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Untangling Socioeconomic Health Inequalities

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General Discussion and Future Perspectives

This chapter summarizes the most important findings and discusses the key public health policy implementations from all chapters. Then, in the light of the post-pandemic world, we highlight the future need to capture insights for action on the determinants and drivers of health and growing inequalities.

Summary of the key findings

Part one:
Socioeconomic Inequalities in Lifestyle Factors and Health Outcomes
- Chapter 1: We investigated the relationship between socioeconomic status (SES) and lifestyle behaviors. Lower individual SES was associated with poorer overall lifestyle behaviors. Neighborhood SES was also associated with health-related lifestyle behaviors. Moreover, individual SES and neighborhood SES interacted and reinforced each other, meaning that individuals with the lowest SES who resided in the most disadvantaged neighborhood had the unhealthiest lifestyle (1).
- Chapter 2: We investigated the relationship between SES and non-communicable diseases. Lower individual SES was associated with a higher prevalence of diagnosed and undiagnosed type 2 diabetes (T2D) and T2D complications (2). Lower individual SES was also associated with higher risks of incident T2D and cardiovascular diseases (CVD). Furthermore, individuals with both the lowest household income and education level had the highest risk of incident T2D and CVD (3).
- Chapter 3: We investigated the relationship between SES and communicable diseases. Lower individual SES was associated with higher risks of SARS-CoV-2 infection and coronavirus disease 2019 (COVID-19) hospitalization.

Part two:
Objective Measurements of Nutritional Factors in Public Health
- Chapter 4: Objective measurements of vitamin status along with an assessment of diet quality were deployed to comprehend the vitamin status among older adults. We found that half of the older adults are at risk of at least one vitamin insufficiency. Low SES was associated with worse vitamin status and diet quality (4).
- Chapter 5: Circulating plasma eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) were applied to objectively estimate the omega-3 fatty acids status in relation to dietary fish intake. Individuals with low SES consumed less fatty and lean fish but more fried fish. Fatty and lean fish intake was associated with EPA and/or DHA, while fried fish was not associated with either EPA or DHA. Hence, socioeconomic differences in fish intake were both quantitative and qualitative.
- Chapter 6: The sarcopenic status, assessed from 24 h urinary creatinine excretion, and body mass index (BMI) were measured in a general middle-aged population. Sarcopenia combined with weight excess elevated the risk of hospitalization for

COVID-19 among those infected with COVID-19 more than weight excess alone, supporting the relevance of sarcopenia as a risk factor beyond the geriatric setting.

- Chapter 7: Dietary sodium and protein intake were measured objectively in older adults to investigate whether the previously observed association between low sodium intake and high mortality risk could be due to concomitantly low protein intake. Our results indeed showed that excessive mortality risk related to low sodium intake was only present when protein intake was also low. The lowest mortality risk was found in subjects with low sodium intake in whom protein intake was adequate (5).
- Chapter 8: The urinary metabolites of tocopherols (CEHCs) were measured and tested for feasibility as a marker for dietary vitamin E intake. CEHCs were shown to be associated with dietary vitamin E intake, while plasma vitamin E status (tocopherols) was not associated with dietary vitamin E intake (6).

In brief, to reinforce the evidence base for public health, this thesis dissected factors contributing to complex health disparities and provided insights for public health policies by endorsing the multilevel and multifaceted nature of socioeconomic determinants and applying objective measurements of nutritional factors. We dissected socioeconomic factors at the neighborhood level and individual level. Within individual socioeconomic factors, we dissected various facets, including educational attainment and household income. Previously unmeasured blind spots were uncovered using objective measurements, including the role of sarcopenia in the relation between weight excess and COVID-19 hospitalization and the role of protein intake in the relation between low sodium intake and mortality risk. Objective measurements of a broad spectrum of vitamins enriched the scarce data on vitamin status at the population level. Objective measurements of CEHCs contributed to the challenge of finding a good marker to assess dietary vitamin E intake. These findings support the notion that dissecting and identifying risk factors that contribute to complex health inequalities can help better target risk populations and develop effective policies and interventions. In the section below, we will elaborate more on public health policy implementations that can be derived from our studies, along with evidence from the literature.

Key Public Health Policy Implementations

Several public health policy implementations emerge from our studies. These could guide two domains of public health policy implementations for both Dutch and international policymakers: 1) collective and multisectoral effort to address socioeconomic determinants of health; 2) integrating objective measurements to uncover relevant neglected blind spots, enrich scarce empirical data, and better assess and monitor health status and inequalities in the population.

