Equity in dementia research: perspectives on risk and diagnosis

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Chapter 1

GENERAL INTRODUCTION

Dementia is an irreversible, progressive neurodegenerative syndrome which manifests itself by a decline in cognitive function and behavioral changes. Early signs can be subtle, but as the disease progresses, individuals lose independence due to impairments in daily functioning. Because of this, the burden of disease is substantial, not only for individuals, but also for their families and society as a whole. As of today, there is no effective, curative treatment available.[1] Age is the strongest risk factor, and with a global population aging, the absolute number of people living with dementia is expected to triple: from 55 million now, to 150 million in 2050.[2-4] In this thesis we focus on identifying dementia risk factors in high risk populations, advancing research methods, and exploring potential intervention strategies. In addition, we evaluate the diagnostic work-up for dementia, along with its possible benefits for patients.

First, I shall pose why equity is such an important concept in dementia research. Second, I will describe challenges that are inherent to doing research in the field of dementia prevention. Third, I will focus on several high-risk populations and elaborate on modifiable risk factors for dementia. Fourth, I will discuss potential interventions to address modifiable risk factors. Fifth, I will elaborate on diagnostic practices and how this relates to the concept of dementia. I will conclude with aims and objectives and a short outline of this thesis.

EQUITY

Equity in research is defined as *'absence of unfair, avoidable or remediable differences among groups of people, whether those groups are defined socially, economically, demographically, or geographically or by other dimensions of inequality (e.g. sex, gender, ethnicity, disability, or sexual orientation).'* [5] Despite advances in diagnostic and preventive approaches for dementia, significant inequities remain in how the diverse needs of high risk populations are addressed. Although global dementia prevalence is rising, in high-income countries (HICs), age-adjusted incidence and prevalence are declining.[6] This is likely attributable in part due to enhanced educational attainment and improved cardiovascular risk management in recent decades.[4, 6] These developments underscore the possibility of delaying or preventing dementia through targeted interventions throughout an individual's life. Conversely, numerous low- and middle income countries (LMICs) are encountering increasing age-adjusted incidence rates.[6] Those facing societal or economic disadvantages may experience unequal access to diagnosis and preventive care.[2, 7, 8] Individuals from some ethnic minorities in HICs, e.g., Black, South Asian, and Hispanic groups, typically have a greater risk of dementia than white populations.[9] In the Netherlands, prevalence of dementia has also been

estimated to be between three and four times greater among most non-European migrant groups as compared to the Dutch host population.[10] Furthermore, evidence generation including diverse populations or from low-resource settings remains limited, hindering the development of contextually appropriate interventions.[11, 12] To ensure that healthcare provision actually benefits those receiving it, it is equally important that healthcare provision aligns with the values, preferences, and needs of patients themselves. Striving for equity in research is an important starting point in addressing the unequal global burden of dementia.[6]

RESEARCH IN THE FIELD OF DEMENTIA PREVENTION

Most evidence on dementia risk factors originates from observational studies, in which individuals are followed over time in real-life conditions without manipulation of exposures.[13] Such studies are valuable for identifying associations, exploring long-term effects, and generating hypotheses. However, they cannot establish causality. Randomized controlled trials (RCTs) remain the gold standard to determine whether modifying a risk factor truly prevents or delays dementia.[14]

Prevention trials in dementia face several methodological and ethical challenges.[15] Most risk factors emerge in midlife, whereas dementia develops decades later, making long follow-up periods necessary.[16] This increases costs, attrition, and difficulties in maintaining adherence to interventions.[17, 18] Moreover, RCTs often include highly selected participants and require strict protocol compliance, which limits their generalizability to everyday practice.[14] Ethical constraints further restrict trial design: withholding established treatments or exposing individuals to harmful factors is unacceptable, leaving only a narrow space of clinical equipoise.

These challenges have prompted interest in quasi-experimental designs, which bridge the gap between observational and randomized studies by exploiting naturally occurring variation in exposure. When underlying assumptions are met, they can yield causal inferences while preserving real-world relevance. Such approaches offer an important opportunity to advance dementia prevention research in settings where traditional trials are not feasible or ethical.

POPULATIONS AT INCREASED RISK OF DEMENTIA

Modifiable risk factors for dementia are lifestyle and health-related conditions that can be influenced to reduce dementia risk. These include physical inactivity, smoking, unhealthy diet, excessive alcohol use, high blood pressure, high cholesterol, obesity, diabetes, social isolation, education and depression.[19] Up to 45% of dementia cases may be attributable to these risk factors, and addressing these factors through healthier lifestyles and preventive care may decrease risk of dementia.[19] As such, they are key targets for public health interventions. Some populations are at increased risk of dementia, potentially due to higher burden of risk factors. This thesis focuses on several such groups: individuals living in LMICs,[3] migrant populations,[20] and those exhibiting symptoms of apathy.[21] Unraveling specific risk profiles in these high-risk populations is a prerequisite for implementing more effective and inclusive prevention practices and reducing the worldwide burden of dementia

In LMIC there is an upward trend of incidence of dementia, which cannot be solely ascribed to demographic aging; it also reflects the increasing prevalence of metabolic risk factors, particularly obesity, diabetes, and hypertension.[22] Hypertension offers a significant opportunity for prevention, since antihypertensive medication treatment is relatively cheap widely available, easy to implement and provenly effective in lowering dementia risk.[23-25] Especially in LMIC this could have large prevention potential since rates of hypertension control are currently below 10%.[26]

Causes for ethnic disparities in dementia incidence in migrant populations are not yet completely unraveled. These inequalities can in part be explained by a greater prevalence of vascular and metabolic risk factors, and by social determinants such as lower educational attainment, higher rates of depression, barriers in access to health care, and histories of facing systematic inequalities.[27-31] Also, factors such as disadvantaged socioeconomic position, migration status, genetics and lifestyle may play a role.[2, 19, 20, 32]

Apathy is a neuropsychiatric syndrome and an important symptom of depression characterized by impaired motivation, decreased interest, attention and emotional reactivity.[33] Apathy regularly precedes dementia and may exist as a standalone syndrome in people without a depression.[21] Apathy has been associated with detrimental health behaviors such as a sedentary lifestyle, poor diet, and low treatment adherence—all proven modifiable risk factors for dementia.[34] This offers a potential window of opportunity for targeted prevention by lifestyle modification.

MODIFYING THE MODIFIABLE

Lifestyle modification offers significant potential for dementia prevention, but sustained behavior change is difficult. The 'intention-behavior gap', along with factors like knowledge, resources, time and social support, affects success.[35, 36] The distant nature of dementia risk reduces urgency, and barriers such as low control and negative self-image are more common in lower socioeconomic and migrant populations, who face higher dementia risk.[37-39] In order to overcome this intention-behavior gap and promote more effective, long-term behavior change, tailored interventions are required.[40] This is where mobile health (mHealth) technologies may offer a promising solution. They can deliver personalized, accessible, and scalable support directly through smartphones or other digital devices, which may help individuals overcome internal and external barriers to change—potentially enabling long-term adoption of lifestyle change. When designing a new intervention for a specific population, involvement of the target population during the development phase may improve engagement and effectiveness of that intervention.[40-42]

DIAGNOSING DEMENTIA

Over recent decades, the concept of dementia has evolved significantly, shifting from a predominantly symptom-based clinical diagnosis towards a more biomarker-informed diagnosis.[43] Nevertheless, according to Dutch guidelines, dementia diagnosis remains fundamentally clinical, relying primarily on a thorough history and cognitive assessment by a physician.[44] Ancillary investigations such as imaging, or cerebrospinal fluid analysis are perceived as supportive rather than a necessary component for the diagnosis. Biomarkers may reveal alterations at a pathophysiological level prior to overt cognitive symptoms.[45, 46] While higher diagnostic rates may contribute to improved patient management and care, at the same time it raises ethical concerns of the desirability of an early diagnosis in absence of a cure and results in increased healthcare spending.[1, 47] The increasing, but still optional use of biomarkers during the diagnostic work-up introduces practice variability,[48] ethical issues related to an early stage diagnosis,[49] increased healthcare costs,[50] and gaps in access to ancillary testing.[51] This trend towards an earlier diagnosis needs to be carefully balanced against the absence of curative treatments available,[1] potential complications associated with invasive ancillary testing[52] and potential incidental findings resulting in patient distress.[53] In the Netherlands, there is a significant inter-hospital variability both by frequency and type of ancillary diagnostics employed that reflects broader uncertainty and inconstancy of clinical practice.[48] These findings raise questions about patient

benefit and clinical relevance of ancillary testing, highlighting the need for careful evaluation of diagnostic timing and modalities to ensure clinical utility for patients and healthcare systems.

AIMS AND OBJECTIVES

To advance equitable dementia prevention and care, this thesis aims to explore:

- What strategies can be employed to generate robust evidence on dementia risk factors, also from low-resource settings to inform preventive strategies?
- How do risk factors play a role in the increased risk of dementia in people with a migration background, those living in LMIC and other groups at elevated risk?
- How can diagnostic and preventive efforts benefit patients and those at risk and how should we align interventions with their needs and preferences?

OUTLINE OF THIS THESIS

In **Chapter II** we investigate quasi-experimental study designs as a practical and feasible alternative to address the common challenges encountered in dementia prevention trials, aiming to study causal relationships in real-world settings. In **Chapter III** we examine variation in risk profiles of modifiable risk factors between groups from six ethnic backgrounds by assessing three commonly used dementia risk scores, showing that those with a migration background have a consistently less favorable risk profile for future dementia. In **Chapter IV**, we explore the needs and preferences of individuals with lower socioeconomic position or a Turkish or South-Asian Surinamese background regarding a blended mHealth intervention for dementia risk reduction, with the aim of actively engaging these end-users and tailoring the intervention to better meet their needs. In **Chapter V** we examine apathy as a key clinical marker that indicates the presence of potentially modifiable risk factors, offering an opportunity for intensive lifestyle interventions. In **Chapter VI** we systematically summarize the available evidence on the association between hypertension and dementia in low- and middle income countries, as hypertension treatment may prove a cost-effective and scalable prevention intervention strategy. In **Chapter VII,** we study the association between the use of ancillary diagnostic testing to diagnose dementia and time to poor outcome (hospitalization and/or death) in order to assess the clinical utility of such testing. Finally, in **Chapter VIII,** we will place our findings in the context of current literature and discuss their implications for future research.

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Chapter II

THE CHALLENGE OF DEMENTIA PREVENTION TRIALS AND THE ROLE OF QUASI EXPERIMENTAL STUDIES

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ABSTRACT

Observational studies have consistently shown that modifiable risk factors during life are associated with increased dementia risk in old age, but randomized controlled trials (RCTs) on dementia prevention evaluating treatment of these risk factors did not find consistent effects on cognitive outcomes. The discrepancy in findings is potentially attributable to inherent differences between the two study designs. Although RCTs are the gold standard for establishing causality, designing and conducting an RCT for dementia prevention is complex. Quasi-experimental studies (QES) may contribute to investigating causality without randomization. QES use variation in exposure to a risk factor or intervention in an observational setting to deduct causal effects. Design specific approaches are used to control for confounding, the main caveat of QES. In this paper, we address the challenges, opportunities and limitations of QES for research into dementia prevention.

HIGHLIGHTS

- In spite of consistent associations between modifiable risk factors and dementia, the mostly neutral effects of RCTs challenge the causality of these associations.
- RCTs in the field of dementia prevention are often problematic due to ethical, practical or financial constraints and their results may have limited generalizability.
- Four QES designs may be suitable to study causality between risk factors and dementia; we critically appraise these study designs for dementia prevention studies.
- We describe how specific QES designs can be used to study the effect of risk factor modification for twelve known risk factors for dementia.

INTRODUCTION

There are currently no effective disease modifying treatments for dementia. This has led to a shift of focus towards prevention.[1] Observational data have shown that up to forty percent of all dementia is associated with potentially modifiable risk factors, including cardiovascular risk factors such as hypertension, obesity, physical inactivity and diabetes.[1] Despite the overwhelming evidence from observational studies, randomized controlled trials targeting these risk factors have not shown a consistent effect on cognitive decline or dementia.[2] In general, systematic reviews comparing results on treatment effects from observational and randomized controlled trials (RCTs) show conflicting results; some find concordant, whereas others find discordant results.[3-5] Several explanations may underlie this discrepancy pertaining to dementia prevention.

Observational studies report associations between (mostly midlife) risk factors and dementia later in life. In spite of controlling for potentially confounding factors influencing the association, residual confounding remains an issue. Therefore, based on these studies, assumptions about causality cannot be made. When analyzing treatment effects in observational data, confounding by indication is a major limitation, again precluding any firm conclusion about causality.

RCTs for dementia prevention come with specific challenges. Firstly, there is a long lag time between exposure to risk factors and incident dementia, which necessitates a very long follow up to measure an effect of the intervention, possibly introducing bias due to selective drop-out and non-sustained adherence to the intervention. Secondly, the associations of several risk factors with dementia attenuates or reverses in later life, making target levels of individual risk factors uncertain.[6-8] Thirdly, an RCT requires 'clinical equipoise' or genuine uncertainty about the right treatment regimen. For most modifiable risk factors, there is no such uncertainty when it comes to overall health benefits, since treatment may prevent cardiovascular diseases (CVD).[9] Therefore, most patients will already be treated according to prevailing guidelines, leaving little ethical margin for a control condition without treatment.[10] Fourthly, results of RCTs often have limited external validity, due to strict in- and exclusion criteria and recruitment of patients which are generally more healthy than those not participating.[4] Finally, RCTs are costly.

Quasi-experimental studies (QES) may overcome some of these challenges. A QES exploits natural variation in exposure to an intervention to deduct causal effects of an intervention in an observational setting. QES date back to the 19th century, when

John Snow famously showed that spatial patterns of cholera outbreaks in London could be linked to whether local water sources drew water from upstream or downstream the Thames, which would now be considered a 'difference in differences' design.[11] Thereafter, QES were predominantly used in the field of econometrics, psychology and social science, and only in recent decades they have made their reappearance in medical research.[12] Although randomized research is the gold standard for causal inference, observational studies, if well designed, may be valuable for exploring questions regarding etiology, risk factors and prognosis. Several comparative studies have suggested equivalence in results from QES as compared to the gold standard (RCT),[13-15] but they have their own limitations. We will discuss if, and how, QES could play a role in the quest for effective intervention strategies to prevent dementia, targeting potentially modifiable risk factors as previously identified.[1] We will discuss the specific opportunities and limitations of four different QES designs.

INSTRUMENTAL VARIABLE DESIGN

The instrumental variable (IV) approach uses 'as-if' randomization, for which a randomly varying 'instrument' that is strongly associated with the risk factor of interest is used as a proxy in causal effect estimations (Figure 1, Panel A). When a solid instrumental variable is present, this can be an alternative method to establish causality when randomization of the intervention is impossible.[16] In the field of dementia prevention, for instance Mendelian randomization studies could use the predicted risk of vascular risk factors based on genetics as an instrument to determine effect of high blood pressure or high glucose on dementia.[17, 18] Another example is using physician prescribing preferences as an instrument for the use of a specific antihypertensive drug class on the risk of dementia.[19] Thus, instead of directly examining the relationship between type of antihypertensive and incident dementia, one estimates the effect of physician prescribing preference on incident dementia. To corroborate to the hypothesis of a causal effect of early life educational attainment and dementia, this study[20] used a comprehensive approach. They analyzed the effect of education on dementia using two different IV's; genetic risk scores for educational attainment and schooling laws and policies. Although both analyses showed a protective effect, consistent with results from observational studies, it was substantially larger in the analyses using schooling laws and policies as instrument. When assessing the assumptions to be met for IV analysis they established that schooling laws and policies were a more credible instrument and therefore these results are likely closer to the true effect. Analysis is performed conducting a two stage least squares (2SLQ) regression. For the example of antihypertensive drug class

and dementia, in the first stage a regression analysis is done in which the independent variable (type of antihypertensive that is prescribed) is treated as the dependent variable (the outcome of the regression) and the instrumental variable (physician's prescribing preference) is included as an independent variable. The result of this first-stage regression substitutes the independent variable in the second stage regression instead of the actual independent variable (type of antihypertensive that is prescribed), to establish the effect of the intervention on the outcome.[21] The use of instrumental variables relies heavily on assumptions (Table 1). That is, (1) a strong association between instrument and exposure,[22, 23] (2) exclusion restriction: the IV should not directly affect the outcome, only through its effect on the exposure,[21] (3) independence: the IV and outcome should not have a common etiology[16, 24] and (4) monotonicity: the instrument has the same effect on exposure for each patient.[25, 26] Only the primary assumption is verifiable. The other three assumptions should be made plausible based on exploration informed by expert opinion. Particularly exclusion restriction and independence of the IV are essential to obtain reliable effect estimates. Obviously, violation of the monotonicity is conceivable in preference-based instruments as used in the example. Physicians might have a preference for a specific class of antihypertensive, but avoid that drug in a certain subpopulation, which may result in bias.[26] Critical appraisal of how violation of the assumptions exactly affects the outcome is essential.[27] An additional weakness of IV methods is the inability to properly deal with time-varying independent variables. Reporting guidelines exist for both Mendelian randomization studies as well as non-MR studies.[24, 28, 29] Monte Carlo simulations of sample size calculations for IV studies showed that in order to generate reliable results, sample sizes between 2400 and 25000 patients are required, depending on the strength of the instrument and the degree of confounding.[30]

REGRESSION DISCONTINUITY DESIGN

Treatment is often initiated based on a marker crossing the line between what we regard as 'normal' and 'abnormal', such as blood pressure, serum glucose, blood cholesterol etc. Patients close to either side of that cut-off value are arguably identical, since in measured values there is random measurement error. A group of patients with a systolic blood pressure of 139 mmHg is thus comparable to a group of patients with 141 mmHg. Nevertheless, the first does not receive anti-hypertensive medication, the latter does, if guideline cut-offs are strictly observed. Apart from initiation of treatment RDD can also be applied to study the effect of exposure to environmental risk factors for dementia. This study[31] used the discontinuity in air pollutant concentration between two river banks due to an arbitrary heating policy

of the Chinese government that resulted in excessive air pollution exclusively on the north side of the river Huai. The results endorsed the role of air pollution as a risk factor for dementia. The regression discontinuity design (RDD) zooms in on the two groups on either side to compare exposed and unexposed units (Table 1).[32] RDD can be of use when randomization is inappropriate due to absence of clinical equipoise. It can be applied for interventions that are common practice. This facilitates longer duration of follow up and adherence to the intervention and it is easier to include larger sample sizes. It does require good quality data, with a high standard of data registration, which is often lacking in data collected in daily practice. A suitable assignment variable in RDD has a strong association with treatment allocation and has no association with confounding factors. Ideally, passing the threshold for intervention results in a 'sharp' jump from unexposed to exposed to intervention.[33] In clinical practice, decision-making can be much more 'fuzzy'. For example, patients can refuse treatment, compliance may vary, or doctors can base their decision not solely on the threshold. For a sharp RDD, analysis is performed fitting a local linear regression of the outcome on a segment around the threshold, whilst adjusting for the assignment variable. Discontinuity in the regression line at the threshold is argued to represent the causal effect Ffigure 1, Panel B).[13, 21, 34] The causal effect can only be deducted for a narrow band around the threshold to guarantee exchangeability of the two groups.[13] For a fuzzy RDD design, the approach resembles the two-stage IV analysis approach.[33] The threshold rule is used in the first stage regression as an instrument for actually receiving treatment in the second stage. Assumptions to be met in RDD are: (1) continuity, which presumes that in absence of treatment the continuous assignment variable would follow the same trend[35]; (2) individuals have no power to influence the explanatory variable (e.g. influence whether they receive treatment for hypertension). Visual inspection should yield a smooth density of the assignment variable around the threshold. If this assumption is violated, a fuzzy RDD approach should be employed; (3) the independent variable must have the same effect on each patient, which is captured in the monotonicity assumption. Best practices for RDD studies in healthcare have been described and can function as guidance on proper design and reporting.[36] As regards sample sizes RDD studies may require up to six times more participants than RCTs to generate similar precision of effect estimates.[13, 37, 38]

INTERRUPTED TIME SERIES

Time series data could be applied to study the causal effect of the implementation of large-scale health interventions, such as nationwide policy changes, on dementia outcome years to decades later. Interrupted time series (ITS) is a variation of RDD,

using a point in time as a threshold (Table 1). For example, the effect of duration of education on cognitive decline have been studied with an ITS design.[39, 40] Recently, the COVID-19 pandemic proved to be an opportunity to study the effect of social isolation on cognitive decline. Two studies found an accelerated cognitive decline in dementia patients following the start of the pandemic.[41, 42] Similar analysis could be performed on a cognitively intact older population to study the effect of social isolation on incident dementia. Introduction of a new law or changes in guidelines automatically affect an entire population, yielding large sample sizes and eliminating selection bias. ITS relies on the collection of data at successive points in time before and after the intervention or policy change (i.e. time series data).[43] Analysis of a population right before and after implementation may result in a discontinuity of the regression line or a change in the slope of the regression line (Figure 1, Panel C). This discontinuity or the slope change in the regression line is seen as the effect of the intervention. ITS is mostly analyzed using a segmented regression technique, with a linear regression pre- and post-intervention.[44, 45] Multiple alternatives for analysis exist.[46] As with RDD, ITS relies on the continuity assumption. It is important to establish that no other interventions that could influence the outcome were implemented around that date. It should be ascertained that apart from the intervention of interest, there is continuity of the organization and reimbursement of care and diagnostic criteria of dementia, since they can all influence the registration of the outcome. Continuity is a tricky assumption in time series analysis since policy changes are often preceded by changes in behavior.[47] Importantly, since data are obtained from the same group through repeated measurements over time (i.e. time series data) it is essential to check and account for autocorrelation (correlation of the same variable at two distinct measurements) in the analysis. A common problem for both ITS and RCT in prevention of dementia studies is the known lag time between intervention and outcome. With lag time between exposure and outcome potentially spanning several decades, confounding may be caused by historical trend changes, such as changing diagnostic criteria of dementia, or increase in incidence of risk factors that are not the subject of study. Similar to RDD, the discontinuity or interruption is not always so sharp, since changes in legislation are often preceded by changes in behavior or changes in behavior occur with a lag time following a change in guidelines. Furthermore, multiple time series data on the outcome during the pre-intervention period are required to conduct an ITS analysis. Although no formal guidelines exist for ITS, common pitfalls in reporting have been critically appraised.[48] Additionally, this practical introduction[49] to the use of ITS in the public health sphere can guide proper design and analysis. Population sizes needed for ITS depend very much on quality and structure of the data. Power calculation simulations for ITS showed that increased autocorrelation between measurements decreases study power, and additional data points and a

balanced number of measuring points before and after the intervention both increase study power.[50]

DIFFERENCE-IN-DIFFERENCES

Difference-in-differences (DiD) design can be employed when there are two groups of which one receives the intervention and the other does not (Table 1). In the context of prevention of dementia this method can be apt in the setting of local policy changes or following a natural event. For example, regional changes in air pollution following the closure of a large polluting factory compared to other regions where these changes did not occur. Analogous to the previous example the effect of the China's Clean Air Act on cognition was studied in an older population using a DiD analysis.[51] Following this national policy change provincial governments could install their own target reduction in air pollutants, resulting in an intervention group with substantial reduction targets and a control group without or with very modest targets. Larger reduction of air pollution in the intervention group resulted in less remarkable cognitive decline between pre- and post-intervention. DiD studies exploit changes in trends in a continuous outcome variable in an intervention group as compared to a control group, in absence of random assignment. It combines a cross-sectional and a pre- and post-intervention comparison (Figure 1, Panel D). Outcomes in an intervention and control group may change due to their 'treatment allocation', but also due to time trends that are not the subject of study (i.e. improvement in cardiovascular prevention, implementation of a smoking ban).[52] By comparing the differences in trends in an unexposed to an exposed group, time trends are controlled for by subtracting the time trend in the control group from the effect (Figure 1, Panel D). The result is the DiD estimate, which translates as the average treatment effect in the treated (ATT). The DiD design is a version of a fixed effect model and can thus be modelled using a fixed effect linear regression. The use of DiD relies on several assumptions. (1) In absence of exposure the intervention and control group would have followed a parallel trend.[53] Interestingly, the DiD design does not rely as strong on exchangeability of intervention and control group as do the other QES and RCTs, as long as this first assumption holds. Thus, confounders only pose a threat when they have a time-varying effect on the outcome of the intervention and control group. (2) Consistency, which implies that the independent variable (or intervention) we observe in a study is similar to the true exposure.[53] Therefore, the intervention must be well defined and not be multi-interpretable. (3) Positivity, meaning all groups were eligible to receive the intervention. (4) The dependent variable does not affect assignment to the intervention (strict exogeneity or no anticipation effects of intervention). (5) Common

shocks, which entails that circumstances arising during the study period equally affect both intervention and control group.[54] Contrarily to an RCT, cross-over between intervention and control group is more likely to happen.[55] Additionally, to verify the parallel trend assumption, multiple baseline assessments of intervention and control group are required, which are often not available. For DiD studies a checklist has been developed to ensure quality in conduction and reporting.[54] Simulations of sample size and power calculations for DiD models showed that DiD can perform relatively well as compared to randomized intervention if there are sufficient pre-intervention time points available.[56]

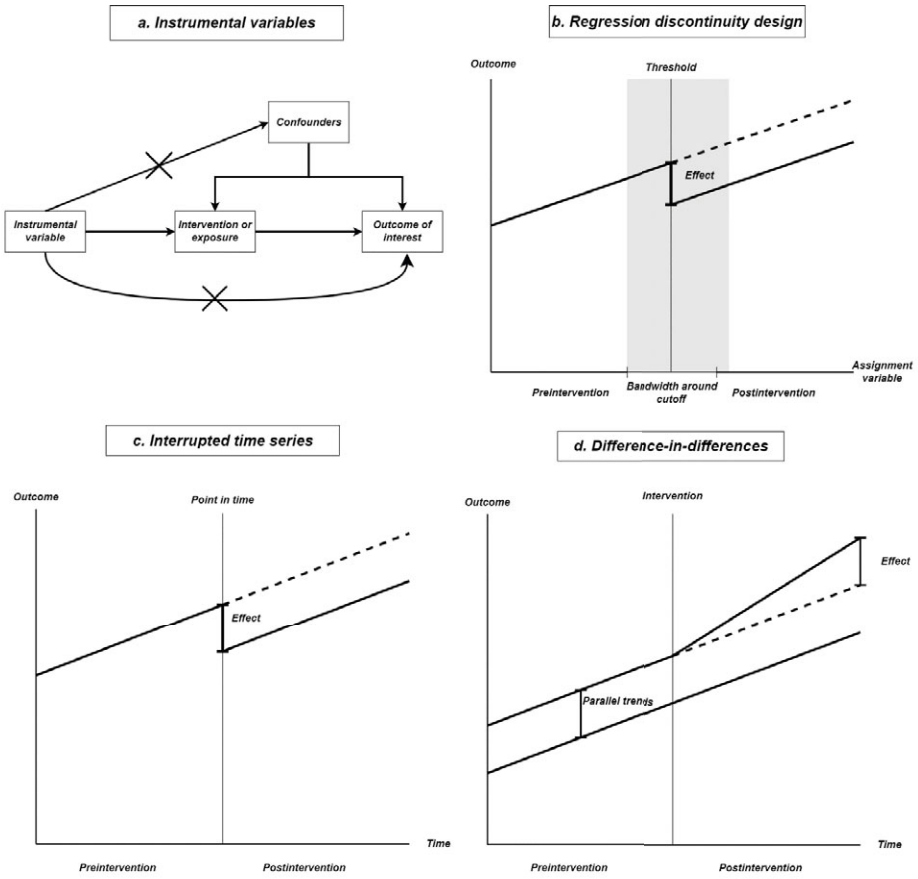

Figure 1: Graphical depiction of quasi-experimental study designs. Panel A. Instrumental variables. Panel B. Regression discontinuity design. Panel C. Interrupted time series. Panel D. Difference-in-differences.

Method	Application	Assumptions	Pitfalls
Instrument variables	Effect of exposure on outcome using a randomly varying instrument that has a strong association with exposure but not with the outcome, as proxy for exposure.	1. Instrument has a strong association with exposure/intervention. 2. Exclusion restriction: instrument is not directly related to the outcome of interest, only through its association with the exposure of interest. 3. Independence assumption: instrument and outcome should not have a common etiology. 4. Monotonicity: exposure has same effect on each patient.	• Strong correlation between instrument and exposure required. • Only the first assumption can be tested; the final three require exploration based on expert knowledge. • Not suitable to study effects of time-varying exposure. • Very large sample sizes are required to generate reliable results.
Regression discontinuity design	Comparing subgroups above and below a threshold that functions as a decision rule for intervention.	1. Continuity: no confounders change at threshold level. 2. Individuals cannot influence their allocation to exposure. 3. The threshold and allocation of exposure must be known. 4. Monotonicity: exposure has same effect on each patient.	• Only suitable to study subgroups in proximity to the threshold, not generalizable to the entire population. • Often clinical decision making is influenced by doctors or patients, thus leading to spill over between intervention and control group. • Large sample sizes required to generate results with similar precision as an RCT.
Interrupted time series	Effect of intervention implemented at a certain point in time.	1. Continuity: no confounders change at threshold level.	• Autocorrelation due to time series data. • Good quality baseline data is required.
Difference-in-differences	Effect of an intervention on a subgroup that is exposed to the intervention as compared to control group. The effect is a change in trend between intervention and control group.	1. Parallel trend assumption: in absence of intervention two groups would have followed similar trends. 2. Consistency: intervention is similar to true exposure. 3. Positivity: all groups were eligible to receive the intervention. 4. Strict exogeneity: no anticipation effects of intervention. 5. Common shocks: circumstances during study period affect both groups equally.	• Autocorrelation due to time series data. • Risk of spill over between intervention and control group. • Good quality baseline data is required.

Table 1: Considerations per study design.

Potentially modifiable risk factors for dementia	Suggestions for quasi experimental design studies
Excessive alcohol consumption	• ITS following introduction of new alcohol laws • IV analysis using alcohol flushing as an instrument for alcohol consumption
Traumatic brain injury	• IV using helmets in boxing as an instrument for traumatic brain injury • ITS following introduction of new guidelines prohibiting heading in amateur soccer
Air pollution	• ITS/DiD after closure of a polluting factory
Less education	• ITS/DiD following introduction of laws on education
Hypertension	• RDD of treatment around threshold blood pressure for intervention • ITS/DiD following introduction of a salt reduction program
Hearing impairment	• IV using occupational noise as an instrument for hearing loss • ITS following introduction of hearing protection laws on dementia
Smoking	• ITS/DiD following introduction of smoking ban • IV using smoking tax as an instrument for effect of smoking on dementia
Obesity	• Mendelian randomization (IV) study using genetic risk of obesity as an instrument for effect of obesity on dementia • IV using sugar tax as an instrument for obesity on dementia
Depression	• Mendelian randomization (IV) study using genetic risk of depression as an instrument for the effect of depression on dementia
Physical inactivity	• IV using membership to a sports club or gym as an instrument for physical activity • DiD following introduction of free access to gym facilities in a neighborhood as compared to a neighborhood without free access
Diabetes	• RDD using the threshold of fasting glucose for initiation of DMII treatment
Social isolation	• ITS of social isolation due to lockdowns during COVID-19 pandemic

Table 2: suggestions of QES per risk factor as identified by The Lancet Commission on dementia.[1] Abbreviations: QES= quasi-experimental study, IV= instrumental variable, RDD= regression discontinuity design, ITS= interrupted time series, DiD= difference-in-differences, DMII= diabetes mellitus type.

