly issued by five Universities from different countries (Norway, Denmark, Germany, Italy & Austria)
09/2011 - 09/2014	**BSc.: Bachelor of Science in Exercise and Health Science** University of Basel (CH)
06/2010	Matura certificate, High School Bäumlihof (Basel) • Major: Biochemistry

PROFESSIONAL EXPERCIENCE

2017-Present	**PhD Candidate – Scientific collaborator** Swiss Tropical and Public Health Institute (CH)
2015 –2016	**Research Assistant** University of Vienna (AUT)

LEADERSHIP

2019 – Present	**PhD student representative** Swiss Tropical and Public Health Institute (CH)

LANGUAGES

German	Native
Italian	Native
English	Proficient
French	Fluent

SELECTED SKILLS

Teaching:

2017 – 2018 KSU (Körper-Subjekt-Umwelt) - Bachelor medical students, University of Basel (CH)

Sport performances:

2006 – 2009 Member of the Swiss National Taekwondo Team
Achieved results:
2005, 2006, 2007, 2008 Swiss Taekwondo Champion (WTF - Olympic federation)
2008 Participation at the Junior World Taekwondo Championship in Izmir

COMPUTER SKILLS

- Statistical analysis software (STATA & SPSS)
- Data capture software (MACRO, REDCap & AskiMed)
- Mac OS/Windows - Microsoft Office (Word, Excel, Power Point)
- Geographical Information System (GIS)