- **Public health policy with a particular focus on individuals with lower socioeconomic status**

Results from chapters 1,2,3,4, and 5 have shown that low SES was a risk factor for poor health-related lifestyle, prevalent and incident T2D, incident CVD, poor diet quality, and vitamin deficiencies and insufficiencies, which can be classified as non-communicable "slow-motion disasters" (7). In addition, low SES was also associated with SARS-CoV-2 infection and COVID-19 hospitalization, a communicable "fast-motion disaster". These findings showed the robustness of SES as an "upstream" determinant of health and, accordingly, a highly relevant factor to target in public health. It is vital to explore and target upstream determinants of health, such as socioeconomic factors, given their impact on a wide spectrum of diseases (8). One of the reasons for the general ineffectiveness of interventions to reduce health inequalities might be the focus on intermediate factors, such as lifestyle factors, without considering their upstream determinants (9). Our results advocate targeted interventions for socioeconomically disadvantaged groups, as SES related inequalities exist in every stage of the disease pathway, from lifestyle and nutritional status to both communicable- and non-communicable diseases (10-19).

Public health policies and prevention budgets might consider investing wisely in tailored strategies for individuals with lower SES and consider socioeconomic factors in public health interventions. Several interventions have been developed with a particular target on low SES groups in disease prevention. Systematic reviews considered, however, the effect of these interventions ineffective, weak, or inconclusive (20, 21). The reason for the poor effectiveness might be that the multilevel and multifaceted nature of SES was not scrutinized. Our results demonstrated the leverage effect of neighborhood SES on individual SES. Accordingly, the impact of such an intervention at the individual level can be neutralized or compensated by the neighborhood SES. Furthermore, we also observed the additive effect of different facets of individual SES on incident T2D and CVD in Chapter 2. Each facet of individual SES might influence the disease pathway differently depending on the health outcome (22). Therefore, to provide evidence on effective interventions targeting socioeconomic health inequalities, it is crucial to consider the multifaceted and multilevel nature of SES when designating risk groups and designing interventions (23).

- **Public health policy with a focus beyond the individuals: place and people**

While incorporating socioeconomic factors is essential in public health policy, the multilevel nature of SES increases the complexity of integrating it into public health policy. Chapter 1 argued that both neighborhood and individual conditions were essential to one's health-related behaviors. Unlike individual SES, neighborhood SES measures SES

at the area level and is often presented as indices of deprivation or disadvantage (24-26). Usually, these indices are aggregated from the individual level or small area data from census or other registration/administrative data, such as the resource (Statistics Netherlands) we used in Chapter 1. Area-based indicators can be theorized as measures of an area's SES (27). Together with evidence from the literature and Chapter 1, we have shown that neighborhood conditions can independently influence lifestyle and health (1, 25, 28, 29). Differences in health effects among different areas/neighborhoods could be explained as contextual (different places) and compositional (different people who live in the place) (27). To tackle health inequalities, it is essential to consider people as well as place (indicators of SES at the individual and area levels) and pay attention to their coherence and synergy.

Thus, prevention policies, especially targeting behavioral changes, might incorporate areas/neighborhoods as an upstream determinant of health. A healthy and beneficial area includes active transportation infrastructure, healthy food environments, smoke-free environments, and green space. For example, a systematic review on interventions on individual physical activity showed the neighborhood environment was conditional for their effectiveness (30). Therefore, prevention policies to increase exposure to green space in cities could promote better health and well-being, reduce natural-cause mortality of the population, and contribute to the development of sustainable and healthy cities (31). More importantly, people with lower SES might benefit more regarding physical activity than people residing in affluence, particularly concerning public green spaces (32).

- **Public health policy with a focus on the food environment**

The food environment is embedded in the neighborhood and can influence people's food and beverage choices and nutritional status (33). The food environment is the interface that mediates people's food acquisition, preparation, and consumption within the wider food system. It encompasses external dimensions such as the availability, prices, vendor and product properties, and promotional information; and personal dimensions such as the accessibility, affordability, convenience, and desirability of food sources and products (34). Chapters 4 and 5 demonstrated that individuals with low SES had poorer dietary choices of fish and poorer overall diet quality, which partially contributed to the worse objectively measured vitamin status. Several elements of the food environment could have contributed to the poor dietary choices of individuals with low SES, including affordability, accessibility, convenience, and knowledge of food sources. Thus, the current food environment might be a risk factor that contributes to nutrition and health inequalities, given that consumption choice is made in the context of the food environment (35-37).

Like other developed countries, food environment in the Netherlands has been characterized by the wide availability of highly processed foods that are typically high in energy, fat, and sugar (38). Healthy foods, including fruits and vegetables, however, are locally less easily accessible, particularly in poor neighborhoods (39). In these areas, residents may have limited access to supermarkets and fresh produce and may rely on convenience stores or fast-food outlets for their food needs. Thus, exposure to unhealthy fast food environments was higher in poorer neighborhoods (40, 41). It is evidenced that a fast-food outlet environment was a risk factor for overweight, obesity, prevalent T2D, incident cardiovascular heart disease, and coronary heart disease (42-44).