DISCUSSION AND RECOMMENDATIONS

The four QES designs discussed above could theoretically all be used for dementia prevention studies depending on the exposure and intervention studied. However, they all have design-specific assumptions that prove challenging to meet. For dementia prevention, most benefit may be expected from targeting any or several of twelve potentially modifiable risk factors.[1] In table 2 we make several suggestions on how one or multiple QES designs could be applied to substantiate the causal relationship between the exposure to one of the twelve modifiable risk factors and incident dementia.

Another emerging alternative to traditional RCTs is target trial emulation, wherein RCTs are emulated in observational data. Subsets complying with strict hypothetical RCT inclusion and procedure protocols are selected, and analyzed adjusting for confounding to emulate random assignment.[57] Although useful, these study designs cannot eliminate bias arising from lack of randomisation.[57] They require detailed knowledge of all possible confounders influencing treatment allocation, which may be unattainable (e.g. confounding by indication, psychological factors, socioeconomic aspects). QES have the distinct advantage of applying randomness in the treatment allocation design. Ultimately, both designs may be complimentary in evaluating the likelihood of causality in settings where traditional RCTs are unreachable.

QES designs could potentially alleviate some of the challenges that are inherent to RCTs. Firstly, feasibility of an RCT can be impeded by ethical or political constraints. Secondly, due to the real world setting and inclusion of entire populations, results of QES can have high external validity.[58] Thirdly, RCTs in dementia prevention often have a limited time span to generate results. Since QES can rely on routinely collected data, this facilitates longer follow-up periods. On the other hand, the risk of bias is higher without randomization.[59] As proposed by the risk of bias in non-randomized studies of interventions (ROBINS-I) tool, there are several fallacies that could undermine valid conclusions in QES.[60] Whereas observed confounding can be controlled for, the risk of unobserved confounding may be larger when there are imbalances in intervention and control group. The time-varying association of risk factors for dementia and the often retrospective nature of QES make it prone to time-varying confounding. The reliance on routinely collected data may result in susceptibility to information bias. Proper data collection requires clear classification criteria, meticulous measurement and correct and complete recording. All of this is guided by clear guidelines in a RCT, but due to the observational nature of QES and the reliance on routinely collected data this will result in data of lower quality and may seriously hinder meaningful interpretation. Even if

the recording of information is not systematically different for the intervention and control conditions, lower data quality may lead to non-differential misclassification, and thereby underestimation of the true effect sizes and/or type 2 errors. Apart from the risk of bias, quasi experiments generally require much larger sample sizes in order to generate results with similar precision to an RCT.[13, 30, 37, 56, 61]

CONCLUSION

RCTs remain the gold standard to confirm causality, but a RCT on dementia prevention comes with serious methodological challenges. QES can solve some issues that hamper the execution of a RCT, such as studying an intervention in absence of clinical equipoise and high costs or long lag time between exposure and outcome. However, they introduce a higher risk of (time-varying) confounding and information bias. Therefore, QES cannot replace RCTs. The use of QES could provide additional insight into the causal relationship between risk factors and incident dementia when a RCT is deemed extremely challenging due to logistical or ethical considerations. But the quality of evidence and the accompanying recommendations will be lower than when based on RCT results.

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Chapter III

MIDLIFE DEMENTIA RISK SCORES IN A MULTI-ETHNIC POPULATION IN THE NETHERLANDS: THE HELIUS STUDY

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ABSTRACT

Background Migrant populations in the Netherlands may face greater dementia risk factor burden than Dutch natives.

Objectives To study whether midlife dementia risk scores differ by ethnicity.

Methods We calculated three validated dementia risk scores in participants aged 40-70 years of Dutch (n=2978), South-Asian Surinamese (n=2084), African Surinamese (n=3135), Ghanaian (n=1699), Turkish (n=2000), and Moroccan (n=2025) background, from the HELIUS study (Amsterdam, the Netherlands): CAIDE, LIBRA and ANU-ADRI. We cross-sectionally compared scores between ethnicities using linear regression.

Results Ethnic minority groups had higher risk scores than those with a Dutch background (CAIDE: +0.66-1.35; LIBRA: +0.66-1.43; ANU-ADRI: +2.75-7.25). CAIDE estimated an absolute 20-year incident dementia risk of 2.6% for Dutch, 3.4% for South-Asian Surinamese, 3.6% for Turkish, 3.7% for Moroccan, 3.7% for African Surinamese and 4.5% for Ghanaian populations. Differences were greater when removing age from scores (CAIDE +0.89-2.22; ANU-ADRI +3.03-8.20), implying that this higher risk score is independent of age.

Conclusion Migrant populations had higher dementia risk scores than Dutch natives. Validation of these scores in migrant populations is warranted. If replicated, ethnicity should be considered when estimating dementia risk and developing preventive strategies for high-risk populations.

INTRODUCTION

Besides the quest for a curative treatment, prevention is the most important strategy to curb global burden of dementia. About 40% of dementia cases are associated with modifiable risk factors.[1] Timely addressing these modifiable risk factors may reduce dementia risk and delay dementia onset. Global burden of dementia is unevenly distributed, with most cases occurring in low- and middle income countries (LMIC), predominantly due to population growth and ageing.[2] However, even within geographical regions the incidence and prevalence of dementia varies across populations with different ethnic backgrounds.[3] To identify high-risk populations that could benefit most from preventive measures, several risk prediction algorithms can be used.[4,5] Most risk scores for dementia include a combination of modifiable and non-modifiable risk factors, such as cardiovascular disease (CVD) risk factors (e.g. smoking, hypertension, hypercholesterolemia, diabetes, physical inactivity), psychosocial risk factors (socio-economic status (SES), social engagement, cognitive activity, depressive symptoms), and demographic factors (age, sex, education).[6,7] Most risk scores are age-specific and were constructed for risk factors in mid- or late-life, since the strength and direction of the association between risk factors and incident dementia varies over time.[8,9] Addressing modifiable risk factors in midlife may positively influence cognitive health in later stages of life,[1] therefore we chose to focus on dementia risk scores for a middle-aged population.

Dementia risk scores are applied in multiple settings; calculation of individual risk scores in a clinical setting, selection of high-risk participants for randomized controlled trails (RCT's), as a surrogate outcome in dementia prevention trials, or when targeting high risk populations with public health intervention efforts.[4,10] However, most prognostic risk models lack predictive accuracy and underperform when externally validated.[11-13] Therefore, on an individual level they may have limited clinical utility. On a population level however, risk scores may be a valuable indicator of the clustering of risk factors in specific populations. Most studies using dementia risk scores focus predominantly on non-migrant, white populations.[14,15] However, increased dementia risk is well documented in non-white populations[3,16] along with a higher prevalence of certain risk factors including social isolation and depressive symptoms.[17,18] There is also variation in the burden of risk factors between ethnic groups. For example, hypertension is more prevalent among African migrants,[19] while type II diabetes is particularly common in Asian migrants.[20] Turkish migrant populations in Europe have higher rates of obesity, CVD and diabetes.[21] Additionally, depressive symptoms are two to four times more common among Turkish and Moroccan migrants compared to the Dutch host population.[22] Despite this, it remains unclear whether the increased

dementia risk among these groups is reflected in higher risk scores due to clustering of these factors. We hypothesize that this could translate into substantially different dementia risk profiles and elevated risk scores in migrant groups. Identification of populations with a higher composite burden of risk factors will enable a more focused approach to prevention, targeting those with the largest potential for reducing dementia risk.[17,18,23] Therefore, our study aims to explore the variation in midlife dementia risk factors among different ethnic populations in the Netherlands.

METHODS

Design, population and setting

The HELIUS study (HEalthy LIfe in an Urban Setting) is a prospective cohort study of participants aged 18-70 years focussed on understanding causes of health disparities between the six largest ethnic groups in Amsterdam, the Netherlands, with participants of Dutch, South-Asian Surinamese, African Surinamese, Ghanaian, Turkish and Moroccan origin. Between 2011 and 2015, people in the age range of 18–70 years were randomly sampled, stratified by ethnic origin, through the municipality register of Amsterdam. Data were collected by questionnaire and physical examination at the research location, including the collection of biological samples. Participants unable to complete the questionnaire themselves were offered assistance from a trained, ethnically matched, same-sex interviewer, speaking their preferred language. The complete study design and cohort profile have been published elsewhere.[24] For this study, we used cross-sectional data, including participants between 40 to 70 years with available data on dementia risk factors. Of 24,780 participants, 22,162 had completed a questionnaire and a physical examination. Of those, 7827 were excluded because they were younger than 40 or older than 70 years and 414 were excluded because they did not belong to the six largest ethnic groups. Approval for the HELIUS study was granted by the Institutional Review Board of the Amsterdam University Medical Centre (METC 10/100# 10.17.1729).

Ethnicity

A person was defined as of non-Dutch ethnic origin if he/she fulfilled one of two criteria: (1) he/she was born outside the Netherlands and has at least one parent born outside the Netherlands (first generation) or (2) he/she was born in the Netherlands but both parents were born outside the Netherlands (second generation). For the Dutch sample, we invited people who were born in the Netherlands and whose

parents were born in the Netherlands. A limitation of the country of birth indicator for ethnicity is that people who are born in the same country might have a different ethnic background, which in the Dutch context is applicable to the Surinamese population (Table 1). Therefore, after data collection, all participants of Surinamese ethnic origin were further classified according to self-reported ethnic origin (obtained by questionnaire) into 'African', 'South-Asian', 'Javanese', or 'other'.

Risk scores

We used the following externally validated dementia risk scores: 'Cardiovascular Risk Factors, Aging and Incidence of Dementia' (CAIDE)[25] , 'LIfestyle for BRAin Health' (LIBRA) index[26,27] and the Australian National University-Alzheimer's Disease Risk Index (ANU-ADRI).[28]

We calculated the three risk scores separately for all individuals with complete data on the available risk factors (CAIDE, N=13,641; LIBRA, N=13,405, ANU-ADRI N=13,397). Measurement and operationalization of risk factors is made explicit in the supplementary material (Supplementary Table 1-4). CAIDE consists of age, education, sex, systolic blood pressure, body mass index (BMI), total cholesterol and physical activity. For CAIDE, all variables were available in the HELIUS cohort resulting in a potential score range between 0 and 15 (Supplementary Table 2). LIBRA consists of modifiable risk- or protective factors, which are low/moderate alcohol consumption, coronary heart disease, physical inactivity, renal dysfunction, diabetes, high cholesterol, smoking, obesity, hypertension, adherence to the Mediterranean diet, depression and high cognitive activity. For the LIBRA score, Mediterranean diet was not available for all ethnic groups in this study and high cognitive activity was not available, resulting in a potential range between -1 and +12.7 (Supplementary Table 3). ANU-ADRI is a risk score that consists of risk factors that patients should be able to fill in themselves, including sex, age, education, BMI, diabetes, symptoms of depression, high cholesterol, traumatic brain injury, smoking, alcohol intake, social engagement, physical activity, cognitive activity, fish intake and pesticide exposure. For ANU-ADRI data on traumatic brain injury, frequency of social engagement, cognitive activity and pesticide exposure were not available in HELIUS and fish intake was not available for all ethnic groups in this study, yielding a potential score ranging from -6 to 61 for males and 64 for women (Supplementary Table 4).

Main reasons to select these risk models were (1) these risk scores have been recommended by the World Health Organisation to use in guidelines on dementia risk reduction;[29] (2) they have been externally validated in several cohorts across

Europe[14,30-33]; (3) they include modifiable risk factors that may bear relevance for future preventive strategies in public health and primary care; and (4) most risk factors were available within the HELIUS cohort.

Statistical analyses

Separate linear regression models with total dementia risk score as dependent variable and dummy variables for each ethnicity were simultaneously added as independent variable to assess ethnic differences in dementia risk, using the Dutch origin group as a reference category. For the CAIDE we calculated the absolute risk of dementia within 20 years using the available equation.[25] For LIBRA and ANU-ADRI no such prediction model has been developed. Next, we removed age from CAIDE and ANU-ADRI and subsequently adjusted the regression models for mean centred age to account for any baseline differences in age between the ethnic subpopulations.[34] By mean centring the age variable, the values of the intercepts represent the mean risk score for the Dutch group at the mean age of our study sample. The risk score without age had a potential range of 0-11 for CAIDE and -6 to 23 for ANU-ADRI. Finally, we tested for interaction of sex with ethnicity and stratified the analyses if significant at $p < 0.05$ (Supplementary Table 6). We checked the distribution of the residuals by creating q-q normality plots and homoscedasticity with residuals vs. fitted plots (Supplementary Figure 1-6). However, because we used bootstrap analyses to calculate our 95% confidence intervals, any violations of these assumptions did not influence our results. All analyses were performed in Rstudio 4.2.1.

RESULTS

We included 13,921 individuals, 56% of the total HELIUS cohort, distributed across six ethnic subpopulations. Of these 13,303 individuals or 96% had data available on all risk factors included in the three risk scores and baseline characteristics of this sample was comparable to the total sample (Supplementary Table 5). Ethnic minority groups were slightly younger (median age Dutch population 55 years, ethnic minority populations between 49 and 54; Table 1) and had a lower education level compared to the Dutch host population (Dutch population 54.5% had higher vocational schooling or university, ethnic minority population 3.9% to 21.1%; Table 1). Risk profiles differed across ethnicities with higher systolic blood pressure observed in the Ghanaian, South-Asian Surinamese and African Surinamese populations and fewer smokers in the Ghanaian and Moroccan populations. Compared to the Dutch host population, all ethnic minority groups exhibited higher levels of diabetes (Dutch 5.5%, ethnic

minorities ranging from 15.1% to 27.0%) and depressive symptoms (Dutch 2.7%, ethnic minorities ranging from 4.2 to 15.7%), but lower total cholesterol levels (Dutch 5.4 millimol/liter, ethnic minorities ranging from 4.9 to 5.1 millimol/liter).

Ethnicity and risk scores

For CAIDE there were 13,641 complete cases (280 cases with missing values), for LIBRA 13,405 (516 cases with missing values) and for ANU-ADRI 13,397 (524 cases with missing values). Despite variations in the configuration and weighting of risk factors for each score, all risk scores indicated a higher total mean score for populations with a migrant background compared to the Dutch host population, adjusted for age (Figure 1, panel a, b and c). Individuals from the ethnic minority groups showed a higher total risk score for CAIDE (+0.66 to +1.35 points), LIBRA (+0.66 to +1.43 points) and ANU-ADRI (+2.75 to +7.25) (Table 2, model 1). CAIDE scores were used to calculate absolute 20-years dementia risk. This resulted in an absolute risk of developing dementia within 20 years of 2.6% for de Dutch population, 3.4% for South Asian Surinamese, 3.7% for African Surinamese, 4.5% for Ghanaian, 3.6% for Turkish and 3.7% for the Moroccan population. After removing age from the CAIDE and ANU-ADRI risk score and adjusting for age, differences further increased (CAIDE: +0.89 to +2.22, and ANU-ADRI: +3.03 to +8.20 points) (Table 2, model 2). Finally, we explored whether the associations of ethnicity with risk scores were modified by sex (Supplementary Table 6). This revealed that, for the Ghanaian, Turkish and Moroccan groups, the difference in scores compared to the Dutch host population was consistently larger across all three risk scores in women than in men. For the Dutch, South Asian Surinamese and African Surinamese groups the interaction with sex was inconsistent across risk scores (Table 3).

The differences between predicted dementia risk scores in ethnic minority groups compared to the Dutch host population were most apparent for the CAIDE and ANU-ADRI risk score (Figure 1; Table 2). For these two, highest mean risk scores were present in the Turkish, Moroccan and Ghanaian groups.

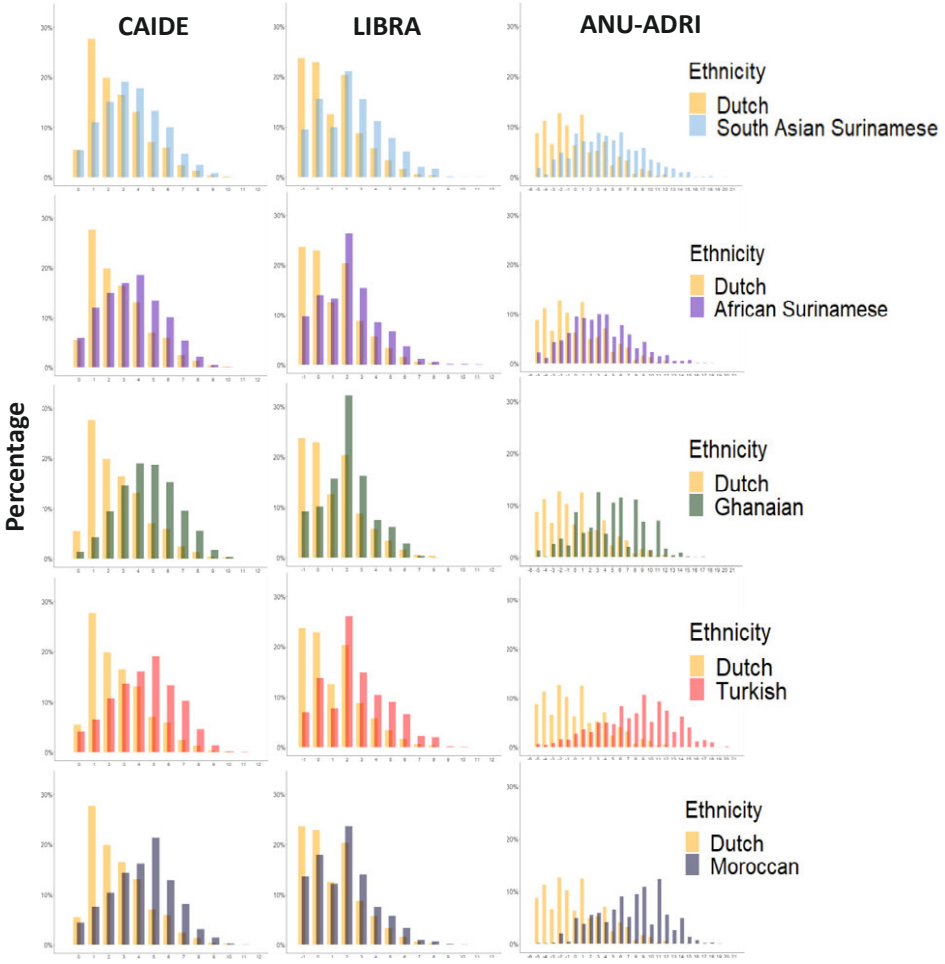

Figure 1: Relative frequency of risk score comparing Dutch with ethnic minority population (South Asian Surinamese, African Surinamese, Ghanaian, Turkish, Moroccan). Bar charts represent the variation in distribution of risk scores excluding age between different ethnicities.

	Dutch	South-Asian Surinamese	African Surinamese	Ghanaian	Turkish	Moroccan
n	2978	2084	3135	1699	2000	2025
Age (median [IQR])	55 [48, 62]	53 [47, 59]	54 [48, 59]	50 [45, 55]	49 [44, 53]	50 [45, 56]
Female (n, %)	1589 (53.4)	1169 (56.1)	1923 (61.3)	990 (58.3)	1076 (53.8)	1181 (58.3)
Educational level 1 (n, %)	128 (4.3)	394 (19.0)	197 (6.3)	570 (34.2)	960 (48.6)	1070 (53.4)
Educational level 2 (n, %)	587 (19.9)	841 (40.6)	1294 (41.7)	673 (40.4)	481 (24.3)	363 (18.1)
Educational level 3 (n, %)	629 (21.3)	456 (22.0)	959 (30.9)	357 (21.4)	370 (18.7)	425 (21.2)
Educational level 4 (n, %)	1613 (54.5)	**378 (18.3)**	655 (21.1)	65 (3.9)	166 (8.4)	146 (7.3)
Current smoking (n, %)	676 (22.7)	565 (27.2)	984 (31.5)	82 (4.9)	621 (31.4)	223 (11.1)
High alcohol intake (n, %)	541 (18.2)	100 (4.8)	145 (4.7)	18 (1.1)	44 (2.2)	15 (0.7)
Physical inactivity (n,%)	723 (24.3)	902 (43.3)	1157 (36.9)	789 (46.5)	1142 (57.1)	1017 (50.3)
BMI (mean (SD))	25.7 (4.4)	26.9 (4.6)	28.4 (5.5)	29.1 (4.8)	30.3 (5.5)	29.4 (5.0)
Total cholesterol (mean (SD))	5.4 (1.0)	5.1 (1.1)	5.0 (1.0)	5.1 (1.0)	5.1 (1.0)	4.9 (1.0)
Systolic blood pressure (mean (SD))	128 (17)	133 (19)	135 (18)	140 (18)	128 (17)	127 (17)
Cardiovascular disease (n, %)	155 (5.2)	334 (16.1)	346 (11.1)	154 (9.2)	356 (18.0)	295 (14.7)
Diabetes (n, %)	162 (5.5)	561 (27.0)	483 (15.6)	255 (15.1)	339 (17.1)	420 (20.8)
Depressive symptoms (n, %)	80 (2.7)	222 (10.7)	158 (5.1)	70 (4.2)	307 (15.7)	248 (12.4)
Renal dysfunction (n, %)	35 (1.2)	49 (2.4)	96 (3.1)	62 (3.7)	16 (0.8)	18 (0.9)

Table 1: Study sample characteristics. IQR=interquartile range. Educational level: 1=never been to school or elementary schooling only, 2=lower vocational schooling or lower secondary schooling, 3= intermediate vocational schooling or intermediate/higher secondary schooling (general), 4= higher vocational schooling or university. Physical inactivity= less than prescribed by Dutch physical activity guidelines (≥5 days/week 30 minutes moderate activity). High alcohol intake = > 7 units/week for women, > 14 units/week for men.

	CAIDE B (95%CI)	LIBRA B (95%CI)	ANU-ADRI B (95%CI)
Model 1: original risk score.			
Dutch	5.66 (5.57 – 5.76)	1.11 (1.05 – 1.18)	0.82 (0.67 - 0.98)
South-Asian Surinamese	+0.66 (0.50 – 0.82)	+1.23 (1.11 – 1.34)	+3.76 (3.48 - 4.02)
African Surinamese	+0.84 (0.70 – 0.98)	+0.95 (0.85 – 1.05)	+2.75 (2.52 – 2.98)
Ghanaian	+1.35 (1.18 – 1.52)	+0.80 (0.69 – 0.90)	+3.90 (3.63 – 4.17)
Turkish	+0.83 (0.67 – 1.00)	+1.43 (1.32 – 1.55)	+7.25 (6.99 -7.53)
Moroccan	+0.87 (0.70 – 1.04)	+0.66 (0.55 – 0.76)	+6.59 (6.33 – 6.84)
Model 2: risk score without age and adjusted for mean centred age.			
Dutch	2.55 (2.48-2.61)	0.98 (0.91 – 1.04)	0.05 (-0.08 - 0.20)
South-Asian Surinamese	+0.98 (0.88– 1.08)	+1.33 (1.22 – 1.44)	+4.09 (3.85 – 4.32)
African Surinamese	+0.89 (0.80- 0.98)	+1.01 (0.92 – 1.10)	+3.03 (2.83 – 3.23)
Ghanaian	+2.22 (2.10-2.33)	+1.07 (0.96 – 1.18)	+4.87 (4.63 – 5.12)
Turkish	+2.02 (1.90 – 2.13)	+1.74 (1.62 – 1.86)	+8.20 (7.94 -8.46)
Moroccan	+1.74 (1.64 – 1.85)	+0.88 (0.78 – 0.99)	+7.33 (7.10 – 7.57)

Table 2: Dementia risk scores across six ethnic groups. Model 1 and 2 for all three risk scores. M1: original risk score (range CAIDE 0 to 15; LIBRA -1 to +12.7; ANU-ADRI -6 to 64), M2: risk score with age removed and adjusted for mean centred age (range CAIDE 0 to 11; LIBRA -1 to +12.7; ANU-ADRI -6 to 23). All models were bootstrapped 1000 times to obtain confidence intervals. Value of the Dutch host population (reference category in our analysis) is the mean value of the risk score, for the other ethnic subpopulation the mean value of the risk score is their regression coefficient added to the mean value of the Dutch population.

	CAIDE		*LIBRA*		*ANU-ADRI*	
	Women	*Men*	*Women*	*Men*	*Women*	*Men*
	B 95%CI		**B 95%CI**		**B 95%CI**	
Model 2: risk score without age and adjusted for mean centred age						
Dutch	2.03 (1.95 -2.11)	3.15 (3.05 – 3.24)	0.82 (0.74 – 0.91)	1.15 (1.05 – 1.25) *	-0.09 (-0.30 – 0.11)	0.18 (-0.04 – 0.40)
South-Asian Surinamese	+1.12 (0.99-1.27)	+0.84 (0.69 – 1.00)*	+1.26 (1.10 – 1.41)	+1.42 (1.25 – 1.59)	+4.30 (3.98 -4.62)	+3.83 (3.48 – 4.18)
African Surinamese	+1.05 (0.93 – 1.17)	+0.85 (0.70 – 1.00)	+1.27 (1.14 – 1.39)	+0.67 (0.52 – 0.82) *	+3.42 (3.14 – 3.70)	+2.48 (2.16 – 2.81)*
Ghanaian	+2.82 (2.68 – 2.98)	+1.53 (1.36 – 1.69)*	+1.49 (1.35 – 1.63)	+0.54 (0.39 – 0.71)*	+6.44 (6.09 – 6.79)	+2.89 (2.50 – 3.27)*
Turkish	+2.40 (2.25 – 2.56)	+1.58 (1.41 – 1.73)*	+2.07 (1.92 – 2.23)	+1.37 (1.19 – 1.55)*	+9.43 (9.09 -9.76)	+6.85 (6.49 – 7.21)*
Moroccan	+2.24 (2.10 – 2.38)	+1.16 (1.01 – 1.33)*	+1.21 (1.07 – 1.36)	+0.47 (0.30 – 0.64)*	+8.28 (7.96 – 8.60)	+6.09 (5.72 – 6.45)*

Table 3: Sex-stratified analysis of age-adjusted dementia risk scores across six ethnic groups. Value of the Dutch host population (reference category in our analysis) is the mean value of the risk score, for the other ethnic subpopulation the mean value of the risk score is their regression coefficient added to the mean value of the Dutch population. *= significant interaction with sex with p-value < 0.05. For the full interaction terms with their p-values and 95% confidence intervals see Appendix Table 6.

DISCUSSION

Main finding of this study

Our findings show that being part of an ethnic minority group is associated with a higher score on three dementia risk scores, independent of age. For the Ghanaian, Turkish and Moroccan populations, this was stronger in women than in men for all risk scores. For South-Asian and African Surinamese population this was inconsistent across risk scores. This larger contrast may in part be attributable to the finding that in the Dutch population women have a lower mean risk score compared to men.

What is already known on this topic

Our results are consistent with other studies showing higher prevalence of dementia risk factors and dementia in migrant groups all over the world.[16,35-38] Several hypotheses could explain the risk differences in dementia between ethnic groups. First, lower socioeconomic status (SES) plays an important role in the future risk of dementia.[39] Educational attainment may serve as a proxy for SES, and is included in both CAIDE and ANU-ADRI. However, in the HELIUS cohort, differences in multimorbidity between ethnicities persist even after adjusting for several SES indicators.[40] To avoid introducing collider bias[41] and given our interest in the total effect of ethnicity on risk scores,[42] we did not further adjust our models for SES. Secondly, lower cognitive reserve due to fewer years of education might contribute to this increased risk.[43] Interestingly, while the LIBRA score does not include education as a variable, it still indicates higher risk scores for non-Dutch groups. Thirdly, loneliness and the high prevalence of depression may also explain the elevated risk and thus higher risk scores. However, this aspect of dementia risk is not captured by CAIDE, despite the increased risk persisting when using this tool. Finally, a higher prevalence of cardiovascular risk factors may be an important factor.[35] Yet, in our study, this could be partially offset by much lower alcohol consumption and smoking rates among groups with a migrant background. Beyond the higher prevalence of some CVD risk factors, it is possible that the presence of these factors has a larger impact on dementia risk in non-white populations.[44] However, this is something that is not yet captured when using traditional risk prediction models, where equal impact of risk factors across ethnicities is assumed.

What this study adds

A major strength of our study is that we have included a large sample of over 13,000 individuals mostly from understudied populations with extensive information on

known dementia risk and protective factors.[45] The results may also be relevant for other multi-ethnic populations in Europe that have comparable demographics and migration history. Another strength is that we looked at three different dementia risk scores which all showed consistent results in terms of increased risk profile in ethnic minorities. Since we used several risk scores that consist of different variables and assign distinct weights to these variables, we demonstrated that it is likely not a single factor driving the risk, but rather an intricate system of interacting risk factors. The Global Action Plan on Dementia by the World Health Organization (WHO) encourages policymakers to draft diversity-sensitive National Dementia Plans addressing the unique culture and demographics of the nation, specifically mentioning equity and referencing to migrants.[46] This is important as each country has its own diverse demographic makeup of migrant groups, resulting in the need for a culturally tailored approach when it comes to raising dementia awareness, providing patient-centred prevention and care.[47]

Limitations of this study

An important limitation of our study is that, apart from CAIDE,[48] the risk scores have not been developed or validated in an ethnically diverse population. A systematic review on dementia risk prediction models concluded that all risk scores have been developed in a homogeneous Caucasian population and CAIDE is the only risk score externally validated in an ethnically diverse sample with area's under the curve (AUC) of (0.81 for Asian, 0.75 for black, 0.74 for white populations), showing a differential validity of the risk score per ethnicity.[5] This may also be applicable to our study. We were not able to validate the risk scores as currently cognitive function is not measured and dementia incidence is too low in the HELIUS cohort, due to the median age of the participants. Therefore, no conclusions can yet be drawn about which risk algorithm best predicts outcomes in a multi-ethnic population like ours, and it is therefore premature to make any recommendations for clinical practice. All three risk scores were developed more than 10 years ago highlighting the importance of re-assessment of the dementia scores to potentially increase their predictive validity by including new knowledge, such as the role of ethnicity.[49] For LIBRA and ANU-ADRI not all variables were available from the HELIUS cohort, potentially leading to biased results. However, these scores have previously been used and validated in incomplete form.[26,31,50] Finally, some of the risk factors were based on self-report, such as smoking, alcohol intake and physical activity, which could lead to social desirability and recall bias. On the other hand, we have no reason to assume that these biases would differ across ethnic groups, and therefore we do not expect that this has had a large influence on our results.