Therefore, food environment could be a target to shape folk's consumption behaviors. To create a healthier food environment, both supportive policies and interventions are needed, particularly in more disadvantaged communities, to make healthy choices easier and discourage unhealthy ones. For example, food education (e.g., cooking classes) can be a powerful amplifier and enabler of other food environment policies (45). However, the interventions addressing the food environment are still in their infancy due to failures to provide good quality evidence on the impacts of food environment policies on socioeconomic inequalities in diets (46). Also, more rigorous changes to food environments are probably needed for a real modification to occur (47). Still, it is suggested that food taxation may reduce socioeconomic disparities in diets (46), corresponding to the Dutch government's current discussion on sugar taxation (48). However, implementing a food environment policy is not easy, given the counterforces from commercial actors (48) as well as the immense lack of research on the feasibility of specific policy instruments and spatial planning processes for changing food environments, especially when space is designed in co-creation with citizens (49). Therefore, there is still an enormous potential for the Dutch national government to strengthen its policy action and infrastructure support to improve the healthiness of the food environment (50).

- **Public health policy:**
  the potential of objective measurements of nutritional factors

Despite that lifestyle factors, including diet and nutritional factors, are important targets in public health, the empirical foundation can still be reinforced. The persistent health inequalities could be due to the fact that the inequalities in lifestyle factors are not adequately scrutinized because 1) data on lifestyle and nutrition are scarce or of bad quality at the population level; 2) unmeasured blind spots remain in estimating nutritional status; 3) there is a lack of markers of good quality to estimate dietary intake and nutritional status. Albeit routinely used in clinical medicine and several other domains, objective measurements are sparsely applied in public health research, and even more sparsely in public health . Therefore, Chapter 4 implemented objective measurements to monitor the status of several vitamins, including folic acid, vitamin

K, vitamin B12, vitamin B6, vitamin E, vitamin A, and vitamin D. Chapters 6 and 7 used objective measurements to monitor muscle mass status and dietary intake of sodium and protein, respectively. Lastly, Chapter 8 measured the vitamin E metabolites in plasma and urine.

Our results showed that objective measurements of nutritional factors at a large scale are powerful in prioritizing targets and guiding policy in public health. For instance, Chapter 4 discovered that half of older adults are at risk of one or more vitamin insufficiencies (4). Of note, the current Dutch dietary guideline considers that nutrient supplements are not needed, except for vitamin D recommendations for older adults from the health council of the Netherlands (51, 52). Our results suggested that a broader spectrum of vitamins status should be monitored and assessed in the general population, especially older adults, because they might need extra dietary guidelines with a focus on folic acid, vitamin D, vitamin B12, vitamin B6, and vitamin E. Chapter 6 provided evidence that sarcopenia could have additional detrimental risks to middle-aged adults with excess weight. Future interventions focusing on weight loss need to consider stratifying according to sarcopenia status because the presence of sarcopenia could hamper the completion and effectiveness of practicing physical activity, as shown in patients with kidney diseases (53). Chapter 7 showcased applying objective measurement to refute the counterintuitive observation that low sodium intake is detrimental to one's health. Instead, sufficient protein intake and reduced sodium intake should to be recommended (5, 54, 55). One prerequisite of applying objective measurements at a large scale in public health is to find a validated marker. Chapter 8 demonstrated that urinary metabolites of tocopherols (CEHC) could have the potential to be an effective and susceptible marker to estimate dietary vitamin E intake (6). Hopefully, accumulated evidence from more investigations on the relation between CEHC and vitamin intake can facilitate the development of dietary guideline on vitamin E intake (56).

All these results call for more robustly measured and well-documented data on nutritional factors at the population level. Of note, the misreporting of subjective dietary intake across socioeconomic levels could impede diet-health or nutrition-health research (57). Policymakers should be aware of these results, as interventions will become more cost-effective if we can better identify, prioritize, and target risk groups and offer appropriate interventions with measurements adapted to their specific needs. For instance, older adults, individuals with low SES, individuals with low muscle mass, and excessive body weight, all being at-risk groups of considerable size, contribute substantially to the total healthcare expenditure (58, 59). In addition, we should consider multiple factors instead of single-factor interventions when designing interventions, as the risk factors could interact, and moreover, blind spots might remain in existing counter-intuitive findings (5). To support such an approach with empirical evidence, public health nutrition policy should incorporate population cohorts and laboratories and

invest in and utilize available robust measured data when designing interventions, and when evaluating trends in health and lifestyle factors over time. Such robust measured data are available in national population cohorts and biobanks such as Lifelines Cohort and Biobank and European Prospective Investigation into Cancer and Nutrition (EPIC). The well-structured and well-documented data from cohorts and biobanks could serve as a solid and empirical basis for developing, monitoring, and evaluating public health nutrition policy.