Future studies should focus on validation (and recalibrating if appropriate) dementia risk scores for an ethnically diverse population, as has been done with CVD risk prediction models.[51,52] This may improve risk classifications and thus guide more active preventive strategies in certain groups, which in turn could decrease health disparities. Another important aspect that remains to be elucidated in future research is how ethnicity influences the increased risk of dementia by examining potential mediating factors, such as SES, cognitive reserve, and mental wellbeing (e.g. loneliness and depression). Taking ethnicity into consideration when drafting public health measures could contribute to more equitable dementia prevention, empowering the most vulnerable, high-risk populations in society.

CONCLUSION

Dementia risk scores were higher amongst migrant populations as compared to the Dutch host population, signalling the clustering of multiple dementia risk factors. Given the increased window of opportunity for risk factor modification in ethnic minority populations, it may be valuable to take ethnicity and cultural context into account when designing novel preventive strategies. As existing dementia risk scores are mostly developed in ethnically homogenous populations they may have limited generalizability to more heterogeneous populations. Future efforts should be made in reassessing these prediction models, so they effectively support public health intervention and contribute to a more inclusive and culturally sensitive approach towards dementia prevention.

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SUPPLEMENTARY MATERIAL

Variable	Measurement in HELIUS
Age	In years.
Education	Highest finished level of education, either in the Netherlands or country of origin. 1 = never been to school or elementary schooling only 2 = lower vocational schooling or lower secondary schooling 3 = intermediate vocational schooling or intermediate/higher secondary schooling (general) 4 = higher vocational schooling or university
Systolic blood pressure	Systolic blood pressure measured sitting down, average of two measurements.
BMI	Body Mass Index in kg/m2.
Total cholesterol	Total cholesterol mmol/L.
Physical inactivity	Self-reported physical activity using SQUASH questionnaire. Physically inactive = not adherent to Dutch guidelines (>5 days a week 30 moderate/vigorous activity.
Alcohol consumption	Self-reported low (men 0-4, women 0-2 units/week), moderate (men 5-14, women 3-7 units/week), high (men >14, women >7 units/week).
Smoking	Self-reported current, stopped or never.
Coronary heart disease	Corrected prevalent cardiovascular disease (intermittent claudication, possible infarction, angina pectoris) according to Rose questionnaire.
Diabetes	Diabetes based on self-report, increased fasting glucose (>=7 mmol/l) or use of glucose lowering medication.
Renal dysfunction	eGFR< 60 ml/min/1,73m2 calculated based on creatinine umol/L using ckd-epi 2021.
Depression	Patient Health Questionnaire – 9 (PHQ-9)

Supplementary Table 1: Measurement of variables in HELIUS.

Risk factor	Score
Age	
<47 years	0
47-53 years	3
>53 years	4
Education	
≥10 years	0
7-9 years	2
0-6 years	3
Sex	
Women	0
Men	1
Systolic blood pressure	
≤140 mmHg	0
>140 mmHg	2
Body-mass index	
≤30 kg/m2	0
>30kg/m2	2
Total cholesterol	
≤6.5 mmol/L	0
>6.5 mmol/L	2
Physical activity	
Active	0
Inactive	1

Supplementary Table 2: calculation of CAIDE score. All variables were available from the HELIUS cohort.

Modifiable risk factor	Score
Low/moderate alcohol consumption	-1.0
Coronary heart disease	+1.0
Physical inactivity	+1.1
Renal dysfunction	+1.1
Diabetes	+1.3
High cholesterol	+1.4
Smoking	+1.5
Obesity	+1.6
Hypertension	+1.6
Mediterranean diet**	-1.7
Depression	+2.1
High cognitive activity*	-3.2
Low unsaturated fat intake**	

Supplementary Table 3: calculation of LIBRA index. *Variable unavailable from the HELIUS cohort. **Only measured in a subsample and not in Ghanaian group, therefore excluded from analysis.

Risk factor	Score
Age for males	
<65 years	0
65 years- 70	1
70 years- 75	12
75 years- 80	18
80 years- 85	26
85 years- 90	33
>90	38
Age for females	
<65 years	0
65 years- 70	5
70 years- 75	14
75 years- 80	21
80 years- 85	29
85 years- 90	35
>90 years	41
Education	
>11 years	0
8 to 11 years	3
<8 years	6
Body Mass Index (age < 60)	
Normal	0
Overweight	2
Obese	5
Diabetes	
No diabetes	0
Diabetes	3
Symptoms of depression**	
CES-D < 16	0
CES-D > 16 Depression	2
High cholesterol (aged < 60)	
≤6.2 mmol/L	0
>6.2 mmol/L	3
Traumatic Brain Injury(TBI)*	
No TBI	0
TBI	4

Smoking	
Never	0
Ever smoking	1
Current	4
Alcohol intake	
No alcohol	0
Light-mod	-3
Social engagement*	
Highest	0
Lowest	6
Low to med	4
Med to high	1
Physical activity	
Lowest	0
Medium	-2
Higher level	-3
Cognitive activity*	
Lowest	0
Middle	-7
Highest	-6
Fish intake*	
<0.25 p p/week	0
0.25–2 p p/week	-3
2–4 p p/week	-4
>4 p p/week	-5
Pesticide exposure*	
Never	0
Ever	2

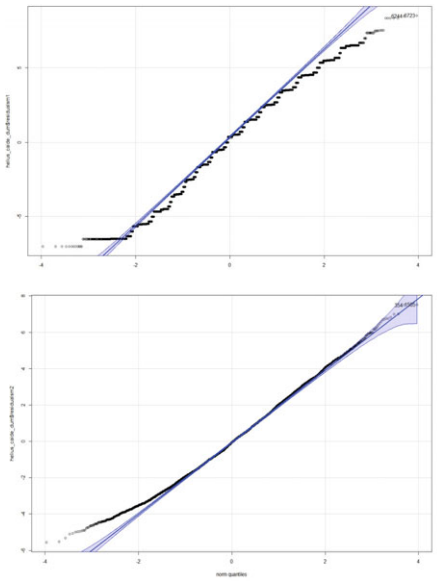
Supplementary Table 4: calculation of ANU-ADRI score. All variables in ANU-ADRI are based on self-report. *Variables unavailable from the HELIUS cohort. ** Measured in HELIUS using PHQ-9 questionnaire, using algorithm to define significantly depressed mood.[1]

	Dutch	South-Asian Surinamese	African Surinam-ese	Ghanaian	Turkish	Moroccan
n	2918	2008	2985	1579	1874	1939
Age (median [IQR])	55 [48, 62]	53 [47, 59]	54 [48, 59]	50 [45, 55]	49 [44, 53]	50 [45, 56]
Female (n, %)	1555 (53.3)	1119 (55.7)	1832 (61.4)	918 (58.1)	1017 (54.3)	1142 (58.9)
Educational level 1 (n, %)	123 (4.2)	372 (18.5)	186 (6.2)	537 (34.0)	896 (47.8)	1032 (53.2)
Educational level 2 (n, %)	576 (19.7)	821 (40.9)	1228 (41.1)	641 (40.6)	458 (24.4)	355 (18.3)
Educational level 3 (n, %)	619 (21.2)	442 (22.0)	931 (31.2)	338 (21.4)	357 (19.1)	409 (21.1)
Educational level 4 (n, %)	1600 (54.8)	373 (18.6)	640 (21.4)	63 (4.0)	163 (8.7)	143 (7.4)
Current smoking (n, %)	658 (22.5)	544 (27.1)	937 (31.4)	78 (4.9)	592 (31.6)	211 (10.9)
High alcohol intake (n, %)	537 (18.4)	99 (4.9)	139 (4.7)	18 (1.1)	43 (2.3)	15 (0.8)
Physical inactivity (n,%)	708 (24.3)	869 (43.3)	1089 (36.5)	737 (46.7)	1058 (56.5)	973 (50.2)
BMI (mean (SD))	25.6 (4.3)	26.9 (4.6)	28.4 (5.5)	29.2 (4.8)	30.3 (5.4)	29.4 (4.9)
Total cholesterol (mean (SD))	5.4 (1.0)	5.1 (1.1)	5.0 (1.0)	5.1 (1.0)	5.1 (1.0)	4.9 (1.0)
Systolic blood pressure (mean (SD))	128 (17)	133 (19)	135 (18)	140 (19)	128 (16)	127 (16)
Cardiovascular disease (n, %)	158 (5.4)	541 (26.9)	457 (15.3)	231 (14.6)	317 (16.9)	396 (20.4)
Diabetes (n, %)	77 (2.6)	214 (10.7)	150 (5.0)	66 (4.2)	288 (15.4)	236 (12.2)
Depressive symptoms (n, %)	148 (5.1)	325 (16.2)	327 (11.0)	147 (9.3)	340 (18.1)	286 (14.7)
Renal dysfunction (n, %)	35 (1.2)	47 (2.3)	92 (3.1)	61 (3.9)	16 (0.9)	18 (0.9)

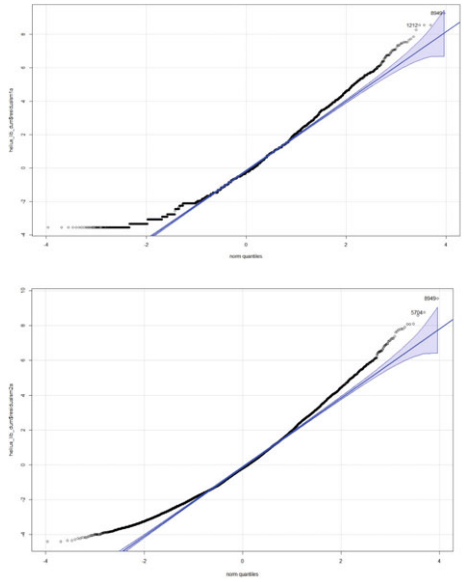
Supplementary Table 5: Study sample characteristics of complete cases (n=13,303). IQR=interquartile range. Educational level: 1=never been to school or elementary schooling only, 2=lower vocational schooling or lower secondary schooling, 3= intermediate vocational schooling or intermediate/higher secondary schooling (general), 4= higher vocational schooling or university. Physical inactivity= less than prescribed by Dutch physical activity guidelines (≥5 days/week 30 minutes moderate activity). High alcohol intake = > 7 units/week for women, > 14 units/week for men.

	CAIDE		LIBRA		ANU-ADRI	
	B (95%CI)	p-value	B (95%CI)	p-value	B (95%CI)	p-value
Model 3: Age-adjusted and sex added as an interaction term						
Intercept	2.09 (2.00 – 2.17)	0.000	0.86 (0.77 – 0.95)	0.000	0.01 (-0.20 – 0.21)	0.949
South-Asian Surinamese	1.10 (0.96 -1.24)	0.000	1.26 (1.11 – 1.40)	0.000	4.26 (3.94 – 4.58)	0.000
African Surinamese	1.03 (0.91 – 1.17)	0.000	1.26 (1.13 – 1.39)	0.000	3.39 (3.11- 3.67)	0.000
Ghanaian	2.76 (2.60 -2.91)	0.000	1.45 (1.31 – 1.60)	0.000	6.30 (5.96 – 6.64)	0.000
Turkish	2.34 (2.19 – 2.49)	0.000	2.04 (1.88 – 2.19)	0.000	9.29 (8.96 -9.62)	0.000
Moroccan	2.20 (2.06 – 2.33)	0.000	1.19 (1.05 – 1.33)	0.000	8.18 (7.86 – 8.50)	0.000
Age	0.08 (0.08 -0.09)	0.000	0.06 (0.06 – 0.06)	0.000	0.11(0.10-0.12)	0.000
Male sex	-0.01 (-0.15 – 0.11)	0.852	0.25 (0.12 – 0.39)	0.000	0.06(-0.25 – 0.36)	0.709
South-Asian Surinamese:Male sex	-0.23 (-0.44- -0.02)	0.042	0.18 (-0.04 – 0.39)	0.130	-0.37(-0.84 – 0.11)	0.128
African Surinamese:Male sex	-0.17 (-0.35 – 0.02)	0.088	-0.58 (-0.78 - -0.39)	0.000	-0.88 (-1.31 - -0.45)	0.000
Ghanaian:Male sex	-1.18 (-1.41 - -0.93)	0.000	-0.88 (-1.11 - -0.66)	0.000	-3.31 (-3.82 - -2.80)	0.000
Turkish:Male sex	-0.68(-0.89 - -0.45)	0.000	-0.61 (-0.86 --0.38)	0.000	-2.27 (-2.76 - -1.79)	0.000
Moroccan:Male sex	-0.97 (-1.18 - -0.77)	0.000	-0.69 (-0.90 - -0.46)	0.000	-1.98 (-2.46 - -1.50)	0.000

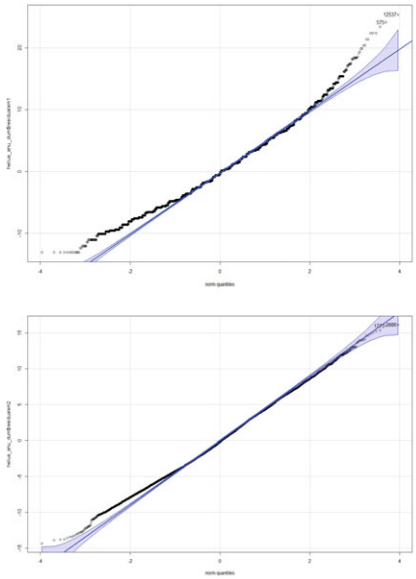
Supplementary Table 6: Exploration of effect modification by sex in mean centred age adjusted models. Depicted are the results for all covariates included in one single model, with interaction terms for each ethnicity with sex. Interaction terms denote the interaction for male sex as opposed to female sex.



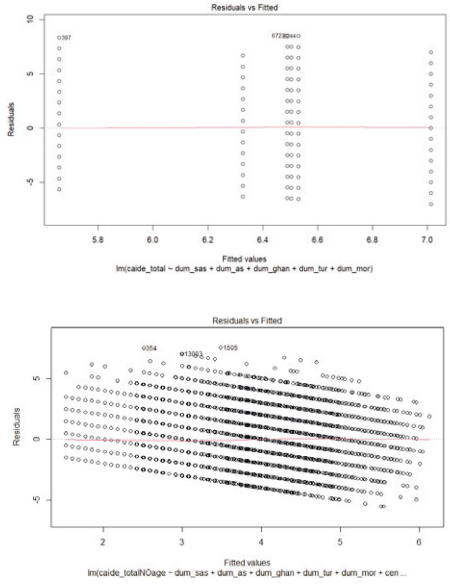
Supplementary Figure 1: Q-Q plots of CAIDE crude Model 1 and mean centred age adjusted Model 2.



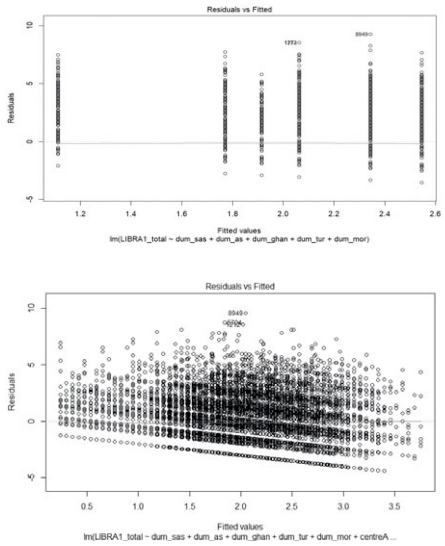
Supplementary Figure 2: Q-Q plots of LIBRA crude Model 1 and mean centred age adjusted Model 2.



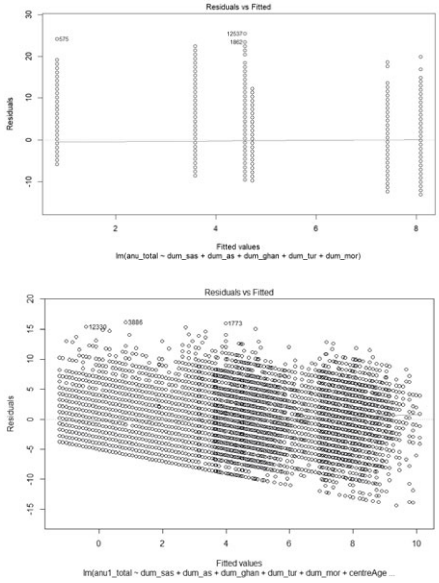
Supplementary Figure 3: Q-Q plots of ANU-ADRI crude Model 1 and mean centred age adjusted Model 2.



Supplementary Figure 4: Residuals vs. fitted plot of crude Model 1 and mean centred age adjusted Model 2 CAIDE score.



Supplementary Figure 5: Residuals vs. fitted plot of model 1 of LIBRA score.



Supplementary Figure 6: Residuals vs. fitted plot of crude Model 1 and mean centred age adjusted Model 2 ANU-ADRI score.

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Chapter IV

A COACH-SUPPORTED MHEALTH LIFESTYLE INTERVENTION TO REDUCE DEMENTIA RISK IN PERSONS WITH LOW SOCIOECONOMIC STATUS OR A MIGRATION BACKGROUND: QUALITATIVE CO-DESIGN STUDY

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ABSTRACT

Background The prevalence and incidence of dementia are higher in migrants and those with low socioeconomic status (SES). Mobile health (mHealth) interventions offer a potentially scalable way to reduce dementia risk via risk factor modification.

Objective We co-designed the MIND-PRO app—an mHealth intervention targeting dementia risk factors through self-managed lifestyle changes and remote coaching—specifically designed for Dutch individuals with low SES and those with Turkish or South-Asian Surinamese migration backgrounds. We focused on these migrant populations as they are the largest in the Netherlands and have the highest risk of developing dementia.

Methods In this qualitative study we explored the needs and preferences of our target populations aged 50-75 years old at increased dementia risk by conducting semi-structured interviews and focus groups. Participant feedback was used to iteratively refine and adapt a prototype intervention based on insights from prior mHealth trials.

Results We interviewed 23 participants (median age 59, IQR 55-63 y; n=15, 65% female) and conducted two focus groups with 7 Turkish women and 13 Dutch participants with low SES. The target populations emphasized personalization features such as: goal setting, self-tracking, educational material, and remote coaching. Participants highlighted the importance of social interaction and autonomy in achieving sustainable lifestyle changes. Tailoring coaching and lifestyle advice to cultural practice were deemed beneficial.

Conclusion Optimal mHealth interventions targeting dementia risk factors in migrants and individuals with low socioeconomic status should be personalized and interactive, respect autonomy, and integrate cultural needs and preferences.

INTRODUCTION

The global prevalence of dementia is expected to increase due to population aging and growth, with up to 40% of cases linked to modifiable risk factors such as high blood pressure, physical inactivity, unhealthy diet, overweight, and smoking.[1] High-risk populations, including individuals of lower socio-economic status (SES) and those with a migration background in high-income countries, are particularly vulnerable due to clustering of lifestyle-related risk factors, which provides a significant opportunity for prevention.[2-7]

Mobile Health (mHealth), which involves using mobile communication devices (e.g. smartphones, tablets, and smartwatches) may be an effective medium for interventions as it can reach many people in a cost-effective way.[8] In the Healthy Aging through Internet Counseling of the Elderly (HATICE)[9] and Prevention of Dementia by Mobile Phone Applications (PRODEMOS) trials[10] our research team focused on self-management of lifestyle-related cardiovascular and dementia risk factors through interventions delivered via computer, tablet, or smartphone. Key findings from these studies formed the basis for the current prototype of the intervention, the MIND-PRO app. This new intervention is specifically designed to target individuals at increased risk of dementia, particularly those with lower SES or a Turkish or South-Asian Surinamese background in The Netherlands. Individuals with a Turkish or South-Asian Surinamese background, have the highest age specific prevalence of dementia amongst groups with a migration background as compared to the majority population, and represent large migrant groups in the Netherlands.[4] The needs and preferences for an mHealth intervention may vary between these groups.

mHealth users consistently highlight the importance of personalized content, user friendliness, human guidance, and autonomy in mHealth interventions.[11, 12] Involving end-users in the development process can address these needs and enhance engagement and effectiveness.[13-15] Therefore, we employed a qualitative co-design study to investigate how a blended mHealth lifestyle intervention can be tailored to effectively reach and engage individuals with lower SES or a Turkish or South-Asian Surinamese background.

METHODS

Study design

This qualitative study was based on a prototype of the blended mHealth lifestyle intervention – The MIND-PRO app - built on insights from the HATICE and PRODEMOS trials.[16-22] To ensure usability and cultural relevance, we actively involved our target population by asking for their feedback on the prototype. In iterative cycles of feedback, the researchers and mHealth developers refined the intervention according to participants' input. This co-design process incorporated culture-specific needs and preferences, aiming to align the intervention with its target population (Figure 1). Initially, semi-structured interviews were conducted to explore participants' perspectives and requirements for a coach-supported lifestyle intervention. Among Turkish participants, we observed diverse views on culturally sensitive approaches. To gain a deeper understanding of these different perspectives, we organized a focus group, to facilitate further discussion and refinement of the platform, ensuring that it was both user-friendly and culturally appropriate. For Dutch citizens with low SES perspectives on mHealth interventions had already been qualitatively explored in a previous study[23] and tested in a randomized controlled trial for efficacy and implementation.[17] Therefore, in this study, we directly tested the MIND-PRO prototype in a focus group with this population. This study adhered to the COnsolidated criteria for REporting Qualitative research (COREQ) checklist (Supplementary Checklist 1).

Study population and recruitment

Participants were community-dwelling Dutch individuals with low SES and/or a Turkish or South-Asian Surinamese background. We used convenience sampling by recruiting participants from community centers, with the help of key figures and the authors' networks. For the Dutch/non-migrant group, low SES was defined based on self-reported educational attainment, categorized as none, only primary education, or lower vocational/lower secondary education. A Turkish or South-Asian Surinamese background was defined as having at least one parent born in Turkey or Suriname. Inclusion criteria were being 50–75 years old, owning a smartphone and at least one dementia risk factor (hypertension, dyslipidemia, diabetes mellitus, physical inactivity, smoking, depression, or being overweight). We acknowledge that referring to 'individuals with Turkish or South-Asian Surinamese backgrounds' may insufficiently the diversity within the group. However, specifying cultural background is essential to tailor the intervention effectively.[24] Similarly, using SES as a criterion may not fully capture individuals' competencies and may be perceived as stigmatizing.[25] Our

rationale for these definitions is that these groups are underrepresented in research, often leading to scarce and ineffective interventions targeting their specific needs.

Prototype of the mHealth intervention

The intervention design was guided by Bandura's Social Cognitive Theory, which informed the goal-setting and self-tracking structure.[26] To enhance perceived ease-of-use and usefulness, we applied the frameworks of the Technology Acceptance Model (TAM)[27] and Unified Theory of Acceptance and Use in technology (UTAUT).[27] In the prototype, participants could set lifestyle change goals, record self-measurements, and monitor their progress, i.e., on bodyweight, blood pressure and physical activity duration and frequency. Progress was visually represented through graphs and color-coded diaries. Additionally, participants had the option to send messages to a coach, and the app featured a library of education materials specifically designed for this study (Figure 2).

Data collection

Interviews and focus groups were conducted by six members of the research team: ARvdE (Dutch, female, MD), JL (Dutch, female, MD), RR (Dutch, male, anthropologist, South-Asian Surinamese migration background), RA (Dutch, female, master's student, Ghanaian migration background), ES (Dutch, female, research coordinator, Turkish migration background) and MH-B (Dutch, female, postdoctoral researcher). We worked with a multicultural team to promote alignment between interviewers and participants in terms of language and cultural background. Interviewing experience ranged from novice to highly experienced. Interviews and focus groups were conducted in Dutch or Turkish, with ES providing translation when necessary.[28]

Topic lists were developed by ARvdE and JL under the supervision of senior qualitative researchers (EMvC and MH-B), drawing on the TAM and UTAUT models.[27] ES contributed to ensure accurate translation and clarification of concepts.

Interviews and focus groups began with general discussions on lifestyle perceptions, past behavior changes, and experiences with health apps. The intervention prototype was then introduced with minimal guidance, allowing participants to explore it independently or in small groups while researchers observed usability. Open-ended questions explored key features: user-friendliness, goal setting, progress tracking, coaching, and educational materials. Participants provided input on necessary adjustments to better fit their needs and preferences. Identified themes related to

culture and gender were tested across groups. The interview guide was iteratively refined throughout data collection (Supplementary Text 1 and 2).

Adjustments to the app were made in real time, allowing participants to immediately confirm whether their preferences were understood. Most interviews were conducted individually, though four small-group interviews (up to four participants) were held at participants' request, primarily due to language barriers. All interviews and focus groups were audio-recorded, with two researchers present—one leading the discussion and the other taking field notes.

Data analysis

Data analysis was conducted iteratively, allowing interim findings to inform adaptations to the prototype intervention and interview guide. After data collection, we thematically analyzed the transcripts based on Braun and Clarke's six-phase framework.[29] Firstly, the four interviewers familiarized themselves with the data through listening to the recordings and reading the transcripts. Secondly, each interview was categorized and double-coded by JL and RA using MAXQDA 24 software and discussed with ARvdE and the broader team to discuss initial findings and identify knowledge gaps. Data from the focus groups were directly discussed within the team. In case of uncertainty, the most experienced qualitative researcher (EMvC) acted as an arbitrator. Thirdly, key ideas and concepts were extracted to generate themes and subthemes. Fourthly, these themes were collaboratively reviewed for consistency in interpretation. Fifth, the core research team (JL, RA, RR, ARvdE) refined theme names and definitions before developing a final narrative synthesis.

Ethical considerations

We received a waiver from the Medical Ethics Committee of the Amsterdam UMC (METC reference number: 2023.0578), as the study did not fall within the scope of Medical Research involving Human Subjects Act (WMO) in the Netherlands. Informed consent was obtained from all participants before the start of each interview and focus group. Participants' privacy was protected by deidentifying their data and replacing their names with confidential participant numbers. Participants were compensated for travel costs, where applicable. The intervention developed in this study will subsequently be evaluated for effectiveness and implementation in a randomized controlled trial (MIND PRO: ISRCTN registry: *ISRCTN92928122).*[30]

RESULTS

Overview

Between October 2023 and November 2024, we interviewed 23 participants with a median age of 59 (IQR 55 – 63), of whom 65% (n=15) were female. The sample consisted of 14 participants with a Turkish migration background (10 female and 4 male participants; median age 55, IQR 50-59 y) and 9 participants with a South-Asian Surinamese migration background (5 female and 4 male participants; median age 62, IQR 60-66 y). In the Turkish population, it was more challenging to include men. The focus group with Dutch individuals with low-SES was organized in an area housing mainly factory workers with generally low educational levels. This focus groups consisted of three women and ten men with a median age of 73 (IQR 68 – 73) years. A second focus group was organized at a community center with 7 Turkish women aged between 50 and 63 years, to explore and refine contrasting perspectives observed in the individual interviews and to facilitate group discussion. As findings from the individual interviews with the South Asian Surinamese population were largely consistent, an additional focus group was deemed unnecessary. Our main findings are summarized in Supplementary Table 5, with supporting quotes from all three groups. Specific adaptations made to the mHealth intervention based on our findings are presented in Table 1. In describing the results, we focus on the overall blended mHealth intervention, which combines self-management of health factors with guidance from a remote coach. The app used by participants served as the delivery platform for the intervention.

Usability and cultural adaptation of the intervention

Participants were generally open to mHealth interventions and recognized the importance of a healthy lifestyle. However, most associated this primarily with overall well-being rather than the specific link between an unhealthy lifestyle and dementia risk in later life. User-friendliness of the platform was deemed essential in all three groups, and could be improved through minimal text, visual aids (photos/videos), adjustable font sizes, clear navigation between pages to prevent disorientation, and an intuitive design resembling familiar apps (Q3 and Q4, Supplementary Table 2). While all participants owned a smartphone, many of them - especially those with a low SES - felt less competent with modern technologies compared to younger users, emphasizing the need for clear instructions on app usage (Q4, Supplementary Table 2). To improve the comprehensibility of the information in the app, participants emphasized the use of simple, easy-to-understand language. Specifically, participants with a Turkish

background mentioned the importance of providing a Turkish translation. For them, it was not just about understanding the language but also about the emotional connection it created (Q1, Supplementary Table 2). Many participants with a Turkish and South-Asian Surinamese background emphasized the importance of cultural congruence (Q2, Supplementary Table 2). They expressed a preference for culturally sensitive educational materials and a coach familiar with their cultural background, to better accommodate culture-specific needs and preferences.

Key functionalities of the intervention

Goal setting

Over half of the participants in all three groups wanted to work on a lifestyle goal. The most common goal was increasing physical activity, followed by improving dietary patterns and losing weight. The importance of personalization of goals was frequently mentioned, particularly by the focus group with participants with a low SES (Q7, Supplementary Table 2). They also emphasized that a healthy lifestyle is not achieved by reaching a single health goal but requires working on multiple aspects, such as physical activity, healthy eating, and not smoking. Participants - mainly those with a Turkish background - highlighted that incorporating a healthy lifestyle into their daily routine can be challenging when it is not yet an established habit. Across all groups, participants reported feeling demotivated when goals seem unattainable, and therefore preferred to take small, manageable steps toward lifestyle changes (Q5 and Q8, Supplementary Table 2).

Self-tracking

Most participants viewed the ability to track their own progress as motivating and a way to maintain accountability (Q9, Supplementary Table 2). However, there was also some ambivalence towards self-tracking across all groups, as not reaching a goal might be demotivating (Q 10 and 11, Supplementary Table 2). Using only positive reinforcement in the intervention was suggested as a solution to mitigate negative emotions associated with self-tracking. Also, some participants mentioned the requirement to manually enter physical activity as a barrier. Comparing progress with others - whether on an individual level or a broader demographic level (i.e., women of similar age and ethnic background) - was generally not perceived as desirable, particularly by women, as it could lead to feelings of jealousy, worthlessness, or guilt (Q12, Supplementary Table 2).

Education material

General

All participants were open to receiving information on a healthy lifestyle. They preferred practical information that is relevant to their personal health goals (Q15, Supplementary Table 2). A key factor when seeking information was the perceived trustworthiness of the source (Q13, Supplementary Table 2). Some expressed distrust toward online resources, preferring to seek advice directly from their general practitioner (Q16, Supplementary Table 2). In response to educational items presented in the prototype of the intervention, most participants indicated they would trust the information provided, particularly if it came from recognized experts or familiar figures, such as a lifestyle coach. Additionally, participants emphasized the importance of a positive, non-pressuring tone when presenting information (Q14, Supplementary Table 2).

Healthy eating

The need for cultural tailoring varied between the ethnic groups. South-Asian Surinamese participants displayed strong adherence to their traditional dietary patterns (Q18 and 19, Supplementary Table 2), whereas the Turkish participants emphasized the significant diversity within Turkish dietary practices, even within Turkey itself (Q17, Supplementary Table 2). This diversity facilitated their adaptation to new dietary habits, as they were already accustomed to cultural variation. In addition, integration into Dutch culture had already influenced their dietary patterns. In contrast, South-Asian Surinamese interviewees stressed the historical significance and perceived health benefits of their traditional Hindustani cuisine, including Ayurvedic cooking (Q19, Supplementary Table 2). Maintaining a healthy diet was often hampered by cultural factors, such as the social expectation to partake in abundant meals during gatherings. In both Turkish and South-Asian Surinamese cultures, visits are traditionally accompanied by sweets, making dietary adjustments difficult. While some participants successfully modified their eating habits within their households, social settings -such as hosting visitors or dining with friends- posed greater challenges (Q20, Supplementary Table 2). Specific advice on portion control (e.g., 'What is a healthy amount of rice?') was suggested as a practical way to navigate these social influences.

Physical activity

Several interviewees stressed the importance of finding the motivation for gradually increasing physical activity, as it is not inherently part of the Turkish or South-Asian Surinamese culture (Q21 and 24, Supplementary Table 2). Turkish interviewees often mentioned the inability to cycle as a limitation (Q21, Supplementary Table 2). A South-Asian Surinamese woman highlighted her inability to swim, which limited her advised exercise options. The Dutch rainy weather was widely perceived as a significant barrier to engaging in outdoor physical activities, particularly among South-Asian Surinamese participants. Some Turkish and South-Asian Surinamese women favored home-based exercises as a more accessible alternative, with this preference being especially pronounced among Turkish women (Q22 and 23, Supplementary Table 2).

Remote coach

Some participants from all groups were skeptical about combining a lifestyle app with a human coach (Q26, Supplementary Table 2). This skepticism stemmed from lack of experience with coach-supported interventions and concerns about intrusiveness, fearing it might undermine their autonomy in lifestyle decisions.

Others recognized potential benefits, viewing the coach as a source of information (especially on healthy food choices) and as motivation and accountability support (Q25, Q29 and Q30, Supplementary Table 2). Most preferred contact on their own request via chat, voice messages, or video calls, with frequency ranging from daily to monthly. While many were initially hesitant, trust was a key factor in accepting a coach (Q26, Supplementary Table 2). Especially participants with a low SES emphasized the need for a personalized approach, with tailored advice based on their individual situation (Q30, Supplementary Table 2). Some also stressed the importance of building a relationship before feeling comfortable enough to ask questions (Q31, Supplementary Table 2).

Preferences regarding cultural and gender matching varied. South-Asian Surinamese participants did not consider cultural matching essential but emphasized that the coach should be knowledgeable about their dietary habits. Turkish participants, however, valued a Turkish-speaking coach for guidance. Some women from both ethnic groups preferred a female coach, believing they would better understand their concerns or help avoid tensions with their spouses (Q27 and Q28, Supplementary Table 2).

Implementation requirements

Autonomy

Almost all participants across all groups explicitly mentioned that respecting their autonomy was essential for the intervention to be accepted as a tool for lifestyle change and to prevent disengagement. Most expressed an appreciation for receiving information but stressed that guidance from the coach should be offered in a non-obligatory way and with positive messaging. The importance of respecting an individuals' autonomy was ubiquitous across all groups and participants viewed this an essential condition to be willing to participate in a blended intervention (Q32-34, Supplementary Table 2).

Social environment

Participants across all groups emphasized that their interpersonal relationships significantly influenced their ability to change their lifestyle. A supportive social environment that aligned with their personal health goals was seen as beneficial, such as having a partner join in the lifestyle change or friends supporting dietary adjustments (Q37 and 40, Supplementary Table 2). Conversely, many Turkish women and South-Asian Surinamese men and women mentioned that family responsibilities often conflicted with their ability to change their lifestyle, reducing the perceived usefulness of the intervention (Q38, Supplementary Table 2). Sharing progress with their social environment was seen as motivating by most participants in all three groups (Q36 and 39, Supplementary Table 2). However, it was stressed that this feature should remain optional. Not all participants felt the same about sharing progress; some regarded lifestyle changes as a personal journey, making comparisons difficult, while others feared that seeing others achieve greater success might discourage them.

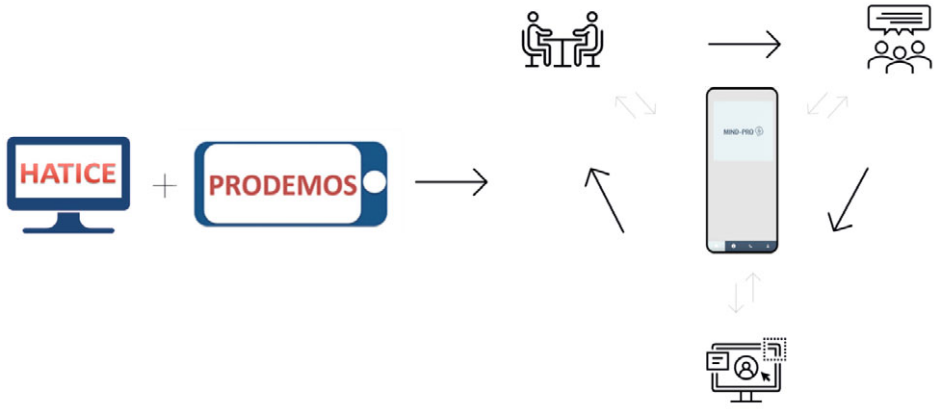

Figure 1: Illustration of co-design process. A prototype of the intervention was designed, in collaboration with the mHealth developers and the research team, based on prior eHealth and mHealth trials. This prototype was then presented to participants during interviews and focus groups, after which their feedback was used in iterative cycles to make adjustments to the prototype. This process ultimately led to the final version of the intervention. HATICE: Healthy Ageing Through Internet Counselling in the Elderly Study (eHealth) PRO-DEMOS: Prevention of Dementia using Mobile Phone Applications Study (mHealth)

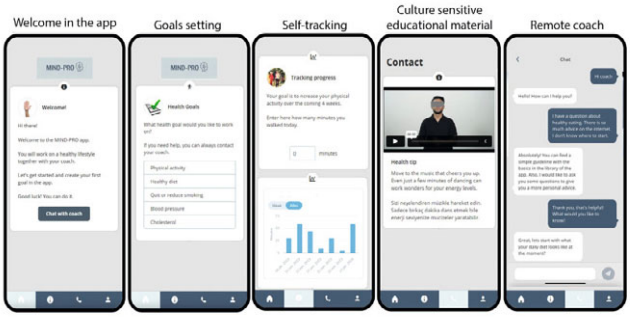

Figure 2: The MIND-PRO app. Overview of some key functionalities available in the app. Users can set lifestyle goals, track their progress, receive videos from their personal coach, and chat with their coach.

Domain and goal	Adaptation in the intervention
Usability and cultural adaptation of the intervention	
Appropriateness	
Improve cultural and contextual fit	• Provide the intervention in the first language of users • Provide a culturally tailored intervention with advice and guidance that is sensitive to cultural preferences and needs
Acceptability	
Enhance user acceptance	• Provide adaptable font sizes • Minimize the text in the app and use short videos as educational material • Use a positive, motivating tone throughout the intervention
Key functionalities of the intervention	
Goal setting	
Enhance self-efficacy	• Users are motivated by the coaches to come up with their own goals
Achieve sustainable lifestyle changes	• Coaches encourage participants to take small steps toward achieving their goals
Strike a balance between the flexibility to work toward several goals that are yet manageable	• Participants can set a maximum of 2 goals at a time and are free to adjust their goals whenever they want
Coaches monitor whether goals are attainable to inhibit demoralization	• The first goal will be set together with the coach using motivational interviewing techniques
Self-tracking	
Sustain motivation	• Personal performance feedback will be given by the coach • Tracking should be nonobligatory without an abundance of reminders, as this may lead to demoralization and guilt toward oneself or the coach
Educational material—general	
Improve trustworthiness	• Provide videos with a familiar face, for example, their remote coach, to engage and instruct participants

Educational material—diet	
Provide culturally sensitive information	• Both culturally sensitive content that incorporates commonly used recipes and ingredients familiar in Turkish, South Asian Surinamese, and Dutch culture, as well as "general" healthy recipes
Educational material—physical activity	
Provide culturally sensitive information	• Content on physical activity provided options for indoor activities • Being sensitive to the content about certain activities that are not common among Turkish people in the Netherlands (such as biking, which is very common in Dutch culture) • Addition of dancing and household chores as physical activity goals
Remote coach	
Build a bond of trust	• After a first face-to-face meeting with the coach, users will be able to contact their coach via chat • Participants will receive prerecorded videos of the coaches in the app to enhance familiarity
Provide culture-sensitive guidance	• Coaches will be culturally matched and be able to speak Turkish if applicable
Implementation requirements	
Autonomy	
Enhance the feeling of self-efficacy	• Reduce notifications; too many messages are overwhelming • Messages should be in a positive, nonobligatory tone; if not, they can be considered demotivating • Coaches will match recommendations for physical activity to ability and preference to accommodate lifestyle changes at an individualized pace
Social environment	
Engaging the social context	• Participants are motivated to involve their social environment to participate in the lifestyle change

Table 1: Adaptations made to the intervention based on findings.

DISCUSSION

Principal findings

This study explored the views and preferences of Turkish and South-Asian Surinamese individuals, as well as Dutch individuals with low SES, regarding a blended mHealth intervention. Using the MIND-PRO app as a prototype, we assessed its usability and acceptability across these populations.

Participants recognized the importance of a healthy lifestyle for disease prevention but found it challenging to sustain long-term behaviour changes. They indicated that the MIND-PRO intervention could assist them in making lifestyle changes and serve as a personalized guide with tailored information to keep them motivated and engaged. In the context of individuals with low SES and migration background who often have a shorter educational attainment, participants appreciated the app's simple and familiar interface, which made it easy to navigate. Most participants identified at least one lifestyle goal they wished to achieve, highlighting the importance of making gradual, manageable changes. They regarded the app as a reliable source of information for healthy lifestyle education. Although tracking progress was seen as useful, some participants felt uncomfortable comparing their progress with others. To build trust, a face-to-face meeting with the coach and personalized advice were suggested, as remote coaching was unfamiliar to many. The ability to make independent choices within the intervention was particularly important, as participants valued autonomy in their decision-making. Social support played a significant role in behavior change, with encouragement from partners and peers viewed as beneficial, whereas family obligations were sometimes seen as a barrier. The expressed need for cultural tailoring varied. While some valued adaptation in dietary and physical activity guidance, Turkish participants felt their cultural diversity already facilitated adaptability to Dutch customs. In contrast, South-Asian Surinamese participants remained more attached to traditional dietary patterns as part of their cultural identity. Across groups, there was a preference for culturally aware coaching, tailored language options, and personalized physical activity guidance.

mHealth interventions have demonstrated their potential in lifestyle modification for dementia prevention,[31] and can be suitable for ethnically diverse populations if barriers related to accessibility and usability are addressed.[32] Nevertheless, most studies on mHealth interventions for lifestyle modification and healthy ageing show only modest effects and have high attrition rates.[13, 23, 31, 33, 34] Strengthening engagement strategies is essential to employ the full potential of mHealth for lifestyle modification.

Self-Determination Theory suggests that behavior change is more sustainable when it is driven by intrinsic motivation rather than external pressure.[35] This principle of choice and self-governance is incorporated into our intervention, allowing users to customize the intervention by setting personal goals and self-tracking their progress to enhance the feeling of autonomy. A remote coach can further support motivation by using techniques such as motivational interviewing to identify goals aligned with each user's needs and values.[36] Positive reinforcement from a coach can improve usability, adherence, and health outcomes.[37] Furthermore, self-tracking is a well-established strategy to improve adherence, which this intervention supports through simple graphs and color-coded feedback in progress journals.[38]

In addition to coaching, social interaction with peers is often mentioned as a valuable tool for behavior change, such as by enabling users to share their progress.[39] Our study participants had mixed views on this: while some valued privacy and felt discouraged by others' success, others found social support and a sense of healthy competition motivating. This contrast is supported by a systematic review on social features in mHealth interventions, which reported varying preferences for social involvement.[40]

Culturally tailoring the intervention was deemed important by some participants, and previous studies have shown that tailored web-based interventions enhance patient engagement and are more effective at facilitating lasting behavior change.[15] However, cultural tailoring assumes that ethnic groups are homogeneous and share similar core values, whereas individuals bring their own unique social, cultural, and historical experiences. Both groups expressed the need for tailored physical activity guidance suited to individual abilities and skills. Facilitators for physical activity included exercising with peers and receiving suggestions for activities that could be done at home. To address these cultural nuances, the intervention will feature culturally sensitive content on topics such as language, diet, physical activity, and health goals, shared on users' timelines to support lifestyle education (Figure 2). Such tailored content, aligned with cultural norms, beliefs, and practices, is easier to integrate into daily life,[41] increases trust in the intervention, and improve users' self-efficacy.[15] We aimed to balance cultural tailoring with personalization through features like goal setting, self-tracking, and personalized coaching. This dual approach acknowledges multiple cultural identities while remaining sensitive to individuals' unique needs.[42]

Strengths and Limitations

A key strength of this study is its focus on diverse populations, particularly those from culturally diverse backgrounds and/or low socioeconomic status, who are often underrepresented in preventive healthcare. Many mHealth interventions primarily target younger, highly educated users, potentially excluding individuals with lower health literacy, lower socioeconomic backgrounds, migration backgrounds, or older adults, thereby exacerbating health inequalities.[43-45] This highlights the need for inclusive interventions tailored to these groups.[45] Another strength is the use of a functional prototype, enabling iterative refinements based on direct participant feedback. Finally, the study benefited from a diverse research team with backgrounds in medicine, anthropology, mHealth, and public health, including members with Turkish, South-Asian Surinamese and Dutch backgrounds. This diversity enhanced cultural sensitivity and facilitated theoretical triangulation.

The study also has limitations. First, although a bilingual researcher (ES) facilitated communication with Turkish-speaking participants, the use of interpreters and translation may have led to a subtle loss of nuance or introduced bias, particularly given the cross-cultural nature of the discussions. However, as ES was part of the study team, she was able to indicate during the Turkish-language interviews which information was relevant and aligned with the aims of data collection. In addition, we engaged in regular reflection with her on culturally specific concepts that were challenging to translate. Second, the gender imbalance—characterized by underrepresentation of men among Turkish participants and overrepresentation of men in the focus groups with Dutch individuals with a low SES—limited our ability to assess gender-specific preferences. However, a similar prototype was previously tested extensively among Dutch individuals with low SES, where no significant gender differences in user preference and needs were observed.[46] Third, this intervention was tailored to the culturally specific preferences of Turkish and South- Asian Surinamese populations in the Netherlands, as well as to the Dutch host population with a low SES. The transferability of our findings regarding culturally sensitive content to other contexts or populations is, therefore, limited. Future studies developing mHealth lifestyle interventions in other countries or for different target groups should explore and integrate the cultural needs of those populations. This study could offer a useful guide to which components may require adaptation, such as language, culturally sensitive educational content (eg, on physical activity and nutrition), and culturally aware coaching. At the same time, several of the core functionalities we identified—such as goal setting, self-tracking, accessible educational materials, and remote coaching—may be broadly applicable across diverse settings.

CONCLUSION

This study highlights the importance of tailoring mHealth interventions for lifestyle modification to reduce dementia risk factors in migrants and individuals with low SES. To be effective, interventions should integrate cultural preferences, provide positive and nonobligatory content, and respect users' autonomy while ensuring that information is relatable and easy to understand. A crucial factor for success is the active involvement of end users in the development process, allowing for the identification and integration of context-specific needs and preferences. Notable cultural differences emerged: South- Asian Surinamese participants placed strong value on traditional dietary patterns, whereas Turkish participants prioritized language accessibility, preferring an app that ranged from general guidance to culturally tailored support. These findings underscore the need for a balance between cultural adaptation and personalization, ensuring inclusivity while addressing individual variation in preferences and needs.

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SUPPLEMENTARY MATERIAL

COREQ (COnsolidated criteria for REporting Qualitative research) Checklist

No. Item	Guide questions/description	Reported on Page #
Domain 1: Research team and reflexivity		
Personal Characteristics		
1. Interviewer/facilitator	*Which author/s conducted the interview or focus group?*	4
2. Credentials	*What were the researcher's credentials? E.g. PhD, MD*	4
3. Occupation	*What was their occupation at the time of the study?*	4
4. Gender	*Was the researcher male or female?*	4
5. Experience and training	*What experience or training did the researcher have?*	4
Relationship with participants		
6. Relationship established	*Was a relationship established prior to study commencement?*	3
7. Participant knowledge of the interviewer	*What did the participants know about the researcher? e.g. personal goals, reasons for doing the research*	Appendix 2&3
8. Interviewer characteristics	*What characteristics were reported about the inter viewer/facilitator? e.g. Bias, assumptions, reasons and interests in the research topic*	Appendix 2&3
Domain 2: study design		
Theoretical framework		
9. Methodological orientation and Theory		4
Participant selection		
10. Sampling	*How were participants selected? e.g. purposive, convenience, consecutive, snowball*	3
11. Method of approach	*How were participants approached? e.g. face-to-face, telephone, mail, email*	3
12. Sample size	*How many participants were in the study?*	5
13. Non-participation	*How many people refused to participate or dropped out? Reasons?*	n/a
Setting		
14. Setting of data collection	*Where was the data collected? e.g. home, clinic, workplace*	4
15. Presence of non-participants	*Was anyone else present besides the participants and researchers?*	4,5
16. Description of sample	*What are the important characteristics of the sample? e.g. demographic data, date*	5

Data collection		
17. Interview guide	*Were questions, prompts, guides provided by the authors? Was it pilot tested?*	Appendix 2&3
18. Repeat interviews	*Were repeat inter views carried out? If yes, how many?*	n/a
19. Audio/visual recording	*Did the research use audio or visual recording to collect the data?*	5
20. Field notes	*Were field notes made during and/or after the interview or focus group?*	5
21. Duration	*What was the duration of the inter views or focus group?*	Appendix 2&3
22. Data saturation	*Was data saturation discussed?*	12
23. Transcripts returned	*Were transcripts returned to participants for comment and/or correction?*	n/a
Domain 3: analysis and findings		
Data analysis		
24. Number of data coders	*How many data coders coded the data?*	5
25. Description of the coding tree	*Did authors provide a description of the coding tree?*	n/a
26. Derivation of themes	*Were themes identified in advance or derived from the data?*	5
27. Software	*What software, if applicable, was used to manage the data?*	5
28. Participant checking	*Did participants provide feedback on the findings?*	n/a
Reporting		
29. Quotations presented	*Were participant quotations presented to illustrate the themes/findings? Was each quotation identified? e.g. participant number*	Supplementary Table 5
30. Data and findings consistent	*Was there consistency between the data presented and the findings?*	5-9
31. Clarity of major themes	*Were major themes clearly presented in the findings?*	5-9
32. Clarity of minor themes	*Is there a description of diverse cases or discussion of minor themes?*	5-9

Supplementary Table 1: COREQ Checklist

Supplementary Text 1: Interview Guide – the MIND-PRO app

1. Introduction

My name is [name], and I am a researcher at the Amsterdam UMC. These are [other people present during the interview]. I am part of a research group studying brain health.

Together with you, we would like to explore how we can best design and improve the MIND-PRO app so that people are more likely to use it regularly and enjoyably. It greatly helps us to understand your needs and wishes.

Since I will be asking for your opinions and experiences during this interview, everything can be said—nothing is strange or wrong. Please share as much as possible; we find all of it important and interesting.

I would already like to thank you very much for taking the time to participate in this study.

To ensure the interview runs smoothly, I'd first like to go over a few practical matters with you:

- We would like to record this interview. This makes it easier to listen back and process your responses later. Your anonymity is guaranteed, and everything you say will remain confidential. Once the study is completed, the recordings will be destroyed. If you are not comfortable with this conversation being recorded, please let me know. In that case, I will not record it and will only take notes during the interview.
- During our conversation, I will take notes for my own reference—this has nothing to do with the answers you give. I will place a large sheet of paper between us so that you can see what I write down.
- Our conversation will last about an hour. If you wish to stop or take a break at any point, please let me know.

If you agree, I would like to begin and start the recording.

Do you have any questions before we start the recording and begin the interview?

---------- [start recording] ----------

2. Introduction – 5 minutes

Before we begin, I'm curious to know who I'm speaking with.

- Could you first tell me a bit about yourself? [For example: partner, children, grandchildren, family, friends, distance to family and friends, work status, previous occupation, hobbies, daily activities.]
- Why did you decide to participate in this study? What would you like to gain from it yourself?

3. Experience with smartphone use – 5 minutes

- Do you have a smartphone yourself? [or tablet, if only in possession of a tablet]
- What do you mainly use it for? When do you use it? [only at home, or also on the go, e.g. in line at the supermarket?]
- Have you ever used an app to improve your lifestyle, such as apps for exercising more, eating healthier, etc.?
- If the participant has used a health app before: Why (or why not)? What kind of app was it? When did you use it? How did that go? How did the app help you? How long did you use it? What made you use it less?
- If the participant has never used a health app: Why not? What has prevented you from doing so? What held you back? What would you need to start using one?

4. Introduction to the MIND-PRO app – 5 minutes

Explain that this app was developed by a company and that we are now in the process of adapting it. Your opinion on the app is therefore highly valued, as there is still plenty of room for improvement.

- The researcher gives a short introduction about the app – (It is an app that can help you work on your lifestyle, set health goals, and track your progress.)
- The participant is then given the phone to explore the app at their own pace and share their first impressions.
- What is the participant's first impression? How does it look? What feeling does it give you? Would you want to use it? What do you find appealing or less appealing?

- Does this app resemble any apps you currently have on your phone or tablet? What is different about it?

5. Discussing personal health goals

Explain that with the help of the app, a participant can work on certain lifestyle-related risk factors with the aim of keeping the brain healthy.

- Ask which lifestyle-related risk factors the participant has or would like to work on. This will serve as the starting point for the conversation and allows us to explore different parts of the app based on the participant's needs and preferences.

6. Views on (long-term) lifestyle change through a health app – 35 minutes

As mentioned earlier, we want to improve the app. You now have a first impression of it, and I'd like to discuss its various components with you.

For each topic (COACH, GOALS, GENERAL, PROGRESS, EDUCATIONAL MATERIAL), the interviewer gives a short introduction, followed by questions to the participant.

COACH

- There is someone in the app who can help you with lifestyle change. What would you expect from such a person? How could they best help you? What would you call this person—buddy, coach, lifestyle expert...?
- What is the role of this person in your opinion? Motivation? Providing information? Confirmation? Advice? Help with using the app?
- Would it add value if the coach is culturally matched? Why yes/no?
- In the app, you can contact your coach/buddy/lifestyle expert [show chat page]. Is it clear how to reach out?
- Do you think you would want additional communication options?
- How often would you like to have contact with this person? Via chat or video call?

GOALS

- How many health goals would you like to work on in the app? [show goal-setting questionnaire]. Would you work on multiple goals at once?

GENERAL

- Do you think this app could help people in your surroundings? Why or why not? Could your family use this app?
- Could this app help you? Think, for example, of the risk factor we discussed earlier. Why or why not? What should such an app be able to do? What must it include for you to use it? [think of need for information, tracking weight, informational videos]
- What would initially motivate you to use such an app?
- Follow-up: Would you do it to improve your quality of life or to prevent dementia?
- Do you think it would take much effort to use the app? Why or why not? What could make using it easier?
- What would you use the app for most? [Reading info? Setting goals? Contacting the coach? Tracking progress?]
- When do you think you would use the app? Once a week? Daily? At a fixed time? During the day or evening?
- What benefits do you expect from using the app? And what disadvantages?
- How do you think your surroundings would react if you used this app? Would they influence your use of it?
- Would you like to work on your health together with someone? If yes, would this be someone from your own circle or someone new?
- In what way would you prefer to work on your health together with someone? Why would that appeal to you? Would it affect your motivation? Would it make you more likely to use the app longer or more consistently?

PROGRESS

- How would you like to measure your progress in the app? [show progress page in the app] How often would you track your progress? What do you think of these line graphs and this diary feature?
- Would you like to see how your progress compares to that of others?

EDUCATIONAL MATERIAL

- What makes you trust or distrust certain information?
- Can you give an example of lifestyle information you've received before? What did you like or dislike about it? Did it inspire you to make changes? Why or why not?
- Who do you currently listen to or take information from? Doctor? Family? Friends? Why do you (or don't you) listen to them?
- Would you like to hear personal experience stories?

- How often may we send you push notifications? What kind of information would you find relevant to receive this way?

7. Closing the interview – 5 minutes

We've come to the end of the interview. I really appreciate your stories and experiences, and I hope you've felt comfortable being yourself during the interview.

- Is there anything else you'd like to add? Do you have any questions for me?

Thank you very much for your cooperation and openness. If you have any questions or comments, please feel free to contact us.

Supplementary Text 2: Focus Group Guide – Brain Health with an App

For those who are participating in this study for the first time: welcome! For those we have already spoken to in individual interviews: thank you once again for your participation!

We are [names of all attending researchers, moderators, observers, and mHealth developers → each attendee briefly explains why they are present and what their role will be].

We are part of a research group studying brain health, particularly the prevention of dementia.

An app has been developed for smartphones and tablets that can be used to work on a healthier lifestyle together with a coach. Together with you, we want to explore how we can best design this app to increase the likelihood that people will actually use it—and enjoy doing so. It helps us tremendously to understand your needs and preferences.

During this workshop, we will explore the app together and ask for your opinions about it. We kindly ask you to respect each other's viewpoints, but also not to be afraid to respectfully disagree.

We would like to sincerely thank you in advance for taking the time to participate in this study.

Before we start, I would like to go over a few practical matters with you:

- We would like to record this workshop. This will make it easier to listen back and process your responses later. Your anonymity is guaranteed, and everything you say will remain confidential. Once the research is completed, the recordings will be destroyed.
- During our discussion, notes will be taken to help remember key points. This has nothing to do with the content of your answers.
- The workshop will last about one hour. If you wish to stop or take a break at any time, please feel free to do so.

Has everyone understood this, and are there any questions?

Do you all agree that I start the recording now?

Do you have any questions for me before we start the recording and begin the session?

---------- [start recording] ----------

Depending on the size of the group, we will divide participants into smaller subgroups of 3–4 people to think through the different tasks together. Each group will receive one phone with the app installed.

1. Task 1 – Introduction / Ice-breaker – 10 minutes

Start: Brief explanation of the app – setting your own goals and having a coach.

First, we would like to ask you to explore the app and set a goal within it. Please do this together in your group, and then let us know how it went.

We will then take turns letting each group share their first impressions of the app, making sure that everyone who wants to speak gets the opportunity to do so.

2. Task 2 – Setting goals and tracking progress – 20 minutes

(These two questions will be discussed separately in subgroups, followed by collective feedback.)

QUESTION 1:

Now that you have set a health goal in the app, we'd like to hear your opinions on a few things:

- Imagine you are working on a goal—would you adjust your goal along the way?
- Why or why not? If yes, how often would you do this?

QUESTION 2:

Imagine you are working on a goal in the app:

- Would you track your progress in the app? Please take a look at the progress page. What do you think of it?
- If you track your progress, would you like to compare it? Compare your progress to 1) people similar to you, or 2) the guideline.
- Would tracking your progress motivate you? Why or why not? Would comparing motivate you? Why or why not?
- Would you like to share your progress with family and friends?

3. Task 3 – Content, frequency, and contact with coach – 20 minutes

(These two questions will be discussed separately in subgroups, followed by feedback.)

We have now discussed some practical matters, and we would like to talk with you about the app's content.

QUESTION 1:

Cultural sensitivity – While using the app, you will receive a lot of information. We would like to know what kind of content you would enjoy or find interesting to read. What kind of information fits your daily life? What kind of information connects to your culture? For example: healthy recipes, tips for staying active, etc.

QUESTION 2:

Coach – There is someone in the app who can help you with lifestyle changes and goal setting. What would you expect from such a person? How could they best support you?

How often would you like to speak with this person? Should the contact be initiated by you or by the coach? Only when you have a question, or regularly?

Additional question:

What would help you most in setting and achieving a lifestyle goal?

Four options:

1. The app with a coach

2. The app alone

3. Only an online coach

4. On your own

During Tasks 2 and 3, the mHealth developers will make live adjustments to the app. Then, in Task 4, we will test these changes with the participants.

4. Task 4 – Testing the app together – 15 minutes

Throughout this workshop, we have shaped the app together and made adjustments based on your suggestions. Now, we'd like to go through the app again with you and test the changes or ideas you've provided.

Afterward, participants will again have the opportunity to share their opinions on the modifications made to the app.

5. Closing the workshop

We have come to the end of the workshop. We greatly appreciate your participation and your suggestions—thank you so much for your valuable input!

• Is there anything else you would like to share? Do you have any questions for us?

Thank you very much for your cooperation and openness. If you have any questions or comments, please feel free to contact us.