Public health policy: action to reduce socioeconomic health inequalities

Three aspects are crucial for public health policies derived from the "key public health policy implementations" mentioned above to act on the reduction of socioeconomic health inequalities: 1) usage of scientific evidence; 2) community engagement and empowerment; 3) multi-stakeholder engagement.

When developing prevention policies and interventions, policymakers need to use the available scientific evidence. If not, either due to poor documentation and knowledge circulation or lack of robust evidence, the interventions could be a waste of time and financial resources. A solid example of knowledge-policy infrastructure circulation in the Netherlands in the public health field is nutrition science. First, empirical evidence is translated into (food-based) dietary guidelines (e.g., Richtlijnen Goede Voeding); second, dietary guidelines are translated into the layman's language as the "Schijf van Vijf" (51); third, food consumption questionnaires serve as a feedback loop to monitor and evaluate the effect of the dietary guidelines, which provides updated empirical evidence for cyclical progress regarding the role of nutrition in public health (60). This knowledge-policy infrastructure also implies that, for instance, the detection of blind spots can find its way to both future research projects where needed, and to implementation in public health guidelines where appropriate. However, as mentioned in the introduction of the thesis, the self-reported food frequency questionnaire (FFQ), as well as other questionnaires has its pitfalls. The availability of national cohorts and biobanks like Lifelines provides the opportunity to include more robust assessments in the follow-up and monitoring loop to evaluate the outcomes of a specific policy. With the rich data from such cohorts, we might also be able to evaluate the effect of policies across SES groups, especially individuals with low SES.

Besides robust data and the involvement of academia to acquire the latest scientific insights, community engagement is crucial for effective interventions and policies. Originating from sociology, psychology, and other disciplines, community engagement means engaging the targeted group and contextual factors (61). Specific policies are more useful if they are geared towards the local and cultural context, accessible both

practically and financially, and embedded within social structures. Such strategies, generally, pursue to combine "top-down" and "bottom-up" approaches, expertise, and values. Engaging communities in designing and implementing policies and programs can promote shared responsibility for creating healthier environments and behaviors (62). Community engagement has been shown to be a crucial strategy for addressing health disparities because it can help ensure that interventions are tailored to communities' specific needs and contexts (63). Community engagement could also have the power to overcome imbalances and promote more equitable decision-making, and subsequently promote health equity (64). Evidence has shown that community engagement and participatory approaches could improve the effectiveness of prevention policy and make the effect more sustainable, as apparent from data on obesity prevention policies (65).

To address the upstream socioeconomic determinants of health (e.g., poverty and education), multi-stakeholder engagement is essential for effective public health governance and safeguarding public health. The national government directs research, monitors continuity and long-term vision, and facilitates interdepartmental collaboration among ministries (9, 66). Local authorities take the proactive and coordinating role and incorporate community engagement, creativity, and empowerment. Private/Commercial parties, such as industries that impact population health and result in inequities (tobacco, unhealthy food, and alcohol) and health insurers, need to be monitored and pushed to adequately implement governmental regulations to make a real difference regarding health potential (67). Civil society groups raise their collective voices and articulate visions to bottom-up and hold governments and commercial parties accountable. Academia provides fit-for-purpose empirical evidence and evaluates previous literature. Health actors break the clinical walls and biomedical models of health and diseases and engage in broader determinants of health (68).

To summarize, investment in social determinants and broader determinants (e.g., built environment and commercial determinants) of health in disease prevention and health promotion could benefit the health and prosperity of both individuals and society as a whole (Figure 1)(67, 69). Moreover, additional support and engagement for groups with the greatest health deficit and need, such as individuals with low SES and older adults,

Figure 1. Social determinants of Health, adapted from Healthy People 2030 (Healthy People 2030, U.S. Department of Health and Human Services, Office of Disease Prevention and Health Promotion. Retrieved April 26, 2023, from https://health.gov/healthypeople/objectives-and-data/social-determinants-health).

should be advocated because they have the greatest potential gains. It is also fair to do so. Finally, scientific evidence should be a relevant factor during political discussions and management of conflicts of interest from stakeholders, and population health should be prioritized (70, 71).

Methodological aspects

•   **Indicators of Individual SES**

As a key factor in this thesis, individual SES has been incorporated in most chapters as an independent variable. It is to be noticed that the indicators of individual SES applied in each chapter were not operationalized identically (Table 1). There is no consensus on the best measure of SES, and the selection of SES indicators was mainly based on the specific research questions and the data available in the cohort. In this thesis, we mostly operationalized SES as education attainment and household income, either combined or separated.

A more comprehensive and diverse spectrum of SES indicators has been used in the literature on SES inequalities in health outcomes. SES indicators can be divided into two ecological levels: individual and neighborhood (11, 14, 15, 72-74). Individual SES is mainly indicated by one of the most operationalized categories or an index/composite score derived from them: education, income, and occupation. For example, the education category can be defined as education attainment, years of education, and parents' education attainment; the income category includes household income, household wealth, and monthly purchasing power units; the occupation category includes working-class and types of work. Neighborhood SES is typically indicated by a deprivation or disadvantage index/composite score from the factors of choice, such as unemployment rate, residents who rented, uninsured residents, and median household income.

Studies have suggested that the inconsistent relationship between SES and health outcomes could result from the different indicators of SES used in various studies (11). To ensure comparability, one systematic review has restricted the measurement of SES to education, occupation, employment status, income, and household assets or combinations thereof at the individual or household level (72). For international multi-cohort and meta-analysis studies, a consistent indicator of SES is even more necessary to ensure the power of the analysis and comparability. For instance, SES was indicated by the occupational position (74) and education and household wealth index (14) in two larger pooled analyses, respectively. Therefore, in this thesis, the selection of SES indicators was based on 1) the availability and feasibility of the data and 2) the

Table 1. Summary of SES indicators used as an independent variable in the thesis.

Chapter	SES indicator (number of levels)
1	- Quartiles of individual SES index combining information on education, household income, unemployment, and social benefit.
2.1	- Household income: three levels, low (<2000 euro/month), middle (2000-3000 euro/month), and high(>3000 euro/month).
2.2	- Education attainment: three levels based on International Standard Classification of Education (ISCED), low (junior general secondary education or lower), middle (secondary vocational education or work-based learning pathway and senior general secondary education, pre-university secondary education), and high (higher vocational education and university education); - Household income: four levels, low (<1000 euro/month), lower-middle (1000-2000 euro/month), upper-middle (2000-3000 euro/month), and high (>3000 euro/month).
3	- Education attainment: three levels based on International Standard Classification of Education (ISCED), low (junior general secondary education or lower), middle (secondary vocational education or work-based learning pathway and senior general secondary education, pre-university secondary education), and high (higher vocational education and university education); - Household income: three levels, low (<2000 euro/month), middle (2000-3000 euro/month), and high(>3000 euro/month).
4	- Education attainment: two levels based on International Standard Classification of Education (ISCED), low (junior general secondary education or lower) and high (higher vocational education and university education).
5	- Education attainment: three levels based on International Standard Classification of Education (ISCED), low (junior general secondary education or lower), middle (secondary vocational education or work-based learning pathway and senior general secondary education, pre-university secondary education), and high (higher vocational education and university education); - Household income: three levels, low (<2000 euro/month), middle (2000-3000 euro/month), and high(>3000 euro/month).

comparability of the results across different chapters and with other investigations in the Dutch context.

Although there is no consensus on the best socioeconomic status (SES) measure, commonly used indicators such as education, income, and occupation categories are supported by evidence. SES is a multidimensional construct that includes various aspects of one's life. The discourse on rationalizing SES indicators is ongoing and has

contradictory arguments. Some researchers suggest that occupation categories are not easily hierarchically ordered and vary across countries and communities (75, 76), while others argue that occupation position is a valid SES indicator (74). Moreover, it has also been suggested that occupational class, education, and income cannot be used interchangeably (22). This thesis did not include the occupation category as a measure of SES due to its heterogeneity (75).

We have investigated the effect of education and income on health outcomes both separately (Chapters 2.2, 3, and 5) and combined (Chapters 1 and 2.2). We have combined them in two different approaches: statistical dimension reduction (Chapter 1) and stratification (Chapter 2.2). The choice was primarily based on the study sample size as income is a sensitive issue, and people tend to be unwilling to disclose this information, resulting in a larger proportion of missing data on income. Therefore, education and income were combined when the whole Lifelines population was included. On the other hand, when the research question was more related to SES as a generic factor rather than the interplay between different indicators of SES, we combined these two to provide a more comprehensive estimate of the socioeconomic gradients in health. The multi-dimensional nature of SES is both horizontal and vertical. Not only did we investigate the interplay between education and income at the individual level (horizontal), but we also revealed the interaction between neighborhood SES (vertical) and individual SES (Chapter 1).

• **Causal inference in observational studies**

As interventions and experimental data are rare in population studies, all the chapters in this thesis were observational studies, with either cross-sectional or prospective cohort designs. The relationships observed were associations, and causal inference can hardly be drawn from them. There is no perfect method for estimating a causal effect in observational data because causal effects are impossible to measure directly since they involve comparing unobserved counterfactual outcomes that would have happened under different circumstances (77). Instead, a causal effect is identifiable if it can be estimated using observable data, given certain assumptions about the data and the underlying causal relationships. Such identifying assumptions typically cannot be fully tested statistically. Still, they must be justified based on theory (etiology, physiology, behavior theory) and/or existing evidence about the real-world processes under study (78). Another application to justify causal inference is the so-called triangulation, referring to the integration of multiple methods to test one hypothesis (79).