Findings uniform across all groups	Differing views between groups	Group*	Quote
Usability and cultural adaptation of the intervention			
• Minimal text and easy to understand language is preferable. Make use of figures and videos. • The app should work intuitively and resemble other commonly used app (such as the chat and Whatsapp). • It should be easy to navigate between pages without small buttons. • Small text fonts should be adjustable • The older target population felt less tech-savy and appreciated good instructions in how to use the intervention.	• The content off the app should be available in native language for the Turkish population. • Turkish and South Asian Surinamese individuals prefer a culturally tailored app.	T	*"Right, yes, yes, so it's just a bit cold. You know, how can I explain it? AR: The Dutch? P: Yes, yes, so fake does it feel all of a sudden. I know, it's not fake, and it not very weird or that I don't trust it, but still it feels cold to me."(female, 52 yr)*
		SAS	*"If there are studies on ethnicity for populations such and Hindustan and Turkish people, they can get specific help. Because now, everything - pharmaceuticals and everything - is focused on the white population. The question is, does it help us as well?" (male, 51 yr)*
		Low-SES	*"It's too crowded, the boxes are too small, and my fingers are too thick. The font size needs to be bigger. We had the problem that we pressed the wrong key, and then it disappeared, so we had to start all over again." (focus group)* *"you see, not everyone here is used to working with a smartphone." (focus group)*
Key functionalities of the intervention			
Goal setting			
• Individuals wanted to choose their own goals. • Goal setting should be flexible and adaptable. • Goals should be attainable. Taking small steps can help in achieving sustainable lifestyle changes .	• Some participants mentioned the need to work on several goals at the same time, while others stressed the importance of taken small steps. Highlighting the importance of self-managing goals and personalization.	T	*"Yes, and making it very accessible. […] I used to think that if I wanted to be active, I always had to walk or cycle for an hour with my husband. […] But I get tired so quickly—too tired—and it frustrates me. Then my friend gave me advice. I hadn't thought of it myself, and she said, "Why don't you walk for just 20 minutes instead?" (female, 58 yr)*
		SAS	*"Preferably I want to work on all three goals simultaneously (physical activity, lowering cholesterol and weight loss). […] Because all three are very important to me." (female, 66 yr)*
		Low-SES	*"Yes, we all have different goals, right? Its personal, maybe one person has high cholesterol, another is overweight, so you need to be able to make your own choices." (focus group)* *"If you try to work on too many goals at the same time, I can imagine you might feel like you're spending the entire day just noting things down and keeping track, and then it stops working. […] It shouldn't become too difficult. " (focus group)*

Self-tracking			
• Self-tracking is perceived as helpful as long as its non-obligatory • Works best when it is visualized in simple graphs or diaries. • Will be used to keep themselves accountable and sustain motivation • Most people did not feel the urge to compare their progress with peers or share their progress with others. Could lead to demotivation if they feel they are underperforming. • •	• Generally women preferred to not compare progress to others, not even on a demographic level.	T	*"I just want to see it, and if I achieve the line (goal), then I'm very happy. Maybe it will motivate you like, come on, you can move the line upwards by doing a little more." (female, 55 yr)* *"It has a good side and a bad side. For example, one might say, 'Wow, I've already taken 10.000 steps today', but then you step on the scale and see you haven't lost a kilo - that can demotivate you." (male, 60 yr).*
		SAS	*"And then you get startled, like, well, I haven't exercised. What am I supposed to write? Should I lie or tell the truth?" (female, 59 yr)*
		Low-SES	*On comparing progress: "That's a difficult question. Every person is different. The goal might be the same, but the way you work on it can be different. It is difficult to compare" (focus group)*
Education material – general			
• Practical and tailored information is perceived as helpful in achieving health goals. • Trustworthiness is an important aspect. • Familiarity (knowing the coach) can add to this trustworthiness. • Information should be framed positively, which is perceived as more motivating.		T	*"Yes, or I go to my GP, but not to the internet. Because, if you search online, "I have a headache, what's wrong?" suddenly it tells you that you have a tumor in your head." (female, 52 yr).*
		SAS	*"I am happy if it motivates me, that I am doing something positive and if it (the app) also brings me positivity." (female, 59 yr)*
		Low-SES	*In the library, I can find a lot of practical information which is nice, like cooking with less oil of less fat, that is just practical." (focus group)* *" I do think that someone who has really been trained for it (referring to their general practitioner) and knows all the aspects is better at giving advice." (focus group)*

Education material - diet			
	• Turkish participants expressed the willingness to adjust their diet. • South Asian Surinamese individuals saw diet part of identity, therefore rigid and difficult to change. • For both Turkish and South Asian Surinamese individuals social gatherings and holidays often accompanied with an abundance of food, rude to so "no", therefore difficult to maintain a healthy diet at times.	T	*"But it is half-half now. Half Dutch culture, half Turkish.[…] Eating a sandwich in the afternoon, whereas in Turkish cuisine, it is warm food." (female, 62 yr)*
		SAS	*"It's different you see, you eat potato's we eat rice (in the Surinamese kitchen)." (male, 64 yr)* *"South-Asian Surinamese people have been eating this since 5000 years B.C. And the Ayurvedic kitchen is rich." (male, 58 yr)* *"I can't (ask other people to cook differently). Then she has to take so many things into account; whole grain rice, no salt, no sugar… No, that just won't work." (female, 66 yr)*
		Low-SES	
Educational material – physical activity			
	• Barriers to go to the gym, especially in Turkish women. • For South Asian Surinamese participants bad weather is barrier for outdoor activities .	T	*"No, that's not possible [cycling]. Maybe if a group of women starts walking slowly. They'll start slowly and then it becomes more, more, more." (female, 58 yr)* *"I wanted to do sports. […] I do it at home. (The gym) was too expensive so I quit. (female, 50 yr)* *Many Turkish woman are at home a lot so (doing physical activity) at home during the day should be attainable. (female, 55 yr)*
		SAS	*"But also, I think in general, you need to motivate Hindustans to start exercising. […] It's not part of the culture. It's not ingrained." (male, 58 yr)*
		Low-SES	

Remote coach			
• A face-to-face conversation is a requirement, allowing a relationship of trust to be built and enabling the coach to become aware of the personal situation. • Remote coaches should guide users in a non-obtrusive way to maintain a sense of autonomy. • Coaches are mainly viewed as a source of information and to keep users accountable.	• Turkish and South Asian Surinamese women prefer a female coach • South Asian Surinamese individuals did not perceive a culturally matched coach as requirement, but the coach should have knowledge on dietary habits. • Participants with low-SES viewed personal guidance as essential.	T	*"It (the coach) should motivate them (the app user), not just tell them what to do." (male, 63 yr).* *"Look like here with you we have this conversation. I don't know how that happens with the coach, I don't know him/her […] I should have trust first and then (I will ask questions). I always have that with people." (female, 59 yr)* *"Doesn't matter (having a coach with Turkish or Dutch ethnic background). […] But yes, a woman, because she knows. […] We can share that experience. […] She'll understand that feminine part." (female, 59 yr)*
		SAS	*"Yeah, maybe because it feels familiar or something, like when I tell my husband, I'm going to talk to the coach. […] And yeah, then my husband doesn't have to say, 'Are you talking to that man again?' You know?" (female, 62 yr)* *"The more, the better (contact frequency with the coach). Because then you know that someone is watching over you. Like, you're heading the wrong direction." (female, 59 yr)*
		Low-SES	*"If it's a personal coach who can keep track of your progress and has looked at your data, and there are things you can work on, then it can be useful to get advice." (focus group)* *"Chatting with the coach would be easier after a personal conversation as the coach will already know who you are. […] And if you don't know who is sitting on the other side (of the chat) you will not ask questions." (focus group)*

Implementation requirements			
Autonomy			
• Reduce notification, too many messages is overwhelming. • Messages should be in a positive, non-obligatory tone, they are otherwise demotivating. • Flexibility in the app is important, everyone changes their lifestyle at a different tempo, there should be room in the app for this.		T	*"Every time the phone paged me, it got on my nerves within just two days […] Yes, the following week, I went to my doctor and said: 'I'm going to remove this app." (female, 54 years old)* *"The app would feel restrictive.. I can't stand it when someone tells me what I should or shouldn't do or eat." (male, 49 yr)*
		SAS	*" I don't like to receive such messages (push messages), then you're being pushed. And I don't want that. I don't like it if someone pushes me to do something. Not at work and from such a machine (telephone with app). (male, 62 yr)*
		Low-SES	
Social environment			
• Being physically active together is more motivating and improves sustainability. • An understanding and motivating partner is a big facilitator.	• Especially amongst Turkish and South Asian Surinamese individuals, children could play an important role in motivating their elders to change their lifestyle.	T	*"I think together (preference for working on lifestyle), because alone it gets boring soon. And if you go with a group, then that motivates and by looking at others you can get challenged." (male, 60 yr)* *"I have a 17-year old daughter. She's like a true coach. She says, 'Mama, you eat too much candy, you eat way too sweet." (woman, 50 yr).*
		SAS	*"So from the moment you are born, you are in service of another (your family). Hindustan parents take this very seriously. So your children are your everything and go before anything else, even before your own health." (male, 58 yr)*
		Low-SES	*And of course, it's nice when you train together, and you arrive in class and say. ' Hey, look how I have been working (on my goals).' See, I made progress and then you can get a compliment, I'm really sensitive to that." […] " it's not much about looking at the progress, because it's individual. But you can you it like. 'Hey, I struggled with this, and then you can help each other." (focus group)* *" What's also very important is that you share this with your partner or spouse." (focus group)*

Supplementary Table 2: Summary of findings with supporting quotes.

*Groups: T = Individuals with a Turkish migration background, SAS = Individuals with a South-Asian Surinamese migration background, Low-SES = Individuals with a low socio-economic status with a native Dutch background

Chapter V

THE ASSOCIATION OF APATHY WITH INCIDENT DEMENTIA: A MULTIPLE MEDIATION ANALYSIS OF CARDIOVASCULAR RISK FACTOR

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ABSTRACT

Objectives Despite established links between apathy, cardiovascular disease, and dementia, it remains unclear if cardiovascular risk factors (CVRF) play a mediating role in the association between apathy and dementia. If apathy increases dementia risk via lifestyle-related dementia risk factors, targeted lifestyle interventions could help high-risk individuals.

Methods We used data from the preDIVA study including 3303 individuals aged 70-78 years. Apathy was assessed using the geriatric depression scale, and CVRF (cardiovascular risk factors) (systolic blood pressure, cholesterol, diabetes, body mass index (BMI), smoking, and physical activity) were considered as potential mediators. Outcome was incident dementia during 12 years of follow-up. We assessed mediation using Multiple Mediation Analysis (MMA).

Results Of the association between apathy and dementia (HR 1.49 (95% CI 0.99 – 2.41)), 27% was mediated by physical inactivity, BMI and diabetes combined. Of this total, physical inactivity mediated 28% of the effect (HR 1.12, 95%CI 1.03 – 1.29), diabetes 9% of the effect (HR 1.04, 95%CI 1.02 – 1.10), and BMI counteracted these effects by -12% (HR 0.95, 95%CI 0.88 - 0.98).

Conclusion The relationship between apathy and dementia is partly mediated by physical inactivity, BMI and diabetes. Apathy is an important clinical marker that signals the existence of potentially modifiable pathways, providing an opportunity for lifestyle interventions. To potentially reduce dementia risk via lifestyle modification in patients with apathy, a tailored approach should be taken to overcome the characterizing symptom of diminished motivation.

KEY POINTS

- The link between apathy and dementia is partially explained by physical inactivity, BMI, and diabetes.
- Apathy may serve as a crucial clinical sign, indicating the presence of modifiable pathways and opportunities for lifestyle interventions.
- To reduce dementia risk in patients with apathy, a personalized approach is needed to address their diminished motivation and encourage lifestyle changes.

INTRODUCTION

Apathy is a syndrome of disturbed motivation, manifesting in diminished interest, cognition, and emotional expression.[1] Symptoms of apathy can occur in the context of depression, but also independently as a separate syndrome. Approximately 25-44% of cognitively healthy community-dwelling older individuals are thought to have symptoms of apathy.[2-5] Apathy has a direct and substantial negative impact on both patients and their social environment.[6,7] Cognitively healthy community-dwelling adults with symptoms of apathy are at increased risk of developing dementia as compared to those without.[8,9] The mechanisms underlying this association are unknown. Since apathy is a common symptom of dementia, apathy in older people may partly be a prodromal sign of developing dementia,[10] and therefore not necessarily causally related to dementia risk. Another part of the relation between apathy and dementia may be explained by apathy being associated with individuals' unhealthy lifestyles, which in turn increases dementia risk.[11] Physical inactivity, hypertension, obesity, dyslipidemia, diabetes, and smoking are all independently associated with an increased risk of dementia.[12] Apathy may induce these conditions and their risk factors via symptoms of reduced motivation,[13] decreased engagement in health behaviors[11] or treatment adherence.[14,15] Distinguishing between these prodromal and potentially modifiable pathways in the relationship between apathy and dementia is important, because this may offer leads for prevention: if the association between apathy and an increased dementia risk is due to unhealthy lifestyle, then individuals with apathy may specifically benefit from lifestyle interventions. This is especially important because individuals with apathy may tend to retract from self-care, and therefore form a group that might particularly benefit from active prevention strategies. Furthermore, clues about the extent to which apathy may be prodromal rather than causally related to incident dementia may help elucidating the mechanisms potentially underlying apathy in old age, which may be relevant for developing apathy treatments. We hypothesize that the increased risk of incident dementia in individuals with symptoms of apathy may be due to the association of apathy with cardiovascular risk factors. Therefore, we aim to investigate to which extent the relationship between apathy and increased risk of dementia is due to lifestyle-related dementia risk factors.

MATERIALS & METHODS

Design, population and setting

This study used data from the preDIVA study, a randomized controlled trial including community-dwelling older adults (n=3526) between 70-78 years of age at baseline.[16] The initial study was approved by the medical ethics committee of the Academic Center, Amsterdam, Netherlands. Participants gave written informed consent. This trial studied the effect of a 6-8 year multi-domain intervention on incident dementia and the study was extended with an observational follow-up period up to 12 years. In this study all community dwelling adults registered with one of 116 participating general practitioners were invited. Exclusion criteria were presence of possible dementia, terminal illness or any other condition likely to hinder successful 6-year follow-up according to the general practitioner (e.g. cancer or alcoholism). After completion of the trial no significant effect of the intervention on dementia incidence was found after both the initial trial and the observational extension period.[16,17] In the current context data are analyzed as a prospective cohort study. More information on details of the preDIVA study can be found elsewhere.[16]

Exposure, mediators and covariates

Exposure, mediators and covariates were all measured at baseline. We used the 3-item apathy subscale of the 15-item Geriatric Depression Scale[18] (GDS) to assess apathy, as done in previous studies.[2-5,8] This sub scale was based on previous factor analyses, and includes the items: 'Have you dropped many of your activities and interest? (yes/no: 1/0 point)', 'Do you prefer to stay at home, rather than going out and doing new things? (yes/no: 1/0 point)' and 'Do you feel full of energy? (yes/no: 0/1 point)'.[2] Apathy was operationalized as scoring on ≥2 of these items. The mediating factors included in the analyses were systolic blood pressure (SBP) in mmHg, total cholesterol (TC) in mmol/L, and body mass index (BMI) in kg/m² as continuous variables, as well as physician-diagnosed diabetes mellitus (DM), self-reported current smoking, and physical activity (PA), which was classified as sufficient to meet the WHO guidelines for physical activity, as dichotomous variables. Assessment of risk factors was done by a trained nurse at baseline visit at the general practice.[16] Anthropometrics and blood pressure were obtained using a standardized protocol and blood samples were collected for lipid spectrum and blood glucose analysis. Self-reported presence of risk factors (smoking, medication use and cardiovascular history) was cross checked with patients' electronic health records (EHR). Covariates were age, sex, level of education and history of cardiovascular disease (CVD).

Outcome

Cognitive status and functioning in daily life were assessed in person every two years using the Mini-Mental State Examination (MMSE)[19] and the Academic Medical Center Linear Disability Score (ALDS),[20] respectively. Indications for the presence of dementia was based on these measurements, complemented by information from the general practitioner, hospital admissions and outpatient diagnostic evaluations from EHR, and the National Death Registry during the trial phase (first 6-8 years).[16] During the observational extension phase, dementia was established using a step-wise approach. First, individuals were contacted by telephone, asked whether they had a dementia diagnosis, and administered the telephone interview of cognitive status (TICS).[21] The conventional TICS cut-off to indicate possible dementia is <27 points. In individuals who had a TICS score >30 and who indicated that they did not have dementia or cognitive problems, we recorded 'no dementia'. For individuals with a TICS score ≤30, or those who indicated that they did have dementia or cognitive impairment, we accessed the EHR from their general practitioner to assess whether they had been diagnosed with dementia.[16,17,22] All dementia diagnoses were ascertained and re-evaluated after one year by a blinded outcome adjudication committee consisting of clinicians.

Statistical analyses

First, we tested for differences between individuals with and without symptoms of apathy, using independent samples student's T-test, Chi-square test or the Mann-Whitney-U test as appropriate.[23] Second, we explored the association of apathy with the individual risk factors using logistic or linear regression as appropriate and the association of the individual mediators with incident dementia using Cox regression. We performed multiple mediation analysis (MMA) using the MMA package in R.[24] This method uses simulation with bootstrapping to estimate the mediation effects, and can be applied to binary, categorical and continuous types of exposure, mediator and outcome variables. To identify mediators, the pathway from exposure to mediator and from mediator to outcome were tested. The association of apathy with individual risk factors is tested with ANOVA for continuous, and with Chi-square tests for dichotomous variables. The association of a mediator with incident dementia is tested with Type III tests in a Cox model including all potential mediators and covariates.[25] A Type III test checks for evidence of significant difference in survival functions across strata for dichotomous variables and for a unit increase for continuous variables. The results then indicate if variables qualify as mediators and provide effect sizes of the separate indirect effects, which should be interpreted as the hazard ratio (HR) that is explained by the mediator. Confidence intervals of the effect sizes are based on bias

corrected bootstrap methods.[26] Our main MMA model was adjusted for age, sex, level of education and history of CVD. The second model was further adjusted for treatment arm in the RCT, antihypertensive medication and cholesterol lowering medication. For sensitivity analyses we have repeated the multiple mediation analysis excluding individuals with a total GDS-15 score >6, as this may be indicative of depression. Secondly, we excluded individuals diagnosed with dementia during the first year, to exclude cases in which apathy was an early symptom of dementia. All statistical analyses were performed in Rstudio version 4.2.1.

RESULTS

A total of 3303 (94%) participants had complete data on the relevant mediators and covariates, and were included in the mediation analysis. During the median follow-up time of 10.3 years (interquartile range (IQR) 6.9 – 10.9), 391 (12%) participants were diagnosed with dementia and 974 (29%) died, yielding an incidence rate of 0.013 new cases per person years. Participants with symptoms of apathy (14%) were more likely to be female, currently smoking and having a history of CVD and diabetes, and were less educated and less active compared to those without. Also participants with apathy had a higher GDS-15 score at baseline (Table 1).

Explorative analysis of the association of apathy with potential mediators, adjusted for age, sex, level of education and history of CVD showed that apathy was significantly associated with physical inactivity (OR 2.90, 95%CI 2.33 – 3.60), higher BMI (mean difference 0.80, 95%CI 0.40 – 1.21 kg/m^2), diabetes (OR 1.46, 95%CI 1.15– 1.84) and current smoking (OR 1.97, 95%CI 1.52-2.53), but not with total cholesterol (mean difference -0.03, 95%CI -0.13 – 0.07 mmol/L) nor systolic blood pressure (mean difference -0.77, 95% CI -2.87 – 1.33 mmHg) (Table 2). Analysis of the association of potential mediators with incident dementia showed that only physical inactivity was significantly associated with a higher hazard of developing dementia (HR 1.38, 95%CI 1.09- 1.76) (Table 3).

MMA

In the MMA, overall, individuals with apathy had a 49% higher hazard of incident dementia (total effect HR: 1.49, 95% CI 0.99-2.41). Combined, the mediated effects explained 27% of the association between apathy and incident dementia (indirect HR 1.11, 95% CI 1.01-1.27 compared to the total HR of 1.49). Three variables were identified as significant mediators for the relationship between apathy and incident dementia: physical inactivity (proportion mediation (PM): 28%), BMI (PM: -12%) and diabetes (PM: 9%) (Table 4, Figure 1). The remaining 'direct effect' of apathy on incident dementia (i.e. not explained by the included mediators) was a 34% increased dementia hazard (direct HR 1.34, 95%CI 0.92 – 2.17), making up 73% of the total association between apathy and incident dementia. Results of the fully adjusted MMA model adjusting for intervention status, AHM and cholesterol lowering medication were comparable to main results (Table 4). Sensitivity analysis excluding patients with a GDS-15 > 6 showed comparable results (Supplementary Table 1). Sensitivity analysis excluding individuals diagnosed with dementia during the first year showed comparable results (Supplementary Table 2).

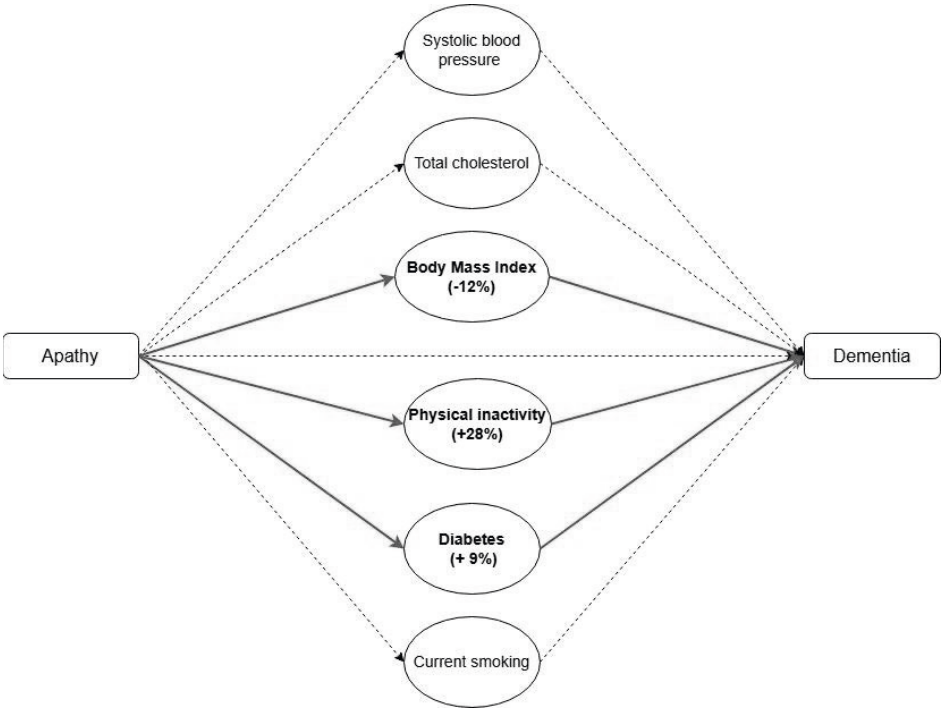

Figure 1: Multiple mediation analysis of cardiovascular risk factors in the association between apathy and dementia. Solid lines indicates significant pathways, dashed lines insignificant pathways.

Characteristic	All	No apathy	Apathy	p-value
N	3303	2835	468	
Female, N(%)	1800 (54.5)	1512 (53.3)	288 (61.5)	0.001
Age (years), mean (SD)	74.34 (2.50)	74.28 (2.50)	74.74 (2.44)	<0.001
History of CVD*, N(%)	977 (29.6)	796 (28.1)	181 (38.7)	<0.001
MMSE† score, (median [IQR])	28.00 [27.00, 29.00]	28.00 [27.00, 29.00]	28.00 [27.00, 29.00]	0.018
GDS-15‡ score, (median [IQR])	1.00 [0.00, 2.00]	1.00 [0.00, 2.00]	4.00 [3.00, 7.00]	<0.001
Education§ , N(%)				<0.001
Basic	800 (24.2)	650 (22.9)	150 (32.0)	
Intermediate	1867 (56.6)	1622 (57.2)	245 (52.4)	
Advanced	636 (19.3)	563 (19.9)	73 (15.6)	
Systolic blood pressure (mmHg), mean(SD)	155.22 (21.35)	155.37 (21.32)	154.30 (21.52)	0.313
Cholesterol (mmol/l), mean(SD)	5.23 (1.10)	5.24 (1.09)	5.17 (1.12)	0.209
Body Mass Index (kg/m2), mean(SD)	27.44 (4.15)	27.30 (3.99)	28.27 (4.93)	<0.001
Diabetes, N(%)	591 (17.9)	478 (16.9)	113 (24.1)	<0.001
Current smoking, N(%)	435 (13.2)	335 (11.8)	100 (21.4)	<0.001
Physically inactive‖, N(%)	610 (18.5)	439 (15.5)	171 (36.5)	<0.001

Table 1: Baseline characteristics of the total population and stratified by apathy status. We tested for differences between those with and without symptoms of apathy. *History of cardiovascular disease excluding stroke or transient ischemic attack. † Mini Mental State Examination. ‡ Geriatric Depression Scale, for n=5 data was missing for MMSE and GDS-15 score. §Basic is primary education. Intermediate is upper secondary or post-secondary non-tertiary education. Advanced is pre-university, higher professional education or university. ‖Physically active is operationalized as being adherent to international World Health Organization guidelines for physical activity.

Continuous risk factor as outcome	Mean difference for apathy (95%CI)
Systolic blood pressure (mmHg)	-0.77 (-2.87 – 1.33)
Total cholesterol (mmol/L)	-0.03 (-0.13 – 0.07)
Body Mass Index (kg/m2)	0.80 (0.40 – 1.21)*
Binary risk factor as outcome	**OR of apathy (95% CI)**
Physically inactivity	2.90 (2.33 – 3.60)*
Diabetes Mellitus	1.46 (1.15– 1.84)*
Current smoking	1.97 (1.52-2.53)*

Table 2: Association of apathy with individual mediators. All models were adjusted for age, sex, level of education, history of CVD. For models with a continuous risk factor as outcome this means that patients with apathy on average have a higher BMI (+0.80 kg/m2, 95CI 0.40 – 1.21). *significant based on confidence intervals.

Mediator	Hazard ratio dementia (95% CI)
Systolic blood pressure (mmHg)	0.99 (0.99-1.00)
Total cholesterol (mmol/L)	1.02 (0.92-1.12)
Body Mass Index (kg/m2)	0.98 (0.95 – 1.00)*
Physical inactivity	1.38 (1.09 – 1.76)*
Diabetes Mellitus	1.27 (0.99 – 1.63)
Current smoking	0.86 (0.61 – 1.22)

Table 3: Association of individual mediators with incident dementia. All Cox models were adjusted for age, sex, level of education, history of CVD. *significant based on confidence intervals.

	MMA model 1		MMA model 2	
Effect	**HR (95% CI)**	**Proportion of total effect***	**HR (95% CI)**	**Proportion of total effect***
Total	1.49 (0.99 – 2.41)		1.49 (0.99 -2.50)	
Direct	1.34 (0.92 – 2.17)	73%	1.35 (0.91 – 2.22)	75%
Total indirect	1.11 (1.01 – 1.27)*	27%	1.10 (0.99 – 1.26)	25%
Body Mass Index (kg/m2)	0.95 (0.88 – 0.98)*	-12%	0.95 (0.87 – 0.98)*	-13%
Diabetes	1.04 (1.02 – 1.10)*	9%	1.03 (1.00 – 1.09)*	7%
Physical inactivity	1.12 (1.03 – 1.29)*	28%	1.12 (1.02 – 1.29)*	28%

Table 4: Multiple mediation analysis showing total, direct and indirect effects of physical activity, diabetes and BMI in the association of apathy on dementia incidence. Model is bootstrapped 1000 times. Indirect effects are mediated via physical activity, diabetes and BMI. Model 1 is adjusted for age, sex, level of education, history of cardiovascular disease. Model 2 is additionally adjusted for intervention status and use of antihypertensive and cholesterol lowering medication use at baseline. Due to correlation in mediator effects, direct and indirect effect do not add up to the total indirect effect.[24] *Proportion mediation is regression coefficient of the direct or indirect effect divided by regression coefficient of the total effect. *significant based on confidence intervals

DISCUSSION

This study aimed to investigate to what extent the relationship between apathy and increased risk of dementia is mediated by lifestyle-related dementia risk factors. In total 27% of the association between apathy and incident dementia was explained by diabetes, physical inactivity, and BMI combined. The higher prevalence of diabetes and physical inactivity in patients with symptoms of apathy explained respectively 9% and 28% of the total association with dementia. Of the total association between apathy and dementia, a higher mean BMI in those with symptoms of apathy mitigated 12% of the total effect.

In older adults, apathy, independent of depression, is a known risk factor for incident CVD.[27] Apathy could render people less inclined to lead a healthy lifestyle, since it is characterized by reduced motivation and goal directed behavior. For instance, it is known that apathy is associated with diminished physical activity and a higher behavioral risk factor score consisting of multiple risk factors (physical inactivity, smoking, alcohol use, unhealthy diet).[11] Our study corroborates these findings by showing that patients with apathy have a higher odds of being physically inactive, and with a proportion mediation of 28%, physical activity was the strongest mediator of the relationship between apathy and dementia. Adherence to treatment for other cardiovascular risk factors may be suboptimal in people with apathy symptoms. Glycemic control is worse in patients with apathy.[14] In our study, participants with apathy had a higher odds of having diabetes and the association of apathy with dementia was partially mediated by the presence of diabetes. We found apathy to be associated to a higher mean BMI, potentially the consequence of more physical inactivity in these individuals, and this association alleviated the effects of apathy on dementia with 12%. This finding is in line with previous studies, showing that a lower or declining BMI in late life is a risk factor for dementia.[28,29] Beforehand we hypothesized that mechanisms of reduced motivation and self–care behaviours in apathetic patients could lead to suboptimal control of blood pressure and cholesterol. However, in our study we did not find a significant relationship of cholesterol nor systolic blood pressure with either apathy or dementia. The literature on the relationship between apathy and blood pressure is heterogeneous. Associations with both higher and lower blood pressure have been reported.[30,31] In the current study we found that apathy was associated with almost a double odds of current smoking, but smoking did not significantly increase the hazard of dementia. In a previous analysis of this cohort smoking mediated the relationship between apathy and risk of incident cardiovascular disease with 4.5%.[32] However, studies specifically addressing the relationship between smoking and apathy are scarce.

Symptoms of apathy may occur in the context of other psychiatric conditions like depression, Parkinson's disease schizophrenia and dementia. However, apathy also occurs as a standalone syndrome in cognitively healthy older people that is strongly associated with elevated dementia risk, even in individuals without depressive symptoms.[8,9] A previous analysis of this cohort showed that individuals with symptoms of apathy, but no depressive symptoms are at an increased risk of developing dementia (HR 1.26, 95% CI 1.06–1.49).[9] Also, when repeating our analysis excluding individuals with depressive symptoms the analysis showed comparable results. This aligns with previous literature, suggesting that apathy is a separate construct and can occur independently of depression.[33]

Our study had several strengths. Our study population had a relatively long total follow-up of up to 12 years (median 10.3 years). Medical history was cross-checked with participants' electronic health records, minimizing the risk of recall or reporting bias. Dementia ascertainment was 99% complete and all cases were evaluated by a blinded outcome adjudication committee, therefore we performed a complete case analysis.[16,17] Even though we cannot exclude residual confounding, the fact that the adjusted model hardly changed the (total, direct and indirect) effects indicates the robustness of our findings. There are some limitations to consider. For one, although our study population was free of dementia at baseline, in some participants neurodegenerative processes may have already commenced. Our research focused on the extent to which clinically measured symptoms of apathy in older adults are related to the risk of incident dementia through lifestyle-related risk factors. This approach aims to determine whether this group could be a suitable target for lifestyle interventions. It is plausible that a significant portion of the association between apathy and incident dementia risk, which is not explained by cardiovascular risk factors, may be attributed to apathy being a prodromal sign of (subclinical) neurodegeneration.[10,34] Secondly, in our study we used the GDS-3A, a three-item subset of GDS-15, to identify symptoms of apathy. Validation of this construct, using the more elaborate Apathy Scale[35] as reference, showed that it is very specific (88-93%), but has a low sensitivity (29-33%) in community-dwelling older adults.[33] This could lead to underestimation of the number of people having symptoms of apathy. In our study population, 14% exhibited symptoms of apathy, which is slightly lower than the 25-44% reported in other studies of cognitively healthy older adults.[5,8,36] One potential reason could be that individuals with prodromal dementia may lack insight into their disease and behavioral changes. Also, people may be inclined to provide socially desirable answers indicating a healthy, active lifestyle. Since the apathy questions of the GDS are self-reported, these factors could have led to an underestimation of the true prevalence of apathy symptoms, resulting in underdiagnosis or misclassification of apathy. This

misclassification might have caused an underestimation of the true relationship between apathy symptoms and incident dementia. However, our findings that the relationship between apathy and incident dementia is in part significantly explained by cardiovascular risk factors remains. Finally, due to the cross-sectional assessment of apathy symptoms and cardiovascular risk factors this study does not provide further indications of a causal relationship between apathy and the subsequent development of cardiovascular risk factors. This is not needed to address the question to which extent the relationship between apathy and dementia is explained by the presence of cardiovascular risk factors. Our findings suggest that older adults with symptoms of apathy may benefit from targeted interventions addressing cardiovascular risk factors to help reduce the risk of dementia. While our results were derived from the general population, it is worth considering whether similar interventions could also benefit individuals experiencing apathy in the context of specific co-morbidities, such as Parkinson's disease. For instance, a recent systematic review and meta-analysis indicates that in Parkinson's disease, stimulating motor activity—such as through various forms of dance—can have positive effects on both quality of life and cognitive functioning.[37] However, given that apathy is characterized by reduced activity and withdrawal from care, addressing these risk factors in this group may be challenging and could require developing a highly intensive approach.