To justify the relevance of our data to identify effectiveness to be causal, we have applied the following three main approaches in this thesis: confounding adjustment, mediation, effect measure modification, and selection bias. Conventional approaches to confounder adjustment restrict the study sample to one level of the confounding

variable, stratifying or matching (80). For instance, the Lifelines-MINUTHE study (Chapters 4, 7, and 8) was built as a sex-balanced and SES-balanced sub-cohort of Lifelines. Other methods include multivariable regression (including confounders as covariates), which was utilized in every chapter. The confounders we used in this thesis were all observed confounders, which referred to confounders for which measures were available in Lifelines. However, residual confounding bias can remain after conditioning on observed confounding, either due to variables not observed in the data (unmeasured or unobserved confounding) or inadequate measurement or modeling of observed confounders. Besides meta-analysis and systematic review, randomized controlled trials (RCTs) have the highest and strongest level of scientific evidence because they strive to achieve exchangeability ("no confounding") by randomly assigning the exposure (81). At the same time, cohort and cross-sectional studies often rely on achieving conditional exchangeability ("no unmeasured confounding") (77). Nevertheless, not every research question can be designed into a RCT due to ethical or practical issues. Therefore, statistical methods have been developed to address causal inference in cross-sectional and cohort studies (82).

Mediation analysis was applied in Chapter 4, estimating the mediator (diet quality) on the causal pathway between SES and vitamin status. Mediation analysis aims to quantify how much of the total effect of an exposure on an outcome is explained by a particular mediator and how much is not (83). We have also observed the multiplicative effect measure modification (EMM) and interaction effect in Chapters 1 and 6. The interaction found between sodium intake and protein intake in Chapter 6 addressed again the importance of applying objective measurements to uncover residual covariates, either mediators, modifiers, or confounders. The presence and extent of EMM and interaction mathematically depend on the choice of an additive or multiplicative scale linking exposure and outcomes. Interaction denotes that the joint effect of two exposures differs from the sum of the individual effects of each exposure (84). "Interaction" is used interchangeably with EMM in this thesis, but it is helpful to think of these as different concepts. Interaction focuses on the joint causal effect of two exposures, while EMM focuses on the effect of one exposure whose effect differs across levels of another variable; with EMM, the causal effect of the effect modifier itself is not of interest (77). Thus, Chapter 1 focused on the interaction of the joint effect of individual SES and neighborhood SES on lifestyle behaviors. In contrast, Chapter 6 focused more on the effect of sodium intake on all-cause mortality across protein intake levels.

Although not utilized in this thesis, there are methods and designs to address unobserved/unmeasured confounding in observational studies, such as instrumental variables (mendelian randomization uses instrumental variables (IV) analysis with genetic variants as instruments), regression discontinuity, interrupted time series, differences in differences (77).

- **Objective measurements of nutritional factors and dietary intake to reinforce the evidence base for public health**

This thesis showcased how to integrate objective measurements of nutritional factors in population studies to provide robust evidence as the basis for prevention policies. The following table summarized the objective measurements included in this thesis, which could be categorized into substances measured in two types of bio samples: fasting blood and 24 h urine. With a focus on nutrition science, we have measured nutritional factors because it is particularly important but challenging to have a less biased assessment of diet and nutrient intake or status in nutrition-health/disease research (85). The systematic error, also known as bias, of the dietary assessment instruments is well-known (86); however, there are a couple of emerging challenges that might hamper the usage of FFQ in several dietary intake related studies.

Table 2. Summary of objective measurements of nutritional factors contributing to the second aim of the thesis.

Chapter	Nutritional factors/objective measurements (bio samples)	Application
4	Blood (serum and plasma): folic acid, vitamin B12, vitamin B6, 25(OH)D, α- and γ-tocopherol, retinol, and dp-ucMGP	Status of folic acid, vitamin B12, vitamin B6, vitamin D, vitamin E, vitamin A, and vitamin K
5	Blood (plasma phospholipids and triglycerides): EPA and DHA	Status of EPA and DHA
6	24h urine: creatinine	Status of muscle mass
7	24h urine: sodium, urea	Surrogate intake of sodium and protein
8	24h urine: α- and γ-CEHC	Surrogate intake of vitamin E

* 25(OH)D: 25-hydroxyvitamin D; dp-ucMGP: desphospho-uncarboxylated matrix Gla protein; EPA: Eicosapentaenoic acid (C20:5 n-3); DHA: Docosahexaenoic acid (C22:6 n-3); CEHC: carboxyethyl hydroxychroman.

The following section describes how can objective measurements of nutrition factors help to address three potential challenges in diet/nutrition-health research.

3.1 Deploying objective measurements for a potential challenge in nutrition-health research: assess animal- and plant-based protein intake

Objective measurements of animal- and plant-based protein intake might support to facilitate the protein transition action (87). We have briefly checked how well the FFQ can capture protein intake from different sources in Lifelines using the baseline FFQ among self-reported vegetarian and vegan dietary status. We found (data not

shown) that even for strict vegans, the FFQ results indicated a non-negligible amount of animal-based protein intake. Whereas adherence could be an issue, it might also well be that the operationalization of FFQ is a source of systematic error in vegans. To operationalize the FFQ, the number of food groups included in FFQ is restricted, and based on the overall dietary habits and culture of the region. For every specific food group, the food composition is derived from a generic food product commercially available in the market, which often contains animal-based substances, even if there is a vegan/vegetarian version. To help with the ''Protein transition'' action (87), we might need an updated FFQ that is designed with options to address vegetarian and vegan food products, as well as dedicated markers for objective assessment of animal- and plant-based protein intake, respectively (88, 89).

3.2 Deploying objective measurements for a potential challenge in nutrition-health research: assess low/no calorie sweeteners intake

The health effects of consuming low/no-calorie sweeteners still need to be clarified because of the inconsistent evidence and limited evidence on the long-term health impacts of low-calorie sweeteners across all life stages (90). The intake of low/no-calorie sweeteners is also mainly estimated from FFQ, focusing on low/no-calorie sweetened beverages. However, the presence of low/no calorie sweeteners goes beyond the beverages, such as toothpaste and medicines, and therefore is hard to capture given the nature of FFQ. A research team at Wageningen University and Research developed an essay to measure markers of low/no calorie sweeteners (triglycerides, gamma-glutamyl transferase, aspartate aminotransferase, and alanine aminotransferase) from 24 h urine within the framework of the EU-SWEET project. Their result showed that almost everyone is unconsciously exposed to low/no-calorie sweeteners, no matter if they consciously avoid consuming low/no-calorie sweetened beverages (unpublished). Objective measurements could provide reinforced evidence and help better understand the health effects of low/no-calorie sweeteners.

3.3 Deploying objective measurements for a potential challenge in nutrition-health research: reporting bias across SES groups

Another reason to incorporate objective measurements of nutrients and nutritional factors is to mitigate the inequality in reporting bias between low and high SES groups and subsequently improve the quality of diet-disease research (91). We have investigated the correlation between protein intake measured from FFQ and 24 h urine (Maroni's formula) in the Lifelines-MINUTHE cohort (Figure 2). Overall, total protein intake was under-reported in FFQ compared to that measured in 24 h urine; Total protein intake from FFQ was positively correlated with that calculated from 24 h urine after adjustments of age, sex, SES, BMI, and total energy intake, with partial correlation coefficient 0.44 and p<0.001. SES seemed to modify the correlation, with higher

partial correlation magnitudes observed among people with high SES (0.46, p<0.001), compared to people with low SES (0.42, p<0.001) (Figure 2). The underreporting degree was more substantial among individuals with low SES, which could attenuate the strength of diet-disease relationships. These preliminary results showed that objective measurements can to some extend avoid the disproportionate reporting bias across different socioeconomic groups. Yet, more studies with larger sample size are warranted to validate these results.
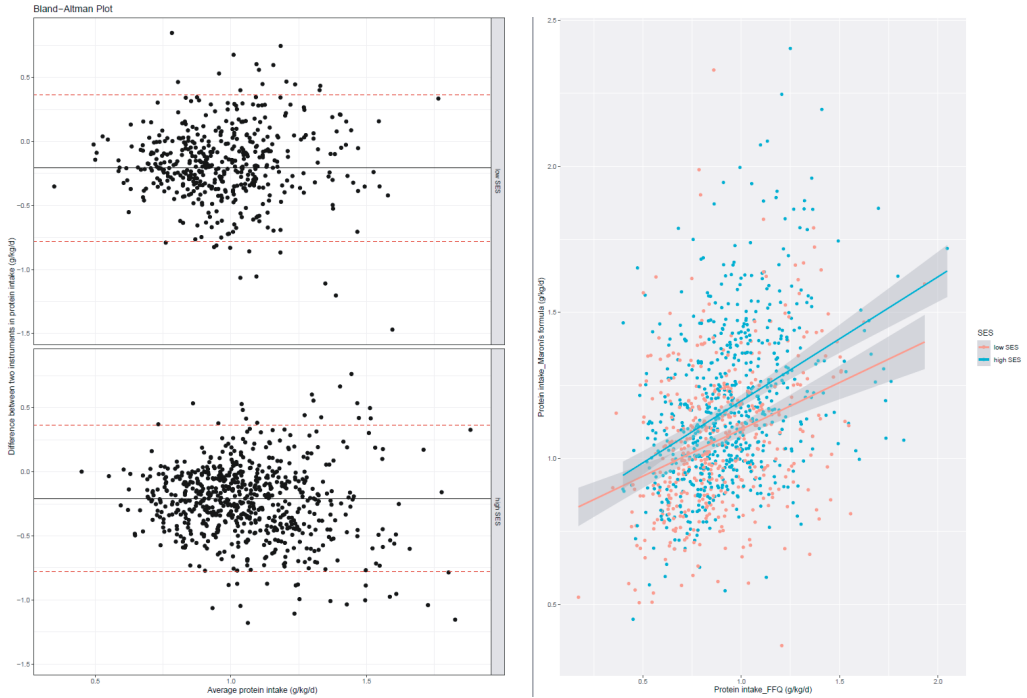
Figure 2. Left: Bland-Altman plots between protein intake assessed from FFQ and Maroni's formula in low and high-SES groups. Right: Adjusted association between protein intake from FFQ and from Maroni's formula across SES groups.