CONCLUSION

In older community-dwelling persons the relationship between apathy and incident dementia is partly explained by physical inactivity, BMI and diabetes. In our study indirect effects played a significant role, which suggests that apathy increases the hazard of dementia, at least in part via its association with these risk factors. Apathy may prove an important clinical marker of individuals at increased risk of dementia due to the presence of potentially modifiable risk factors. Patients with apathy may especially benefit from more intensive prevention and care interventions since this is a vulnerable, less self-reliant population at high risk of dementia with a larger prevention potential.

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SUPPLEMENTARY MATERIAL

	MMA model 1		MMA model 1 excluding GDS>6	
Effect	**HR (95% CI)**	**Proportion of total effect***	**HR (95% CI)**	**Proportion of total effect***
Total	1.49 (0.99 – 2.41)		1.36 (0.98 – 1.96)	
Direct	1.34 (0.92 – 2.17)	73%	1.28 (0.93 – 1.85)	80%
Total indirect	1.11 (1.01 – 1.27)	27%	1.06 (0.99 – 1.14)	20%
Body Mass Index (kg/m2)	0.95 (0.88 – 0.98)	-12%	0.96 (0.91 – 0.99)	10%
Diabetes	1.04 (1.02 – 1.10)	9%	1.02 (1.00 – 1.07)	6%
Physical inactivity	1.12 (1.03 – 1.29)	28%	1.07 (1.03 – 1.14)	22%

Supplementary Table 1: Sensitivity analysis excluding the 139 persons with a GDS > 6. For reference main MMA model 1 on the left side of the table.

	MMA model 1		MMA model 1 excluding first year dementia diagnoses (8 cases)	
Effect	**HR (95% CI)**	**Proportion of total effect***	**HR (95% CI)**	**Proportion of total effect***
Total	1.49 (0.99 – 2.41)		1.48 (0.96 -2.33)	
Direct	1.34 (0.92 – 2.17)	73%	1.32 (0.90 – 2.05)	70%
Total indirect	1.11 (1.01 – 1.27)	27%	1.12 (1.01 – 1.27)	30%
Body Mass Index (kg/m2)	0.95 (0.88 – 0.98)	-12%	0.96 (0.88 – 0.99)	-11%
Diabetes	1.04 (1.02 – 1.10)	9%	1.04 (1.00 – 1.13)	9%
Physical inactivity	1.12 (1.03 – 1.29)	28%	1.12 (1.03 – 1.26)	29%

Supplementary Table 2: Sensitivity analysis excluding first year dementia cases. For reference main MMA model 1 on the left side of the table.

Chapter VI

ASSOCIATION BETWEEN HYPERTENSION AND DEMENTIA RISK IN LOW- AND MIDDLE-INCOME COUNTRIES: A SYSTEMATIC REVIEW

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ABSTRACT

Background Dementia prevalence is rising most rapidly in low- and middle-income countries (LMICs), yet most evidence on risk factors such as hypertension stems from high-income settings. In LMICs, hypertension may have a greater impact due to its high prevalence and poor control. We systematically reviewed evidence on the association between blood pressure and dementia and cognition in LMICs, and compared findings across regions.

Methods We searched PubMed, Embase, PsycINFO, and Global Index Medicus and reviewed reference lists for relevant studies. We included longitudinal studies (follow-up ≥6 months) from LMICs on the association between systolic blood pressure or hypertension and incident dementia, mild cognitive impairment (MCI), or cognition, with a sample size of ≥500 individuals. Risk of bias was assessed using a modified Newcastle-Ottawa Scale.

Results Of 8709 screened articles, 26 were included: 19 from Asia, six from Latin America, and one from Africa. Operationalization of hypertension and cognitive outcome was heterogeneous across studies, ranging from using routine care data to triple blood pressure measurements and comprehensive cognitive screening with expert review and validation. Follow-up duration ranged from 7 months to 16 years. Hypertension was associated with a higher risk of incident dementia (RR 1.26, 95%CI 1.03 – 1.53) and MCI (RR 1.19, 95%CI 1.09 – 1.29). Due to limited number of studies per region, we were unable to compare effect sizes across geographical regions.

Conclusion Hypertension is associated with an increased risk of dementia and cognitive impairment in LMICs, but limited studies from Latin America and especially from Africa prevented reliable regional comparisons.

HIGHLIGHTS

- In Low and Middle Income Countries (LMICs) hypertension is associated with an increased risk of mild cognitive impairment and dementia.
- Our review confirms known associations from High Income Countries, but adds contextual relevance for LMICs.
- The majority of the identified studies originate from China, and we identified very limited studies from Latin-America and Africa, which might limit generalizability of our findings.

INTRODUCTION

The global prevalence of dementia is projected to triple between 2019 and 2050, reaching up to 150 million cases.[1] This rise is unevenly distributed, with the largest relative increase occurring in low- and middle-income countries (LMICs). In response, the scientific community has called for action through 'The Nairobi Declaration on Reducing the Burden of Dementia in LMICs',[2] advocating for greater focus on underrepresented populations in dementia research. The strongest drivers of the growing number of dementia cases in LMICs include population ageing, population growth, and a higher burden of modifiable risk factors.[1, 3] High blood pressure, especially in midlife, is a well-established risk factor for cognitive decline and dementia.[3] In recent decades, changes in diet and lifestyle have led to a rise in the burden of non-communicable diseases in LMICs, with high blood pressure currently being the leading risk factor for disease burden worldwide.[4] However, awareness of hypertension in LMICs remains low, with only one third of individuals aware of their condition, and control rates as low as around 8%.[5] As a result, prevalence of hypertension is higher, making its population attributable fraction for dementia greater in LMICs than the global average (4-9.3% vs 2%).[6] Antihypertensive treatment presents a scalable and cost-effective opportunity for dementia prevention due to its simple, inexpensive, and widely implemented nature.[7,8] Given the rapid aging of populations in LMICs,[4] understanding the relationship between hypertension and dementia and cognitive decline in these settings is particularly relevant. However, most evidence originates from high-income countries (HICs),[9, 10] raising concerns about its generalizability to LMICs.

Our primary aim is to systematically examine the association between hypertension and incident dementia in LMICs and to compare this association across geographical regions. Our secondary aim is to investigate the association of hypertension with mild cognitive impairment (MCI) and cognitive decline.

METHODS

The protocol for this systematic review was registered on Prospero (ID: CRD42024568574).[11] The manuscript followed the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) statement.[12]

Literature searches

We searched PubMed, Embase, PsycINFO, and Global Index Medicus (a database with biomedical and public health literature from LMICs) on July 23, 2024. The search strategy consisted of three components: (1) dementia/MCI/cognition and (2) hypertension/blood pressure had to be included in the title or abstract, and (3) a LMIC had to be mentioned in the full text (Supplementary Methods 1-3: Complete search strategy). We also screened the reference lists of included articles and related systematic reviews to identify additional eligible studies. There were no language or date restrictions. Two authors (TvM and JL) independently screened potentially eligible studies using Rayyan[13] and EndNote,[14] first based on titles and abstracts, then on full texts. In cases of disagreement, a third author MH-B was consulted.

Study selection

The following inclusion criteria were applied: (1) observational study with at least 6 months of follow-up; (2) conducted in LMICs, which we operationalized as being defined as Low, Lower-Middle or Upper-Middle Income Country by the World Bank at time of search in 2024[15]; (3) dementia, MCI, or cognitive functioning as a primary or secondary outcome; and (4) hypertension (defined by mean blood pressure, a clinical diagnosis of hypertension, and/or use of antihypertensive medications (AHM)) or blood pressure as an exposure. Studies were excluded if they had a sample size of fewer than 500 participants or were based on disease-specific cohorts (e.g., post-stroke or myocardial infarction).

Data extraction and risk of bias assessment

Data were extracted using a piloted data extraction form. The extracted information included: first author, year of publication, geographical region, study design, sample size, baseline characteristics of participants, definition of exposure and outcome, covariate adjustments, and effect sizes of the association between exposure (i.e., hypertension or blood pressure) and outcome (i.e., dementia, MCI, or cognition). Risk of bias (ROB) was assessed using the Newcastle-Ottawa Scale for non-randomised

studies.[16] This scale ranges from 0 to 9 and assesses the quality of a study based on three domains: selection, comparability, and outcome. We adapted the scale specifically for this context (Supplementary Table 1). A total score ≥ 7 was classified as low risk of bias, 4-6 as moderate risk, and ≤3 as high risk. Both data extraction and ROB assessment were conducted independently by one author (JL or MH-B) and checked by another author (TvM or JL). For two articles available only in Chinese, JL extracted data using ChatGPT (GPT-4o mini), and Copilot for translation, with verification by two native Chinese speakers (MS and DL).[17, 18] If essential data were missing, corresponding authors were contacted for additional information.

Data synthesis

We performed meta-analyses to assess the association of hypertension with dementia, MCI, and cognitive decline. When possible, analyses were stratified by geographical region (Africa, Asia, Latin America). Data were pooled if there were ≥3 studies that analysed a comparable association. To enable pooling, odds ratios (ORs) were transformed to risk ratios (RRs) using the base-rate risk and the *effectsize* package in R.[19] If the base-rate risk was unavailable for the analytical subsample, corresponding authors were contacted for additional information. Since event rates were low, hazard ratios (HRs) were considered equivalent to RRs to allow for pooling of the data.[20] Effect sizes were pooled using a random-effects model (*meta* package in R version 4.3.2), as we anticipated considerable heterogeneity between studies. Between-study variance was estimated using the Der Simonian-Laird estimator, and confidence intervals were estimated based on standard normal quantiles.[21] Heterogeneity between studies was assessed using the *I*2 statistic, interpreted according to the Cochrane Handbook (<40% might not be important, 30-60% may represent moderate heterogeneity, 50-90% substantial heterogeneity, and >75% considerable heterogeneity).[22] Publication bias was assessed using a funnel plot if more than 10 studies were available for pooling.[23] When pooling was not feasible, we conducted a narrative synthesis. For sensitivity analyses, we excluded studies with high or moderate risk of bias and separately analysed midlife vs. late-life hypertension as exposures.

RESULTS

Selection of articles

We identified 10,297 articles from database searches. After deduplication, 8,698 articles were screened based on title and abstract. Of these, 11 review articles were deemed potentially relevant, leading to citation searching of 804 references. In total, 127 articles underwent full-text review, of which 26 were included in this review reporting on 18 individual cohorts (Figure 1).

Study characteristics

We identified longitudinal studies from eight countries across three geographical regions: 19 from Asia[24-42] (of which 16 from China),[25, 26, 28, 30-42] 6 from Latin America,[43-48] and one from Africa.[49] The studies were based on 18 different cohorts, since five cohorts published multiple articles with different objectives that met our inclusion criteria: the China Health and Retirement Longitudinal Study (CHARLS),[26, 31, 35, 40] Chinese Longitudinal Healthy Longevity Survey (CLHLS),[25, 38, 39] China Health and Nutrition Survey (CHNS),[32, 37] Brazilian Longitudinal Study of Adult Health (ELSA-Brazil),[43, 44] and Mexican Health and Aging Study (MHAS).[46, 47] Of the included studies, 23 were prospective cohort studies[24-29, 31-49] and three were routine healthcare registry studies.[24, 29, 30] The total sample size was 447,097 individuals (range: 602-206,073), with follow-up durations ranging from 7 months to 16 years. Since we included multiple studies with different objectives from the same cohort these are not all unique individuals. Most studies (n=24) were performed in the general population.[24-28, 30-35, 37-49] The remaining studies focused on specific populations: nutritional intervention cohort (n=1)[36] and tertiary care population (n=1)[29] (Table 1).

Exposures

The exposure of interest was hypertension in 18 studies,[24-30, 33-37, 40, 43, 45-48] continuous blood pressure in four studies[32, 38, 41, 42] and four studies analysed both hypertension and blood pressure.[31, 39, 44, 49] Most studies defined hypertension as systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure (DBP) ≥90 mmHg.[26-28, 30, 31, 34, 37, 39, 40, 42-44, 49] However, two studies used higher cut-offs of SBP ≥160 mmHg or DBP ≥95 mmHg and persistently high at 170 mmHg.[25, 36] Five studies measured hypertension,[24, 32, 33, 45, 46] three studies relied on self-report,[35, 47, 48] and one study used registry data (Table 1 and Supplementary Table 3).[29]

Outcomes

Five studies analysed multiple outcomes.[26, 27, 33, 34, 46, 48] Dementia was an outcome of interest in ten studies,[24, 25, 27, 29, 33, 34, 36, 45, 46, 49] MCI in four[38, 39, 46, 47] and cognitive functioning was analysed in 14 studies (Table 1 and Supplementary Table 3).[26-28, 30-32, 35, 37, 40-44, 48] The methods for diagnosing dementia or MCI were heterogeneous across studies, ranging from self-reported dementia and routine health care data diagnosis to comprehensive assessments by expert diagnostic teams, followed by validation procedures. The Mini-Mental State Examination (MMSE), including the Chinese or an adjusted version, was the most commonly (n=9) used cognitive screening tool.[30, 33-35, 38, 39, 41, 42]

Risk of bias in included studies

The included studies scored between 3 and 9 points on the adjusted Newcastle-Ottawa Scale for nonrandomized studies (range 0-9), with higher scores indicating lower risk of bias. Twenty-one studies had low ROB,[25-28, 30, 32-34, 37-44, 46-49] four studies had moderate ROB[24, 35, 36, 45] and one study had high ROB[29] based on the Newcastle Ottawa Scale. The ROB assessment showed that many studies lacked an adequate description and or definition of exposure (n=9)[24, 29, 32, 33, 36, 45-48] and sufficient details on the adequacy of follow-up (n=11)[24, 26, 29, 31, 32, 35, 37-39, 45, 48] (Supplementary Table 2).

Meta- analysis

We pooled the associations of hypertension with dementia (n=7)[24, 25, 29, 34, 36, 45, 49] and MCI (n=3).[34, 39, 47] The outcomes and exposures of the remaining studies were too heterogeneous to conduct a meta-analysis.

Dementia

Seven studies including a total of 349,957 individuals examined the relationship between hypertension and incident dementia, with a mean follow-up duration ranging from 4 to 16 years. Five studies were conducted in Asia,[24, 25, 29, 34, 36] one in Latin America,[45] and one in Africa.[49] Hypertension was associated with a 26% higher risk of developing dementia (Figure 2; RR 1.26, 95%CI 1.03 – 1.53). Heterogeneity was moderate with an $I2$ of 40.4%. For Asian studies, the pooled RR was 1.16 (95%CI 0.90 – 1.51, 5 studies), compared to RR of 1.47 (95% CI 1.01-2.15, 1 study) for the only African study in the meta-analysis and RR of 1.55 (95%CI 1.02-2.37, 1 study) for the only Latin American study in the meta-analysis (Figure 3). Excluding studies with moderate or high risk of bias, did not affect the results (RR 1.30, 95%CI 1.00 – 1.68; Supplementary Figure 2).

Mild cognitive impairment

Three studies including a total of 14,882 individuals reported the association between hypertension and incident MCI, with follow-up durations ranging from 4 to 14 years. The pooled analysis showed a 19% increased risk of MCI in individuals with hypertension (RR 1.19, 95%CI 1.09 – 1.29, $I2$: 15.0%; Figure 4). We did not pool results by geographic region due to the insufficient numbers of studies (two from Asia and one from Latin America).

Narrative synthesis of global cognitive score and cognitive domains

Three studies, including a total of 23,743 individuals, analysed the association between hypertension and global cognitive score, with follow-up durations ranging from 4 to 8 years.[26, 31, 43] Eight studies, including a total of 51,650 individuals, analysed the association between hypertension and memory, most often assessed by delayed word recall.[26, 28, 31, 37, 40, 43, 44] Seven studies found that hypertension was associated with lower memory scores after a median of 6 years (range: 2-8 years) and/or faster memory decline.[26, 28, 31, 37, 40, 43, 44] One study showed no significant association (mean SBP divided in tertiles, highest vs lowest tertile $\beta = 0.01$ (95%CI -0.03, 0.04).[32] Three studies found that hypertension was associated with lower executive functioning.[26, 43, 44]

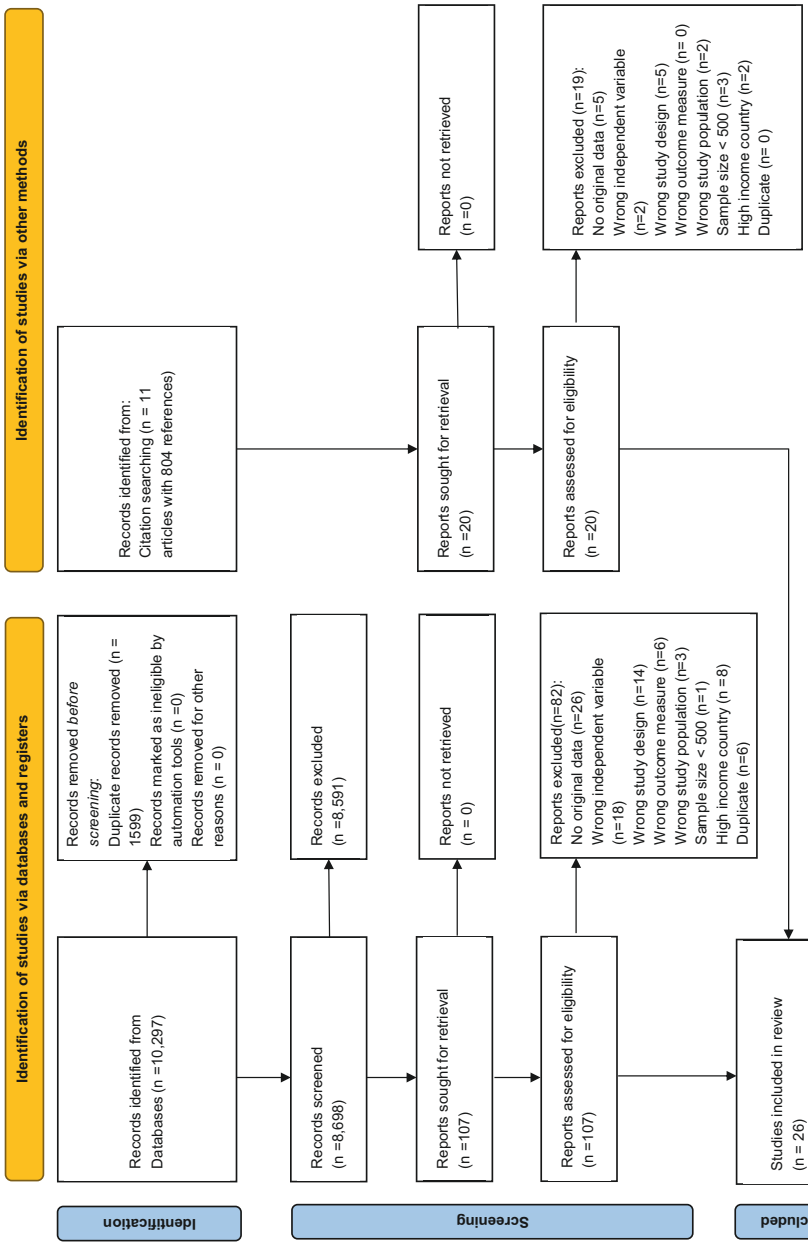

Figure 1: Flowchart screening.

Author (year)	Country	Study period	Study design*	Cohort†	Popula-tion	Sample size	Age (mean, SD)	Sex (% women)	Follow-up (years)	Exposure‡	Outcome§
Africa											
Ogunniyi (2011)	Nigeria	1992-2007	P	IIDRP	General	1753	76 (5)	1210 (69%)	6	1. Ht, 2. SBP x 10mmHg	Dementia
Asia											
Cheng (2021)	China	1998-2018	P	CLHLS	General	10660	N/A	5755 (54%)	6	Ht	Dementia
Ding (2023)	China	2011-2018	P	CHARLS	General	4824	68 (10)	2972 (62%)	8	Ht	CD
Gao (2009)	China	2003-2007	P	N/A	General	1737	71 (5)	922 (53%)	2	Ht	CD
Lee (2013)	China	2005-2011	R	EHC	General	1453	Median 73 (N/A)	913 (63%)	6	Ht	CD
Li (2024)	China	2011-2018	P	CHARLS	General	11671	59 (9)	6155 (53%)	7	1. Ht, 2. SBP	CD
Qin (2016)	China	1989-2004	P	CHNS	General	976	63 (7)	508 (52%)	5	Tertile of SBP	CD
Qu (2005)	China	1998-2001	P	N/A	General	2197	N/A	1640 (56%)	3	Ht	1. Dementia, 2. AD and VD
Ren (2022)	China	2014-2018	P	SYS-AD	General	1843	71 (5)	1577 (57%)	4	Ht	1. MCI, 2. Dementia
Su (2022)	China	2011-2018	P	CHARLS	General	6954	N/A	3243 (47%)	8	Ht	CD
Wu (2003)	China	1984-2000	P	NIC	Nutrition study cohort	602	N/A	N/A	16	Ht	AD
Xu (2018)	China	1997-2006	P	CHNS	General	4847	64 (5)	N/A	N/A	Ht	CD
Yi (2024)	China	2014-2018	P	CLHLS	General	1132	78 (8)	498 (44%)	5	SBP	MCI
Yuan (2019)	China	2000-2014	P	CLHLS	General	12281	Median, IQR 81 (65-109)	6036 (49%)	6	1. Ht, 2. SBP x 10 mmHg	MCI

Zhang (2004)	China	1993-1997	P	N/A	General	2079	69 (6)	1031 (50%)	4	SBP x 30 mmHg	1. MCI, 2. CD
Zhang (2021)	China	2014-2016	P	N/A	General	7874	69 (7)	4081 (52%)	2	SBP	CD
Zhang (2022)	China	2011-2018	P	CHARLS	General	8957	58 (8)	4619 (52%)	8	Ht	CD
Farron (2020)	India	2016-2019	P	LA-SI-DAD	General	2874	69 (7)	1042 (36%)	7 months	Ht	1. CD, 2. Dementia
Boongird (2020)	Thailand	2006-2012	R	HCUR	General	206073	63 (10)	54%	6	Ht	Dementia
Lawongsa (2024)	Thailand	2009-2023	R	PHD	Tertiary clinic	127016	N/A	66,878 (53%)	15	Ht	Dementia
Latin America											
de Menezes (2021)	Brazil	2008-2014	P	ELSA	General	7248	59 (6)	3898 (55%)	4	Ht	CD
Ferreira (2023)	Brazil	2008-2019	P	ELSA	General	11390	51 (9)	6333 (56%)	8	1. SBP, 2. Ht	CD
Ribeiro (2024)	Brazil	2000-2015	P	SABE	General	1042	68 (0)	632 (61%)	15	Ht	CD
Llibre-Rodriguez (2017)	Cuba	2003-2011	P	AAP	Primary care	2010	N/A	N/A	4	Ht	Dementia
Mejia-Arango (2011)	Mexico	2001-2003	P	MHAS	General	6846	N/A	N/A	2	Ht	1.Dementia, 2. MCI
Renteria (2022)	Mexico	2001-2016	P	MHAS	General	758	57 (4)	433 (57%)	14	Ht	MCI

Table 1: Characteristics of studies included in the systematic review ordered by geographic region and country. *Study design: P=prospective, R=retrospective. †Full cohort names: **AAP** – Aging & Alzheimer Project, **CHARLS** – China Health and Retirement Longitudinal Study, **CHNS** – China Health and Nutrition Survey, **CLHLS** – Chinese Longitudinal Healthy Longevity Survey, **EHC** – Elderly Health Centre, **ELSA**– Brazilian Longitudinal Study of Adult Health, **HCUR** – Health Checks Ubon Ratchathani, **IIDRP** – Indianapolis-Ibadan Dementia Research Project, **LASI-DAD** – Longitudinal Aging Study in India (Dementia sub-study), **MHAS** – Mexican Health and Aging Study. ‡Exposure: Ht=hypertension, SBP=systolic blood pressure, SBP x 10 mmHg = SBP ordinalized by 10 mmHg increment, SBP x 30 mmHg = SBP ordinalized by 30 mmHg increment. §Outcome: CD=cognitive decline, MCI=mild cognitive impairment, AD=Alzheimer's disease, VD=vascular dementia.

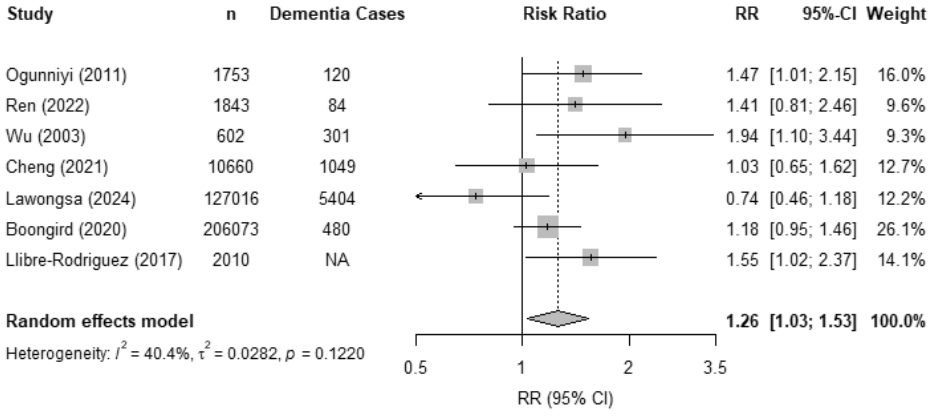

Figure 2: Forest plot of the association between hypertension and dementia.

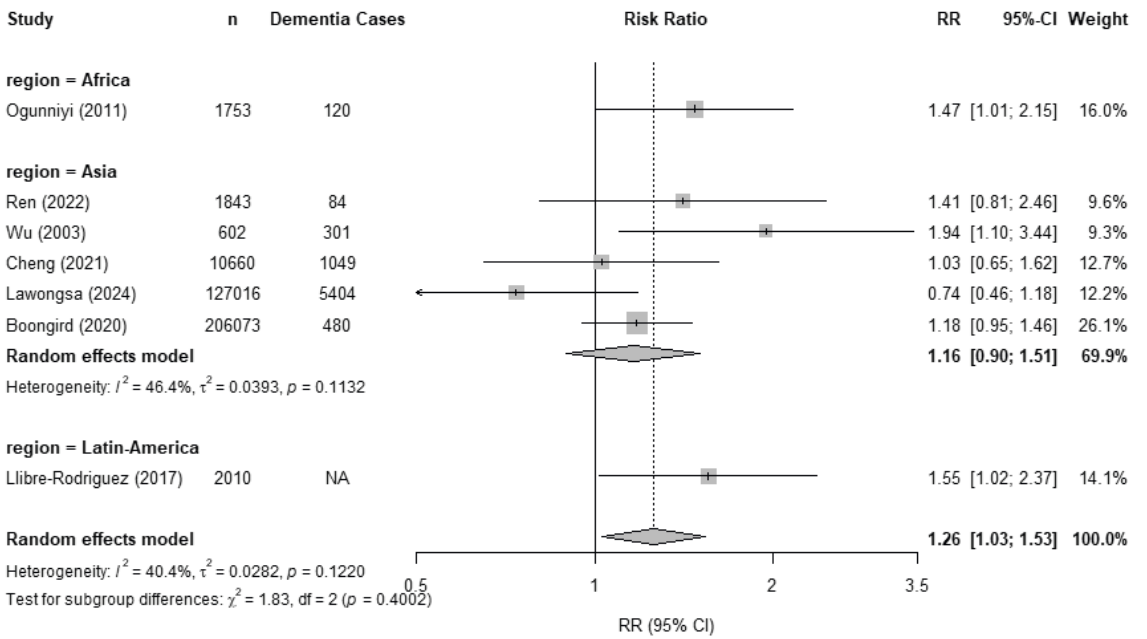

Figure 3: Forest plot of the association between hypertension and dementia pooled by geographic region.

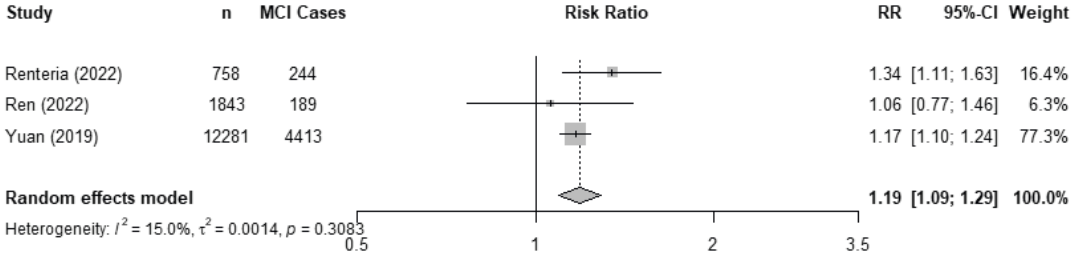

Figure 4: Forest plot of the association between hypertension and mild cognitive impairment.

DISCUSSION

Summary of main results

Hypertension is associated with an increased risk of MCI and dementia in LMICs, based on 19 Asian studies (of which 16 from China), six from Latin-America and one from Africa. Our findings confirm established associations in HICs and add important contextual relevance by demonstrating that the hypertension–dementia link also holds in LMIC settings. Although studies on cognitive domains were too heterogeneous for pooling, most suggested an association between hypertension and lower memory score and/or executive functioning. Geographic differences could not be reliably assessed due to the limited number of studies from Africa and Latin America. In regional analyses, no significant association was found in Asia, whereas significant associations were observed in Africa and Latin America. However, these latter findings were based on single studies only and should be interpreted with caution.