Future perspectives

The urgency of addressing socioeconomic health inequalities is warranted and should be highlighted in public health. Recent monitoring evidence from the Dutch National Institution for Public Health and the Environment demonstrated that the socioeconomic gradients of healthy life expectancy have widened from 2014 to 2017. More strikingly, the healthy life expectancy of individuals with low income was surprisingly decreased between 2017-2020, compared to 2014-2017 (92). Thus, socioeconomic factors, especially poverty, should be addressed and included in the public health policy agenda. This thesis incorporated straightforward conceptual investigations and dissected factors that contribute to one's health and overall health inequalities, including socioeconomic factors, neighborhood, and lifestyle that goes beyond clinical walls (Figure 2 in Introduction). Further studies are warranted to enrich the evidence of the relationship between these factors and health outcomes, which could further add strength and provide valuable policy insights. Nevertheless, several aspects and associated challenges still require further research and policy considerations to supplement the current findings.

To address complex health inequalities, policy continuity, and sustainability are essential since results may take years to become visible. Future public health budgets should invest in researching the effect of interventions on both the population level and specific marginalized groups. Additionally, it is also important to invest in making public spaces, such as the food environment, more sustainable and offering financial incentives for sustainable behavior, which corresponds to the introduction that modifying lifestyle is beyond an individual's responsibility (Figure 3 in Introduction). Simultaneously conducting better research is essential for effective policy development. Developing a comprehensive approach that considers the multifaceted nature of socioeconomic status while involving citizens is crucial. Community engagement or involving citizens can improve the relevance and acceptability of interventions, leading to sustained behavior change. Nonetheless, it is essential to recognize that further research is needed to understand the optimal methods for engaging communities in different contexts and to identify indicators of the process and effectiveness of interventions and policies in the short and long term to promote health equity (93). Research is also urgently needed to understand the impacts of food environment policies on socioeconomic inequalities in diets (46), and modeling and simulation studies with empirical evidence from qualitative or small-scale quantitative studies could complement observational studies that require time to observe outcomes and estimate the long-term effect of preventive policies quickly.

Besides dissecting socio-economic factors contributing to one's health, we applied objective measurements and identified neglected risk factors in the general population. This supports the assumption that prevention policy may be hampered by overlooking

relevant targets. Exclusive focus on high BMI while overlooking the role of low muscle mass, or neglect of inadequate protein intake, simply because these are not routinely available, might lead to policies that "bark up the wrong tree". Still, we need more investigation on various objective measurements to identify the risk factors and uncover the relevant blind spots in a general population, and eventually to get policy swayed towards action to target these risk factors to reduce health inequalities. To implement objective measurements, future research should explore novel markers for dietary intake (e.g., animal- and plant-based protein, low- and no-calorie sweeteners) and classify them systematically to ensure validation and documentation in trusted databases and research tools according to standardized criteria. Improved methods to search the literature for the best markers and update information on their development and validity for various applications are also necessary. Further validation of these markers and their implementation in large-scale cohorts and biobanks can resolve inconsistencies and provide solid evidence for public health policymakers.

To this purpose, objective measurements also require affirmative involvement of laboratories as stakeholders in healthcare and preventive policies, including regular checkups and management of non-communicable diseases. Establishing and maintaining high-quality biobanks is also crucial to enable larger-scale objective measurements of representative populations. Hopefully, solid and consistent evidence will be collected and scrutinized after subsequent and cumulative investigations. The policymakers might be swayed to the following steps: regulatory approval, real-world effectiveness studies, cost-effectiveness analysis, estimation of reimbursement, public health practitioner guidance (their endorsements strongly affect practice), and guidelines for the general population.

Health does not begin in clinics and hospitals, and there is an urgency to address socioeconomic health inequalities from different dimensions, including incorporating objective measurements to uncover blind spots and risk factors to build up a better knowledge basis to drive public health policies. Confidently, this basis will reinforce the translational linkage from scientific evidence to policy practices and strengthen public health surveillance and governance to prioritize public interests and human health and wellbeing.

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