Evidence in context

The association between hypertension and dementia in this review (RR 1.26, 95%CI 1.03 – 1.53) is comparable to the pooled results from predominantly HIC studies in a previous umbrella review (RR 1.20, 95%CI 1.04 – 1.40).[50] This finding is particularly noteworthy, considering that several factors influencing the association between hypertension and dementia differ between LMICs and HICs. First, awareness and control of hypertension are significantly lower in LMICs.[5, 51] This may result in prolonged exposure to more severe hypertension, which could influence the observed association with dementia if the relationship is indeed causal. However, given the similar effect estimates to those from HICs, this influence may be less pronounced than expected. Due to the nature of the included studies, we were unable to adjust for duration and severity of hypertension. However, due to the nature of the included studies we were unable to adjust the analyses for duration of exposure to hypertension or to perform a meta-regression on the association between mean SBP and dementia to assess a dose-response relationship. Second, the higher prevalence of undiagnosed dementia in LMICs could introduce outcome misclassification, which in most cases would bias the association towards the null, potentially underestimating its true strength.[51] Additionally, most research on the association between hypertension and dementia in HICs has been conducted primarily in White populations, limiting the generalizability of findings to ethnically diverse LMIC populations. It has been suggested that dementia risk and the impact of hypertension may vary across populations with different sociocultural backgrounds or genetic ancestry.[52, 53] Supporting this, several commonly

used dementia risk prediction models—developed in HIC using combinations of weighted risk factors—performed inconsistently across LMICs, with accuracy varying significantly by country.[54] This variability implies that the association between risk factors and dementia may not be uniform globally. Although our review was not specifically designed to examine ethnic or ancestral differences, it does highlight evidence from African, South Asian, and Latin American populations—groups that are often underrepresented in dementia research. Studying these populations within their local contexts is essential for deepening our global understanding of dementia risk factors and for developing more inclusive and effective prevention strategies. Hypertension prevention and management have proven cost-effective in HICs. Based on our findings showing that hypertension is associated to MCI and dementia and given the higher prevalence and lower control rates in LMICs, the potential impact of targeting this modifiable risk factor may be even greater in these settings.[55] Effective prevention strategies in LMICs may include community health education, focused on diet and salt reduction, training primary care providers to follow hypertension treatment guidelines, and ensuring intensive follow-up for newly diagnosed patients. Equally important is the availability and affordability of essential medications.[56]

While the projected increase in dementia is largest in LMICs, research on the association between blood pressure and dementia remains limited compared to HICs.[1] Nonetheless, several initiatives are working to strengthen dementia research capacity in these underrepresented populations. The 10/66 research groups conducted surveys among older adults in ten LMICs revealing regional variations in the population attributable fractions (PAFs) of dementia risk factors. In line with our findings, the study reported a higher PAF for hypertension in Latin America (9%) compared to Asia (4–6%).[6] These PAFs primarily reflect the higher prevalence of hypertension in LMICs and are based on risk estimates derived from HIC data. If both the strength of the association and the prevalence of hypertension are greater in certain LMIC regions, actual PAFs could be even higher. Another important initiative, the Cohort Studies of Memory in an International Consortium (COSMIC), aims to harmonize data from global cohort studies—including both LMICs and HICs—on cognitive aging to support pooled analyses.[57] Findings from COSMIC indicate that the association between the Lifestyle for BRAin Health (LIBRA) risk score and incident dementia is modified by geographic region, with a stronger association observed in Asian populations.[58] Since risk prediction models, including LIBRA, are based on multiple weighted risk factors—not just hypertension—these results further underscore the importance of studying context and region-specific risk factor susceptibility.

In this review, several studies utilized routinely collected health care data.[24, 29, 30] Using such data requires a routine health information system (RHIS), and sufficient high data quality. RHIS data are already widely used in sub-Saharan Africa to evaluate interventions for communicable diseases.[59] Its application in dementia research could present both opportunities and challenges. On one hand, RHIS data allow long-term follow-up of large populations at relatively low cost. On the other hand, concerns remain about the validity of dementia diagnoses in RHIS data, particularly given the widespread underdiagnosis of dementia in the general population.[60, 61] A systematic review on the use of RHIS data for dementia research, which only included HIC-based studies, reported wide variation in diagnostic sensitivity (21-86%) depending on the type and number of data sources used.[62] To achieve the best results, a combination of primary care data (which offers high positive predictive value) alongside hospital and death registries (which contribute greater sensitivity) should be used. If data quality standards are met, RHIS data could complement prospective cohort studies in resource-limited settings by enabling extended follow-up, provide valuable insights into disease patterns and risk factors, and ultimately supporting the development of more effective prevention strategies.

Strengths and limitations

This systematic review has several strengths. We employed a comprehensive search strategy, searching four databases, including one with a special focus on studies from LMICs, and without language restrictions. The review comprised only studies with a sample size of at least 500 individuals and a follow up of at least 6 months to ensure the robustness of the evidence. The majority of the included studies had a low risk of bias (n=21 out of 26). However, this review also has some important limitations. The availability of evidence was too sparse in some regions to answer whether there are differences between different geographical regions. The pooled effect size incorporates data from African, Latin American, and other Asian countries, but most studies included in this review are from China, which may introduce bias and limit generalizability. Although no language restrictions were applied to the full text, the search was conducted in English, so studies without English abstracts or keywords may have been missed. Heterogeneity in the definition of exposure (hypertension, SBP, AHM use) and outcome (dementia, MCI, cognitive decline, or decline in cognitive subdomains) hampered the pooling of results. Also the variation in definition of hypertension and dementia may lead to variation in validity of their diagnosis, leading to potential misclassification. For five studies hypertension was, solely or partially, based on self-report. We estimate that the influence of self-reported hypertension on the outcome is limited, because self-reported hypertension is probably a reliable

proxy for objective hypertension.[63] Diagnosis of dementia was mostly based on DSM-IV criteria (n=4), two studies used a combination of cognitive screening test combined with neurologic examination or neuropsychologic testing, one study used self- or proxy reported diagnosis, one used registration data with ICD-10 or prescription data, and one based a cut-off on cognitive screening tests. Self- or proxy-reported hospital diagnosis could lead to underdiagnosis of dementia. Variability in cultural perceptions of illness, healthcare-seeking behavior, access to medical services, diagnostic criteria, and the organization of health information systems can all affect how frequently hypertension and dementia are diagnosed and recorded in medical registries. Consequently, cross-regional comparisons based on registry data could be influenced by these regional differences. We reported on the fullest model reported in each study and all studies at least adjusted for the three most important confounders; age, sex and education. Additional adjustments for other potential confounders varied significantly across studies. Lack of adjustment for other variables such as other vascular risk factors or medication adherence could lead to residual confounding. Finally, due to the limited number of studies specifically focusing on mid- or late life, or stratifying results by age category, we were unable to aggregate evidence by age group—despite the fact that the relationship between hypertension and dementia is known to vary across the lifespan.[9, 50]

CONCLUSION

Hypertension is associated with an increased risk of MCI and dementia in LMICs, comparable to associations found in HIC populations. This conclusion is largely based on studies from Asia, particularly China. While estimates from Africa and Latin America appear to be a bit higher, paucity of data from these regions precludes definitive conclusions about potential geographical differences.

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SUPPLEMENTARY MATERIAL

Supplementary Text 1: Full search PubMed, Embase, PsycINFO

(Dementia.sh OR dement*.ti OR dement*.ab OR Alzheimer*.ti OR Alzheimer*.ab OR cognition.sh OR cognit*.ti OR cognit*.ab OR Memory.sh OR memory.ti OR memory.ab)

AND

(Hypertension.sh OR hypertens*.ti OR hypertens*.ab OR (blood pressure).sh OR (blood pressure).ti OR (blood pressure).ab OR (Antihypertensive Agents).sh OR antihypertensive.ti OR antihypertensive.ab OR anti-hypertensive.ti OR anti-hypertensive.ab)

AND

((Developing Countries.sh) OR (low income countr*.ti) OR (low income countr*.ab) OR (low-income countr*.ti) OR (low-income countr*.ab) OR (middle income countr*.ti) OR (middle income countr*.ab) OR (middle-income countr*.ti) OR (middle-income countr*.ab) OR LMIC.ti OR LMIC.ab OR

Africa.sh OR Afric*.ti OR Afric*.ab OR (Central America.sh) OR (Central Americ*.ti) OR (Central Americ*.ab) OR (Latin America.sh) OR latin*.ti OR latin*.ab OR (South America.sh) OR (south americ*.ti) OR (south americ*.ab) OR Asia.sh OR Asia*.ti OR Asia*.ab OR Arabs.sh OR Arab*.ti OR Arab*.ab OR

Afghan* OR (Burkina Faso) OR Burundi* OR (Central African Republic) OR Chad* OR Congo* OR Kongo* OR Eritrea* OR Ethiopia* OR Gambia* OR Guinea* OR Korea* OR Liberia* OR Madagas* OR Malawi* OR Mali* OR Mozambi* OR Niger* OR Rwanda* OR (Sierra Leone*) OR Somali* OR Sudan* OR Syria* OR Togo* OR Uganda* OR Yemen* OR Zambia* OR

Angola* OR Algeria* OR Bangladesh* OR Benin* OR Bhutan* OR Bolivia* OR (Cabo Verde*) OR Cambodia* OR Cameroon* OR Comoros OR comorians OR d'Ivoire OR ivor* OR Djibouti* OR Egypt* OR Salvador* OR Eswatini OR swazi* OR Ghana* OR Haiti* OR Hondura* OR India* OR Indonesia* OR Iran* OR Kenya* OR Kiribati OR Kyrgyz* OR (Lao PDR) OR (Lao people*) OR Laos OR Leban* OR Lesotho OR Mauritania* OR Micronesia* OR Mongolia* OR Morocc* OR Myanmar OR Burm* OR Nepal* OR Nicaragua* OR Nigeria* OR Pakistan* OR Papua* OR Philip* OR Samoa* OR Tome OR Senegal* OR

Solomon* OR Lanka* OR Tanzania* OR Tajik* OR Timor* OR Tunisia* OR Ukrain* OR Uzbek* OR Vanuatu OR Vietnam* OR Gaza OR Zimbabwe* OR

Albania* OR Argentin* OR Armenia* OR Azerbaijan* OR Belarus* OR Belize* OR Bosnia* OR Botswana* OR Brazil* OR Bulgaria* OR China OR Chinese OR Colombia* OR (Costa Rica*) OR Cuba* OR Dominica* OR Ecuador* OR Fiji* OR Gabon OR Georgia* OR Grenada OR Guatemala* OR Guyan* OR Iraq* OR Jamaica* OR Jordan* OR Kazakh* OR Kosov* OR Libya* OR Malaysia* OR Maldiv* OR Marshall* OR Mauriti* OR Mexic* OR Moldova* OR Montenegr* OR Namibia* OR Macedonia* OR Palau* OR Paraguay* OR Peru* OR Russia* OR Serb* OR Lucia OR Grenadines OR Surinam* OR Thai* OR Tonga* OR Turk* OR Tuvalu*)

Supplementary Text 2: Full search Global Medicus

(ti:dement* OR ab:dement* OR ti:Alzheimer* OR ab:Alzheimer* OR ti:cognit* OR ab:cognit* OR ti:memory OR ab:memory)

AND

(ti:hypertens* OR ab:hypertens* OR ti:(blood pressure) OR ab:(blood pressure))

AND

(ti:(low income countr*) OR ab:(low income countr*) OR ti:(low-income countr*) OR ab:(low-income countr*) OR ti:(middle income countr*) OR ab:(middle income countr*) OR ti:(middle-income countr*) OR ab:(middle-income countr*) OR ti:LMIC OR ab:LMIC OR

ti:Afric* OR ab:Afric* OR ti:(Central Americ*) OR ab:(Central Americ*) OR ti:latin* OR ab:latin* OR ti:(south americ*) OR ab:(south americ*) OR ti:Asia* OR ab:Asia* OR ti:Arab* OR ab:Arab* OR

Afghan* OR (Burkina Faso) OR Burundi* OR (Central African Republic) OR Chad* OR Congo* OR Kongo* OR Eritrea* OR Ethiopia* OR Gambia* OR Guinea* OR Korea* OR Liberia* OR Madagas* OR Malawi* OR Mali* OR Mozambi* OR Niger* OR Rwanda* OR (Sierra Leone*) OR Somali* OR Sudan* OR Syria* OR Togo* OR Uganda* OR Yemen* OR Zambia* OR

Angola* OR Algeria* OR Bangladesh* OR Benin* OR Bhutan* OR Bolivia* OR (Cabo Verde*) OR Cambodia* OR Cameroon* OR Comoros OR Comorian OR d'Ivoire OR ivor* OR Djibouti* OR Egypt* OR Salvador* OR Eswatini OR swazi* OR Ghana* OR Haiti* OR Hondura* OR India* OR Indonesia* OR Iran* OR Kenya* OR Kiribati OR Kyrgyz* OR (Lao PDR) OR (Lao people*) OR Laos OR Leban* OR Lesotho OR Mauritania* OR Micronesia* OR Mongolia* OR Morocc* OR Myanmar OR Burm* OR Nepal* OR Nicaragua* OR Nigeria* OR Pakistan* OR Papua* OR Philip* OR Samoa* OR Tome OR Senegal* OR Solomon* OR Lanka* OR Tanzania* OR Tajik* OR Timor* OR Tunisia* OR Ukrain* OR Uzbek* OR Vanuatu OR Vietnam* OR Gaza OR Zimbabwe* OR

Albania* OR Argentin* OR Armenia* OR Azerbaijan* OR Belarus* OR Belize* OR Bosnia* OR Botswana* OR Brazil* OR Bulgaria* OR Chin* OR Colombia* OR (Costa Rica*) OR Cuba* OR Dominica* OR Ecuador* OR Fiji* OR Gabon OR Georgia* OR Grenada OR Guatemala* OR Guyan* OR Iraq* OR Jamaica* OR Jordan* OR Kazakh* OR Kosov* OR Libya* OR Malaysia* OR Maldiv* OR Marshall* OR Mauriti* OR Mexic* OR Moldova* OR Montenegr* OR Namibia* OR Macedonia* OR Palau* OR Paraguay* OR Peru* OR Russia* OR Serb* OR Lucia OR Grenadines OR Surinam* OR Thai* OR Tonga* OR Turk* OR Tuvalu*)

	Item	Operationalization
Selection	1. Representativeness of the exposed cohort	Truly or somewhat representative of the average older adult without dementia in the community (*/-)
	2. Selection of the -n-exposed cohort	Drawn from the same community as the exposed cohort
	3. Ascertainment of exposure (hypertension/ systolic BP)	Continuous or categorized by established cut-offs
	4. Demonstration that outcome of interest was present at start of study	yes/no
Comparability	Study controls for	Age
	Study controls for	Sex
	Study controls for	Education
	Total comparability score	*=controls for age, **= controls for age, sex and education, -=crude only
Outcome	1. Ascertainment of outcome	Independent assessment (NPO/MMSE/other validated cognitive test)
	2. Was follow-up long enough for outcomes to occur?	≥ 1 year
	3. Adequacy of follow up of cohorts	Adequate description or > 80%
	Total score (max. 9)	0-9

Supplementary Table 1: Operationalization of Newcastle-Ottawa-Scale for this review

Study	Exposed cohort relevance	Non-exposed selection	Exposure check	Outcome absent at baseline	Comparability score	Outcome verification	Duration of follow-up	Adequacy of follow-up	Quality score (0-9)
Ogunniyi 2011	*	*	*	*	**	*	*	*	9
Cheng 2021	*	*	*	*	**	-	*	*	8
Ding 2022	*	*	*	*	**	*	*	-	8
Gao 2009	*	*	*	*	**	*	*	*	9
Lee 2013	*	*	*	*	*	*	*	*	8
Li 2024	*	*	*	*	**	*	*	-	8
Qin 2016	*	*	-	*	**	*	*	-	7
Qu 2005	*	*	-	*	**	*	*	*	8
Ren 2022	*	*	*	*	**	*	*	*	9
Su 2022	*	*	*	*	-	*	*	-	6
Wu 2003	*	*	-	-	-	*	*	*	5
Xu 2018	*	*	*	*	**	*	*	-	8
Yi 2024	*	*	*	*	**	*	*	-	8
Yuan 2019	*	*	*	*	**	*	*	-	8
Zhang 2004	*	*	*	*	**	*	*	*	9
Zhang 2021	*	*	*	*	**	*	*	*	9
Zhang 2022	*	*	*	*	**	*	*	*	9
Farron 2020	*	*	*	*	**	*	-	*	8
Boongird 2020	*	*	-	*	*	-	*	-	5
Lawongsa 2024	-	-	-	*	*	-	*	-	3
de Menezes 2020	*	*	*	*	**	*	*	*	9
Ferreira 2023	*	*	*	*	**	*	*	*	9
Ribeiro 2024	*	*	-	*	**	*	*	-	7

Llibre-Rodriquez 2017	*	*	-	*	-	*	*	-	5
Mejia-Arango 2011	*	*	-	*	**	*	*	*	8
Renteria 2022	*	*	-	-	**	*	*	*	7

Supplementary Table 2: Risk of bias assessment according to the Newcastle-Ottawa Scale of studies included in the systematic review.

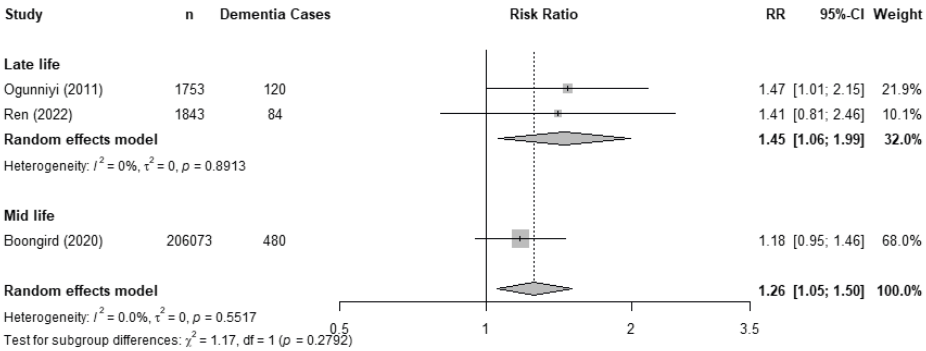
Author (year)	Exposure*	Operationalization†	Outcome‡	Operationalization§
Africa				
Ogunniyi (2011)	1. Ht, 2. SBP x 10mmHg	1. SBP≥140 mmHg, DBP≥90 mmHg (mean of 3 measurements), 2. SBP x 10mmHg.	Dementia	1. CSI-D + Informant Score. 2. clinician home-based interview, neurologic & physical examination + structured interview of a relative.
Asia				
Cheng (2021)	Ht	Persistantly high at 170 mmHg.	Dementia	Self- or proxy-reported hospital diagnosis.
Ding (2023)	Ht	SBP≥140 mmHg, DBP≥90 mmHg or use of AHM (including traditional Chinese herbal medicine).	CD	Global cogniton z-score
Gao (2009)	Ht	SBP≥140 mmHg, DBP≥90 mmHg (mean of 2 measurements), or self-reported.	CD	Decline on CERAD word list learning and word list recall.
Lee (2013)	Ht	SBP≥140 mmHg or DBP≥90 mmHg.	CD	Dementia, scoring below the cutoff point on C-MMSE, and a global CDR of 1–3.
Li (2024)	1. Ht, 2. SBP	1. SBP≥140 mmHg, DBP≥90 mmHg or use of AHM, 2. SBP x 10mmHg.	CD	Global cogniton z-score
Qin (2016)	Tertile of SBP	N/A	CD	Δ in TICS-m
Qu (2005)	Ht	N/A	1. Dementia, 2. AD & VD	1. MMSE screening, 2. NPT for those with a lower MMSE and those with self-reported memory decline but without a lower MMSE, 3. Suspected cases were re-evaluated 6 months after the initial assessment.

Ren (2022)	Ht	SBP≥140 mmHg, DBP≥90 mmHg or use of AHM.	1. MCI, 2. Dementia	1. a. subjective cognitive complaints, defined as self-rated AD8 score≥2; and b. objective impairment in global cognition, defined as the MMSE score≥1 standard deviation (SD) below the age- and education-specific mean MMSE scores. 2. According to DSM-IV by trained neurologists based on clinical examinations, assessment of cognitive and physical functioning using structured questionnaires.
Su (2022)	Ht	Self-reported	CD	Δ C-MMSE
Wu (2003)	Ht	SBP ≥160 mmHg or DBP ≥95 mmHg.	AD	DSM-IV criteria, based on clinical data reviewed by diagnostic team.
Xu (2018)	Ht	SBP≥140 mmHg, DBP≥90 mmHg or use of AHM.	CD	TICS-m
Yi (2024)	SBP	SBP continuous (mean of two measurements)	MCI	C-MMSE. Normal cognition 25-30, Mild CI 18-24, Moderate CI 10-17, Severe CI 0-9.
Yuan (2019)	1. Ht, 2. SBP x 10 mmHg	SBP≥140 mmHg or DBP≥90 mmHg	MCI	MMSE < 24
Zhang (2004)	SBP x 30 mmHg	SBP≥140 mmHg, DBP≥90 mmHg or use of AHM	1. MCI, 2. CD	1. Adjusted MMSE scores: Illiterate: ≤17, Primary school: ≤20, Middle school: ≤22, University: ≤24, 2. Δ 4 MMSE points
Zhang (2021)	SBP	SBP continuous (mean of two measurements).	CD	Δ MMSE
Zhang (2022)	Ht	SBP≥140 mmHg, DBP≥90 mmHg or use of AHM.	CD	Total score of word recall test, TICS and redrawing picture.
Farron (2020)	Ht	SBP≥140 mmHg, DBP≥90 mmHg, or self-reported	1. CD, 2. Dementia	1. A summary cognition score, derived from the sum of 18 cognitive tests.
Boongird (2020)	Ht	N/A	Dementia	Physician diagnosed dementia according to DSM-IV in medical record
Lawongsa (2024)	Ht	ICD-10: I10-I15	Dementia	ICD-10 code of F00-F03, G30, or a prescription for a cholinesterase inhibitor or an N-methyl-D-aspartate receptor antagonist.

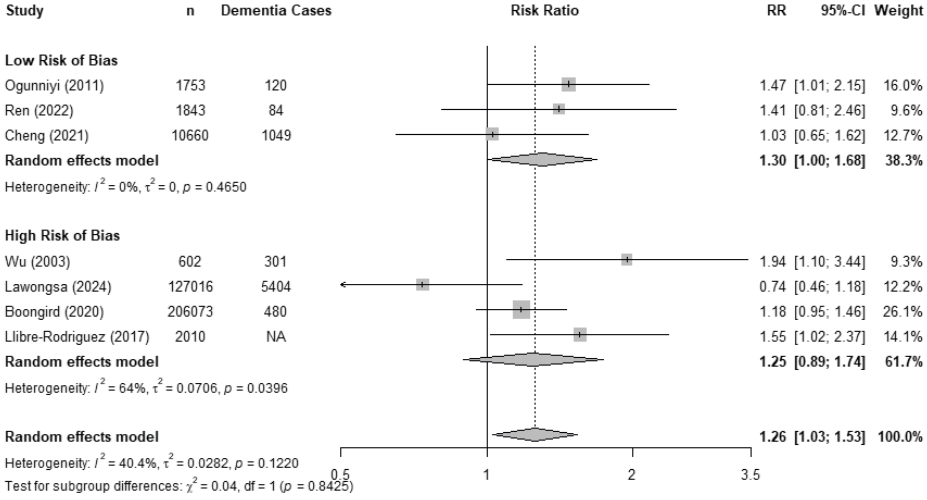
Latin America				
de Menezes (2021)	Ht	SBP≥140 mmHg, DBP≥90 mmHg or use of AHM	CD	Global cogniton z-score
Ferreira (2023)	1. SBP, 2. Ht	1. SBP continuous, 2. SBP≥140 mmHg or DBP≥90 mmHg	CD	Global cogniton z-score
Ribeiro (2024)	Ht	Self-reported	CD	1. scoring ≤12/19 on abbreviated MMSE 2. Δ abbreviated MMSE
Llibre-Rodriguez (2017)	Ht	N/A	Dementia	DSM-IV
Mejia-Arango (2011)	Ht	N/A	1.Dementia, 2. MCI	1. DSM-IV by a group of Geriatricians and Neuropsychologists, 2. Cognitive, but no functional impairment on the CCCE
Renteria (2022)	Ht	Self-reported	MCI	Composite cognitive domain score ≥1.5 SD below demographically corrected T-scores

Supplementary Table 3: Operationalization of exposure and outcome.

*Exposure: Ht=hypertension, SBP=systolic blood pressure, SBP x 10 mmHg = SBP ordinalized by 10 mmHg increment, SBP x 30 mmHg = SBP ordinalized by 30 mmHg increment. †Operationalization exposure: SBP=systolic blood pressure, DBP= diastolic blood pressure, AHM= antihypertensive medication, ICD-10= international classification of disease, N/A= not available. §Operationalization outcome: CSI-D= community screening interview for dementia, CERAD= Consortium to Establish a Registry for Alzheimer's Disease, C-MMSE= Chinese mini mental state examination, CDR= Clinical Dementia Rating, TICS-m= Modified Telephone Interview for Cognitive Status, NPT= Neuropsychological testing, DSM-IV= Diagnostic and Statistical Manual of Mental Disorders, fourth version, MMSE= Mini Mental State Examination, CCCE= Cross Cultural Cognitive Examination. ‡Outcome: CD=cognitive decline, MCI=mild cognitive impairment, AD=Alzheimer's disease, VD=vascular dementia.



Supplementary Figure 1: Forest plot of the association between hypertension and dementia pooled by age category of the exposure.



Supplementary Figure 2: Forest plot of the association between hypertension and dementia pooled by risk of bias rating.

Chapter VII

THE ASSOCIATION OF ANCILLARY DIAGNOSTIC TESTS WITH OUTCOME IN DEMENTIA

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ABSTRACT

Objectives Dementia is a clinical diagnosis without curative treatment. It is uncertain whether ancillary testing is beneficial for patients. This study investigates the association between use of diagnostic tests and time to poor outcome and healthcare costs.

Design Nationwide register-based cohort study using healthcare reimbursement data in the Netherlands.

Setting and participants All Dutch hospitals, including 13,312 patients diagnosed with dementia in 2018.

Methods Diagnostic testing included computed tomography or magnetic resonance imaging (CT/MRI); neuropsychological examination (NPE), nuclear imaging (PET/SPECT), electroencephalography (EEG) and cerebrospinal fluid testing (CSF). We compared time to poor outcome (institutionalization or death), and costs per month from 2018 to 2021 between those who underwent a specific diagnostic test in previous years to controls, propensity-score matched for age, sex, type of hospital and comorbidity.

Results Time to poor outcome in those who underwent CT/MRI, EEG or CSF was similar to those who did not, but was longer for those who underwent NPE. Time to poor outcome was shorter in patients who underwent PET/SPECT. Patients who underwent CSF testing or PET/SPECT had higher mean total healthcare costs as compared to controls (CSF €248, 95% CI 64-433; PET/SPECT: €315, 95% CI 179-451). NPE during the diagnostic trajectory was associated with lower total healthcare cost (-€127 95% CI 62-193).

Conclusion and implications NPE was associated with longer time to poor outcome and lower healthcare costs, potentially due to confounding by indication. Patients who underwent neuroimaging (CT, MRI, SPETC/PET), CSF or EEG for dementia diagnostics did not experience a longer time to poor outcome or lower healthcare costs. This emphasizes the importance of clinical examination as anchor for the diagnosis of dementia.

INTRODUCTION

Clinical guidelines across the globe emphasize the need for a timely diagnosis of dementia.[1-3] The diagnostic trajectory may involve several diagnostic tests, to test differential diagnostic hypotheses, to rule out rare reversible causes of cognitive decline and to diagnose subtypes of dementia with more certainty.[4] Brain imaging with computed tomography (CT) or magnetic resonance imaging (MRI) is recommended as part of investigations of people with suspected dementia in a specialist care setting in UK[2], European,[3] and US guidelines.[5] Additional available tests include PET (positron emission tomography), SPECT (single-photon emission CT), cerebrospinal fluid (CSF) analysis, electroencephalography (EEG) and detailed neuropsychological examinations (NPE).

Diagnosis may relieve uncertainties about one's cognitive impairments and may pave the way for access to appropriate care, including advance care planning.[6] The right timing and setting for diagnosis relies heavily on patient and caregiver preferences.[7] In younger patients, broad differential diagnostic testing in a specialized memory clinic may be warranted, however, in older patients the added value of diagnostic testing may be limited due to overlapping pathologies and absence of curative options.[8-12] This raises the question if patients benefit from extensive diagnostic testing compared to more restrictive testing. Diagnostic studies often focus on diagnostic accuracy, whereas clinical utility and patient benefit are of equal importance in the evaluation of diagnostic testing.[13-16] In the Netherlands, dementia is diagnosed in a hospital setting in 58% of cases[17] and use of ancillary tests for dementia varies substantially across hospitals.[18] Clinical utility of ancillary diagnostic testing heavily relies on improving decision-making and, consequently, patient health outcomes.[19] In absence of cure, a diagnosis may still impact health outcomes such as daily functioning or healthcare costs by facilitating improved disease management through the arrangement of formal or informal care that better aligns with a patient's individual needs. In this study, we investigate whether patients who received a dementia diagnosis in a hospital and underwent an ancillary diagnostic test have a different outcome compared to those diagnosed without that specific ancillary test. We aim to go beyond the point of diagnostic accuracy and focus on a pragmatic clinical outcome; how long is a patient able to live at home following a diagnosis of dementia and is this altered by using ancillary tests?

METHODS

Study design and participants

We performed a nationwide register-based cohort study on all patients who received a new diagnosis of all-cause dementia in a Dutch hospital in 2018. We used data from the Dutch national healthcare insurance declaration database (Vektis).[20] In the Netherlands, having healthcare insurance is mandatory and as a result >99.8% of the population in 2018 was insured for healthcare costs and is hence included in this database.[21] The cohort included all patients > 40 years of age that were newly diagnosed with dementia in the Netherlands in 2018 in a hospital setting, based on (a combination of) healthcare insurance declarations validated by Vektis[20] for the presence of all-cause dementia. In the Dutch healthcare system, each new diagnosis is registered for insurance reimbursement purposes.[22] Patients were included in our cohort if they received a dementia diagnosis registered by a neurologist or, alternatively, by a geriatrician, internal medicine specialist or psychiatrist. In the latter cases, patients had to fulfill a second criterion, which included having declarations for psychogeriatric nursing care, declarations under the long-term care act with a dementia-related care package, or the use of pharmaceuticals exclusively indicated for dementia (galantamine, memantine, rivastigmine and donepezil). This combination rule to establish the dementia population in the Netherlands is based on a report from the Dutch national statistics office (CBS) to enhance validity of the diagnostic categorization.[23] The methodology is in line with Eurostat Morbidity Statistics, an initiative to collect nationally representative, internationally comparable diagnosis-based information on morbidity for the European Union.[24] While health care declaration data can indicate the presence of all-cause dementia, it does not allow for accurate nosological diagnoses.

According to Dutch guidelines a diagnosis of dementia is always based on patient history, informant reports and objective cognitive testing. Ancillary testing occurs upon indication.[25] We compared patients who underwent a specific diagnostic test during the diagnostic trajectory (cases) to patients who did not receive that specific diagnostic test (controls). We also contrasted patients receiving an extensive battery of tests (4 or 5) to patients subjected to restrictive diagnostic testing with none or only one ancillary test. Controls were propensity-score matched for age, sex, type of hospital and comorbidity. Type of hospital was operationalized as academic, teaching or general. Burden of comorbidity was operationalized using pharmacy-based cost group (PCG), which categorizes medication per somatic chronic disease indication, and serve as a an indicator for the presence of comorbidities.[26] This categorization

system is used for risk adjustment by the Dutch healthcare insurance sector. PCGs are ordinally categorized as 0, 1, 2, or ≥3, reflecting an increasing burden of chronic disease (Supplementary Text 1).

Exposure and outcome

Exposure of interest was the use of an ancillary test during the diagnostic phase in the years before the diagnosis of dementia: between 01-01-2015 and 31-12-2018 (Supplementary Figure 1). For reimbursement purposes, all healthcare activities related to diagnosing dementia are defined by the Dutch Healthcare Authority (agency of the Dutch Ministry of Health, Welfare and Sport). To facilitate analysis, two experienced neurologists clustered all diagnostic activities in 5 subgroups; 1) structural imaging of the brain using CT or MRI (CT/MRI), 2) neuropsychological examination (NPE), 3) imaging of the brain function using PET or SPECT (PET/SPECT), 4) electroencephalography (EEG) and 5) cerebrospinal fluid testing (CSF).

We tracked the occurrence of institutionalization or death and healthcare costs per month alive between 01-01-2018 and 31-12-2021 (Supplementary Figure 1). Primary outcome measure was time to poor outcome, defined as institutionalization in a long-term care facility or death, whichever came first. We expressed the results as median time to poor outcome, referring to the moment at which 50% of the population had experienced the outcome. We also analyzed these two poor outcomes separately (Supplementary Figure 2). Secondary outcome measures were total mean healthcare costs per month, mean total pharmaceutical costs per month, and mean costs per month for cholinesterase inhibitors (ChEIs) (Table 2). Total mean healthcare costs were operationalized as direct healthcare costs; which entails the expenses attributable to medical interventions, treatments, pharmaceuticals, and associated elements, such as hospitalization, clinical consultations, long term care and diagnostic assessments based on reimbursement by healthcare insurances.

Statistical analysis

We used Kaplan-Meier survival analysis to compare the occurrence of poor outcome between cases and controls during the follow-up period. Time to institutionalization and time to death were examined both separately and as a combined outcome. For mean total pharmaceutical, mean ChEIs and mean healthcare costs we used Welch's two sample t-tests. Matching was performed using the matchit package in R. We used a nearest neighbor matching, with a caliper width of 0.2 standard deviation without replacement technique, based on propensity scores using logistic regression.[27]

We used a variable control to case ratio with a minimum ratio depending on the number of available cases and a maximum of 3:1 ratio to ensure optimal reduction in bias and maximal gain in precision.[28,29] Statistical analysis was conducted using R, version 4.1.3.

RESULTS

In 2018, 13,312 patients received a new diagnosis of dementia in a Dutch hospital. The majority were female (51.9%) and the mean age at diagnosis was 77.3 (SD 8.2), of whom 6.9% were <65 years. Comorbidities were present in 73.9% of the population, with 14.1% in the highest ordinal category of medication costs (Table 1). Ancillary testing was performed in 85.6% of the population during the diagnostic phase of dementia. The most commonly used diagnostic test was CT/MRI (80.9%), followed by NPE (40.5%), PET/SPECT and EEG (both 7.6%) and CSF (4.1%). Between January 2018 and December 2021 more than half of those who were diagnosed with dementia in 2018 experienced a poor outcome (54.6%), of whom 40.1% were living in an institution, 32.3% died in an institution and 26.7% died at home.

Time to poor outcome in those who underwent CT/MRI, EEG or CSF was not different from respective controls (Figure 1, Panel A, C and D). For CT/MRI and CSF, this was consistent with both time to institutionalization and time to death (Supplementary Figure 2, Panel A, D, F and I). For patients exposed to EEG we did find a lower risk of institutionalization (RR 0.86, 95% CI 0.77-0.96), but no difference in risk of death (Supplementary Figure 2 Panel C and H). Patients subjected to a NPE had a lower risk of experiencing a poor outcome during the follow-up period compared to controls (Relative Risk (RR) 0.85, 95% CI 0.82-0.88). Median time to poor outcome was 3.1 years (or 1129 days, 95% CI 1102-1161) in matched patients that were not subjected to NPE as compared to a median time to poor outcome of 3.7 years (or 1367 days, 95% CI 1333-1407) in patients who underwent NPE (Figure 1, Panel B). This result was consistent when the outcome was analysed separately for time to institutionalization and death. Patients that underwent PET/SPECT during the diagnostic phase had a higher risk of experiencing a poor outcome (RR 1.09, 95% CI 1.02-1.17). Median time to poor outcome was 3.2 years (or 1157 days, 95% CI 1090-1261) for patients receiving a PET/SPECT and 3.5 year (or 1274 days, 95% CI 1218-1341) for control patients that did not (Figure 1, panel E). When analysed separately, patients who underwent a PET/SPECT had a higher risk of death (RR 1.55, 95% CI 1.40–1.71), but no differences in risk of institutionalization (Supplementary Figure 1, Panel E and J). Patients exposed to a combination of diagnostic tests, did not have a different time to poor outcome

as compared to patients receiving none or only one diagnostic test (Supplementary Figure, 3 Panel A, B and C).

Total healthcare costs in those who underwent CT/MRI or EEG did not differ from those who did not (Table 2). NPE as compared to no NPE during the diagnostic trajectory was associated with significantly lower total healthcare costs per month (difference in mean costs -€127 95% CI -61 to -193). Significantly higher total healthcare costs per month were found in patients that underwent CSF testing (difference in mean costs=€248, 95% CI 64-433) or PET/SPECT (difference in mean costs €315 95% CI 179-451). Mean total pharmaceutical costs per month were comparable for most groups, but higher in patients who underwent PET/SPECT as compared to controls (difference in mean costs €15 95% CI 8-22) (Table 2). The costs for ChEIs per month were significantly higher for patients receiving CT/MRI, CSF, and PET/SPECT, but not for patients receiving NPE or EEG (CT/MRI difference in mean costs €0.52, 95% CI 0.33-0.70; CSF difference in mean costs €1.40, 95% CI 0.76-2.04; PET/SPECT difference in mean costs €0.64, 95% CI 0.21-1.06) (Table 2).

		CT/MRI†		NPE		EEG		CSF		PET/SPECT	
	Total population	**Cases**	**Controls**	**Cases**	**Controls**	**Cases**	**Controls**	**Cases**	**Controls**	**Cases**	**Controls**
n	13312	7635	2545	5392	5392	1018	3054	541	1623	1016	3048
Female (n,%)	6911 (51.9)	4306 (56.4)	1547 (60.8)	2655 (49.2)	2690 (49.9)	366 (36.0)	1091 (35.7)	243 (44.9)	685 (42.2)	434 (42.7)	1282 (42.1)
Age (mean)	77.3	79.5	80.7	75.2	76.1	71.8	72.0	67.9	67.8	74.3	74.4
Hospital (n,%)											
General	5825 (43.8)	3196 (41.9)	1024 (40.2)	2475 (45.8)	2469 (45.9)	452 (44.4)	1413 (46.3)	211 (39.0)	665 (40.1)	376 (37.0)	1138 (37.3)
Teaching	6745 (50.7)	3990 (52.3)	1366 (53.7)	2682 (49.7)	2677 (49.7)	498 (48.9)	1467 (48.0)	275 (50.8)	840 (51.8)	570 (56.1)	1724 (56.6)
Academic	742 (5.6)	449 (5.9)	155 (6.1)	235 (4.4)	246 (4.6)	68 (6.7)	174 (5.7)	55 (10.2)	118 (7.3)	70 (6.9)	186 (6.1)
Comorbidity operationalized as PCG* (n,%)											
0	3468 (26.1)	1832 (24.0)	635 (25.0)	1461 (27.1)	1391 (25.8)	241 (23.7)	694 (23.7)	208 (38.4)	587 (36.2)	218 (21.5)	615 (20.2)
1	4487 (33.7)	2592 (33.9)	859 (33.8)	1810 (33.6)	1814 (33.6)	286 (28.1)	901 (29.5)	169 (31.2)	527 (32.5)	273 (26.9)	834 (27.4)
2	3480 (26.1)	2121 (27.8)	700 (27.5)	1369 (25.4)	1463 (27.1)	282 (27.7)	892 (29.2)	106 (19.6)	336 (20.7)	271 (26.7)	891 (29.2)
≥3	1877 (14.1)	1090 (14.3)	351 (13.8)	752 (13.9)	724 (13.4)	209 (20.5)	567 (18.6)	58 (10.7)	173 (10.7)	254 (25.0)	708 (23.2)

Table 1: Baseline characteristics of total population and cases and controls. *PCG=pharmacy-based cost group (a proxy for burden of comorbidity, a higher number indicates a higher burden of comorbidity) †=a total of 10767 patients received CT/MRI, but only 7635 were included as cases in the analysis, due to a maximum case: control ratio of 3:1. Cases were patients with an ancillary test and controls were patients without that specific test. We used a variable case to control ratio.

		CT/MRI		NPE		EEG		CSF		PET/SPECT	
	Total population	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
Total healthcare costs	1893	2046	2017	1711**	1838	1826	1689	1696**	1448	2105**	1789
Pharmaceutical costs	45	45	43	45	44	54	51	41	44	69**	54
Cholinesterase inhibitors costs	1.76	1.73**	1.22	1.92	1.83	2.13	1.86	3.22*	1.83	2.38**	1.73

Table 2: Healthcare costs per month in euro's. Cases were patients with an ancillary test and controls were patients without that specific test. *=p<0.01, **=p<0.001

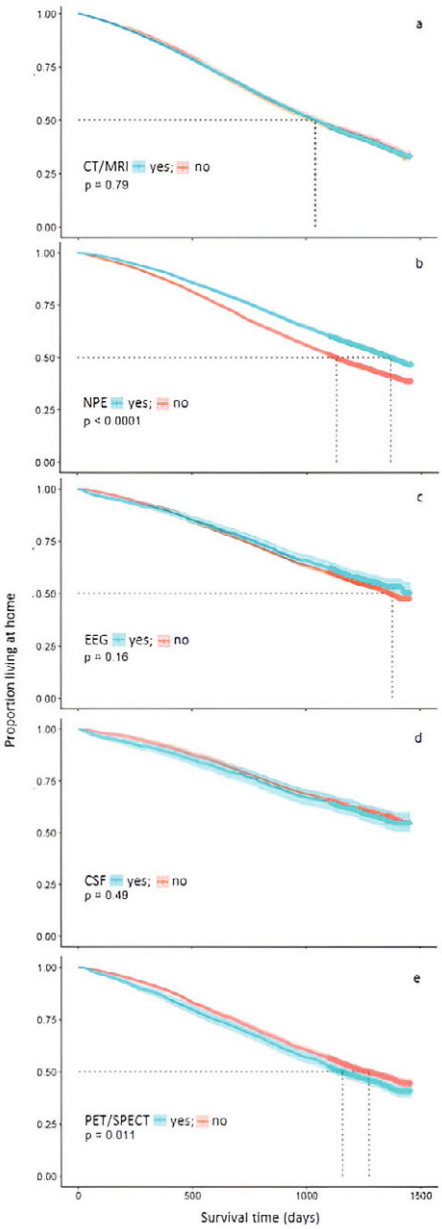

Figure 1: Kaplan-Meier analysis of time to poor outcome (institutionalization or death) in patients receiving an ancillary testing as compared to matched controls. a= CT/MRI vs. controls, b=NPE vs. controls, c=EEG vs. controls, d=CSF vs. controls, e=PET/SPECT vs. controls

DISCUSSION

Patients with dementia who underwent ancillary investigations including neuroimaging (CT, MRI, SPET, or PET), CSF or EEG examination during the diagnostic phase, did not have a different time to poor outcome. Those who underwent PET/SPECT had a shorter time to poor outcome as compared to controls. Undergoing an NPE during the diagnostic phase was associated with a longer time to poor outcome. Total mean healthcare costs were higher for patients undergoing CSF testing or PET/SPECT scanning. Conversely, patients with an NPE during the diagnostic work-up generated lower total mean healthcare costs. Pharmaceutical costs were similar for most case-control comparisons, only patients with a PET/SPECT scan had higher mean pharmaceutical costs. The fact that many patients did not experience a disadvantageous outcome when dementia was diagnosed without the use of imaging or CSF biomarker corroborates the hypothesis that these tests may not benefit patients with regard to time to institutionalisation or death.

Strengths of this study are the large number of patients included, the population-based design and the complete and long-term follow-up for our outcomes. Our study is based on healthcare insurance reimbursement data and due to almost complete coverage of the Dutch healthcare insurance system,[21] the effects of selection bias and loss to follow up are negligible. However, our study has several limitations. Privacy legislation in the Netherlands prohibited coupling of reimbursement data with specific clinical characteristics, including symptom severity at time of diagnosis. Particularly results with respect to NPE may be influenced by confounding by indication, i.e. those in whom NPE is ordered may be in earlier stages of dementia compared to those in whom NPE is not deemed necessary, despite matching for age, sex, type of hospital and comorbidity.[30] PET/SPECT scanning is mostly used to distinguish between possible cases of Frontotemporal dementia (FTD) or Dementia with Lewy Bodies (DLB) and Alzheimer's dementia (AD). FTD and DLB typically have a more progressive disease course, more disability and associated costs, and a shorter median survival than AD.[31-34] In a nation-wide study, based on health insurance data, potentially relevant questions relating to clinical details remain necessarily unanswered. A second limitation is that the accuracy of identified dementia cases with routinely collected health data varies per setting and data source.[35] However, an American study showed that insurance claim data perform relatively well with a sensitivity of 85% and specificity 89% for all cause dementia.[36]

These results underscore the pivotal role of the clinical examination, which is supported by most guidelines. In a systematic review from 2015 on dementia practice guidelines, only nine out of thirty-nine guidelines recommended to perform structural imaging in a specialist care setting.[1] Main argument for the use of neuroimaging or other biomarker tests during the diagnostic phase of dementia is ruling out of reversible causes of dementia and facilitating an early diagnosis. However, actual reversal of dementia is extremely rare (<<1%).[37,38] Moreover, use of diagnostic testing is not without drawbacks. Hospital visits to undergo testing can be burdensome for older patients and the use of biomarkers have potential side-effects, including adverse procedural events[39] and the consequences of false positive test results or incidental findings.[40] The rationale behind striving for an 'early' diagnosis is the suggestion that it could delay institutionalization by optimizing care and support in the home setting in order for patients to be able to stay at home.[41] This was not confirmed by our findings, although other studies presented conflicting results. A recent non-randomized study compared time to institutionalization or death and healthcare costs in two groups of relatively young patients referred to a tertiary memory clinic, in which the intervention group underwent an amyloid PET scan to facilitate a more precise diagnosis as compared to a propensity matched control group.[42] They reported a lower hazard of poor outcome in patients that underwent amyloid PET (HR=0.54 [95% CI: 0.40-0.73]). These disparate results are likely attributable to a much younger study population, showing that the clinical utility of amyloid PET may be higher in rare young onset dementia cases. Another population-based study found a higher rate of institutionalization amongst patients that consulted a specialist early in the disease course (HR= 2.00, [95% CI: 1.09- 3.64]).[43] However, if more efficacious disease modifying therapies for Alzheimer's disease may become available in the future, this could have impact on diagnostic procedures.

Our secondary outcome was healthcare costs. Worldwide, total dementia related costs are estimated to be around 1% of the global gross domestic product, and 0.65% if informal care costs are excluded.[44] Institutionalization is the main cost driver in dementia care, with on average threefold higher costs for the population living in a long term care facility. In contrast, in the community-based population the main cost-drivers are pharmaceutical costs and non-medical support.[45] The use of ancillary testing could influence healthcare costs in two ways. Firstly, by influencing time to institutionalization. An early diagnosis could provide an opportunity for timely interventions to support (in)formal care at home and hence postpone institutionalization. However as discussed, literature is inconclusive on this part.[42,43] Secondly, undergoing ancillary testing contributes to healthcare costs. Especially in low- and middle income countries, direct medical costs add substantially to total

healthcare costs.[44] Critical evaluation of the indication for ancillary testing could contribute to curtailing global dementia costs.

Our study was designed based on the principle that the purpose of diagnostic testing goes beyond an accurate diagnosis. A diagnostic test or procedure should also lead to a measurable improvement of patient's health outcomes to have clinical utility.[13,19] In absence of convincing disease modifying treatments for dementia, clinical utility of ancillary investigations to facilitate (early) diagnosis is up for debate. Aside from offering treatment options, a diagnosis could influence the outcome for a patient on other levels. For some patients, diagnosis can end the uncertainty of experiencing complaints and facilitate advance care planning. For others, receiving a diagnosis of a progressive disease for which no treatments exist may cause emotional distress and anxiety. Individual patient preferences and the previously mentioned considerations should all be taken into account when finding the right timing for diagnosis.[7,46,47]

The lack of convincing evidence in favour of ancillary testing for dementia diagnosis, confirmed by our study findings, supports guideline recommendations for a strong emphasis on a clinical diagnostic work-up in primary care. This may not only decrease diagnostic burden for the individual patient, but, in light of the expected global increase in dementia prevalence,[48] facilitate efficient use of specialist diagnostic services.

CONCLUSION AND IMPLICATIONS

Patients with dementia who underwent ancillary investigations including neuroimaging (CT, MRI, SPECT, or PET), CSF or EEG examinations during the diagnostic phase did not have a different time to poor outcome. Patients who underwent NPE testing had a slightly longer time to poor outcome, potentially due to confounding by indication. Healthcare expenses were higher in patients who underwent CSF testing or PET/SPECT scanning as part of the diagnostic workup for dementia. The already overburdened health care systems and society as a whole may benefit from reducing the number of ancillary investigations in dementia diagnostics, without harming patients and caregivers. To definitively answer the question if patients that were diagnosed using ancillary investigations fare better than those who were not, a randomized controlled diagnostic trial is required.[13,19]

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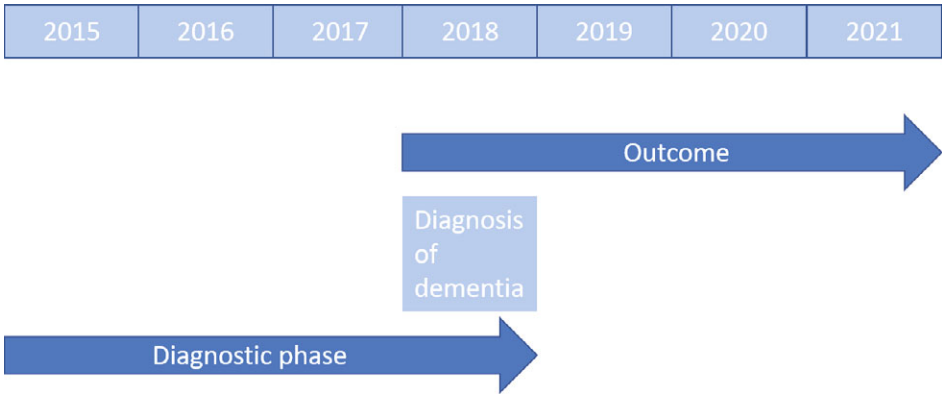
SUPPLEMENTARY MATERIAL



Supplementary Figure 1: Timeline of study. Diagnostic phase between January 2015 and December 2018, diagnosis of dementia between January and December 2018, outcome between January 2018 and December 2021.

SUPPLEMENTARY TEXT 1: PHARMACY-BASED COST GROUP (PCG)

This is a model used in the Dutch healthcare insurance sector since 2002 for risk adjusted capitation.[1] Pharmaceuticals prescribed to an individual for more than 6 months in the base year, are regarded as markers of an associated chronic condition in that year. PCG's used in this study include only somatic conditions. It is shown that PCG's are good predictors for future direct health care costs.[2] Somatic PCG's in this model include diabetes, cardiovascular, auto-immune, kidney, respiratory and oncological diseases.

SUPPLEMENTARY REFERENCES

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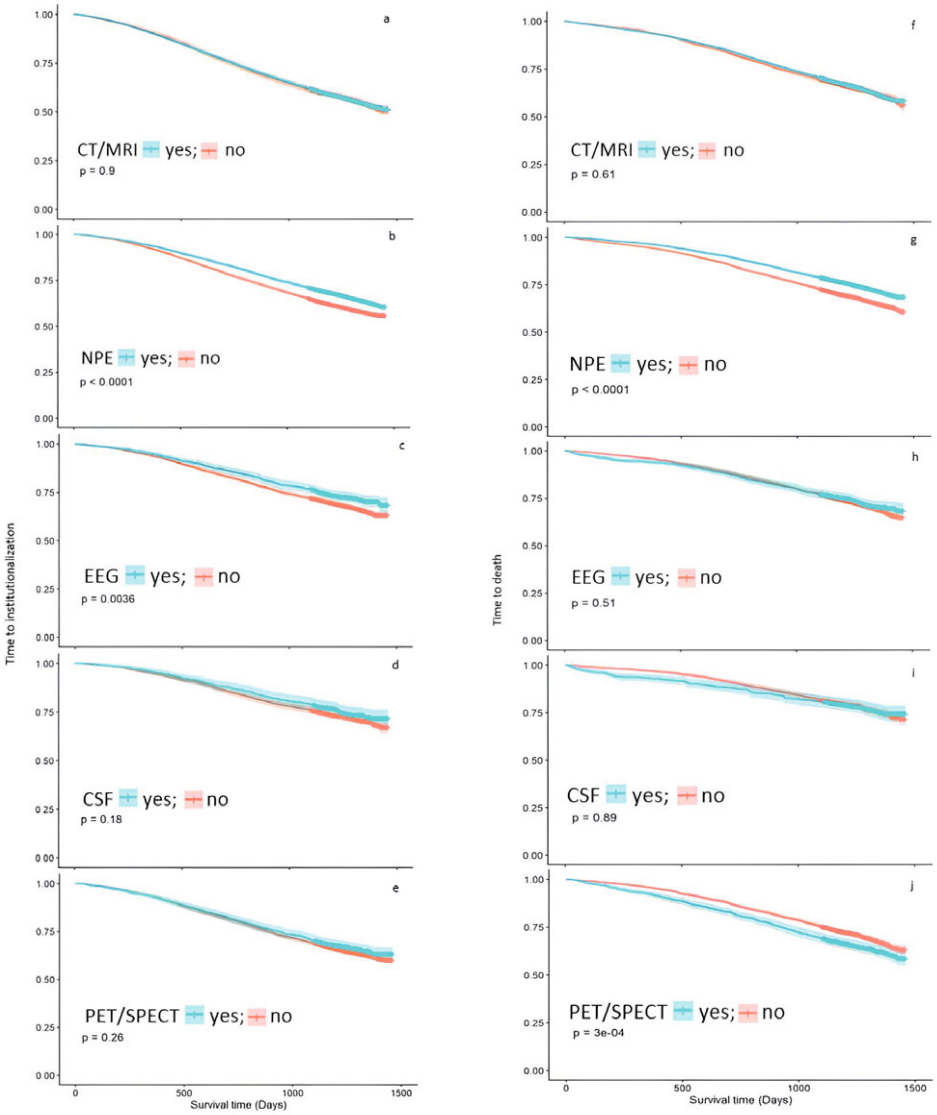
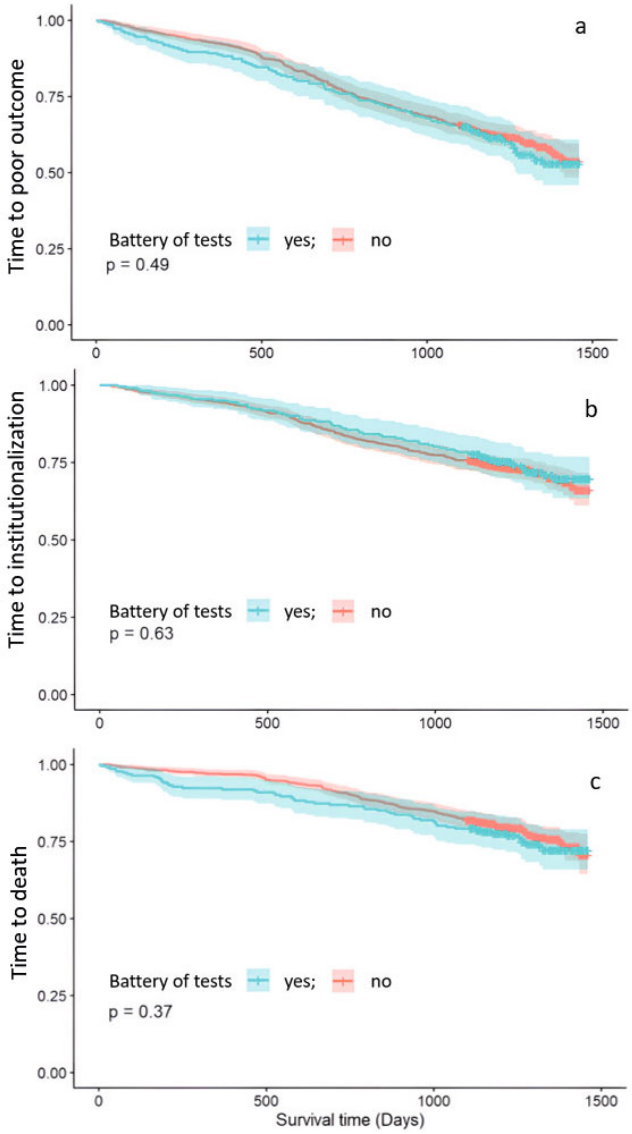


Supplementary Figure 2: Kaplan-Meier analysis separated for of time to institutionalization (left) and time to death (right) in patients receiving diagnostic testing as compared to controls. a. CT/MRI vs. controls, b. NPE vs. controls, c. EEG vs. controls, d. CSF vs. controls, e. PET/SPECT vs. controls, f. CT/MRI vs. controls, g. NPE vs. controls, h. EEG vs. controls, i. CSF vs. controls, j. PET/SPECT vs. controls



Supplementary Figure 3: Kaplan-Meier analysis comparing patients receiving a battery of tests (4 or 5) to controls receiving none or just one test for a. time to poor outcome, b. time to institutionalization and c. time to death.

Chapter VIII

GENERAL DISCUSSION

Research in this thesis is centered around risk factors for dementia in diverse populations and exploring the role of ancillary testing during the diagnostic trajectory. We investigate alternative strategies for evidence generation on risk factors for dementia, unravel population specific risk profiles, develop strategies to address risk factors in high-risk populations aligned with their needs and preferences and critically evaluate diagnostic practices. Collectively, this work aims to generate evidence that supports more inclusive, equitable, and epidemiologically grounded approaches to dementia prevention, particularly for populations historically underrepresented in research. This chapter begins by presenting the principal findings of the thesis, followed by an interpretation of the results within the context of the existing literature. It concludes with recommendations for future research directions and an overall conclusion.

MAIN FINDINGS

Chapter II Four quasi experimental study designs could be suitable to use in the context of dementia prevention, namely 1. Instrumental variables, 2. Regression discontinuity design, 3. Interrupted time series, 4. Difference-in-differences. They all have very strict design-dependent assumptions, but if these are met, they could contribute to causal evidence generation on dementia prevention.

Chapter III Comparing three dementia risk scores between six different ethnic populations in Amsterdam, showed that those with a migration background all had an elevated composite risk score as compared to the Dutch host population. The association with higher risk score was even stronger in Ghanaian, Turkish and Moroccan women. Important limitation of this study was that the risk scores were not specifically developed for a multi-ethnic population.

Chapter IV Dutch individuals with low socioeconomic status (SES) or with a Turkish or South Asian Surinamese migration background were interviewed to explore their needs and preferences for a mobile health (mHealth) application aimed at addressing dementia risk factors. All groups emphasized that an mHealth intervention supported by a coach should respect individual autonomy and facilitate social connections and support. Tailored coaching and lifestyle advice to align with cultural habits was deemed beneficial.

Chapter V The association between apathy and increased risk of dementia is 27% mediated by a composite of physical inactivity, BMI, and diabetes. Among these factors, physical inactivity accounted for 28% of the mediating effect, diabetes for 9%, whereas higher BMI demonstrated a protective influence, attenuating the effect with 12%. Limitation of this study was the cross-sectional assessment of apathy and cardiovascular risk factors, which precludes causal inferences from the observed associations.

Chapter VI The longitudinal association between hypertension and incident dementia or mild cognitive impairment in LMIC is comparable to global effect estimates. Based on 26 identified articles in LMIC, hypertension increases the risk of dementia with 26% and MCI with 19%. The limited number of studies originating from Africa and Latin America impeded comparisons of effect sizes across geographic regions.

Chapter VII Use of ancillary testing during the work up for dementia and time to poor outcome (institutionalization/death) was comparable between patients who did and did not undergo CT/MRI, EEG, or CSF testing, but was longer in those receiving neuropsychological evaluation (NPE). In contrast, it was shorter among patients who underwent PET/SPECT. Mean total healthcare costs were higher for patients who received CSF testing or PET/SPECT compared to controls. NPE was associated with lower total costs. Given the study's observational design, results may be affected by confounding by indication, particularly in the NPE and PET/SPECT groups.

EVIDENCE IN CONTEXT

Global research inequities

Most evidence generated on dementia prevention comes from Northern America and Europe, whereas the largest projected increase in absolute number of persons with dementia is anywhere but these regions.[1] This is consistent with the fact that only 12% of studies published in leading medical journals originate from non-American or non-European countries, despite these countries accounting for 88% of the world's population.[2] In **chapter II**, we address this imbalance by exploring alternative quasi experimental study (QES) designs that may provide an addition to randomized controlled trials in generating causal evidence. Such approaches can help overcome ethical, financial, and logistical barriers that often limit RCTs, particularly in low-resource settings. QES exploit naturally occurring or random variation in exposure to infer causal effects on dementia outcomes. They are less costly and more pragmatic

than RCTs but depend on strict design-specific assumptions and remain more prone to unmeasured or time-varying confounding and information bias.

Two recent examples illustrate their potential. The first, examining herpes zoster vaccination, applied an interrupted time series design comparing individuals eligible versus ineligible for vaccination based on a one-week difference in birth date, showing a 20% relative reduction in dementia incidence over seven years. The second, from Sweden, evaluated prolonged compulsory education (six vs. seven years) and found no causal effect on dementia risk (HR 1.01, 95% CI 0.98–1.04).[3] Both studies minimized time-varying confounding by comparing cohorts within a narrow time frame, though reliance on registry data may have introduced information bias, particularly in the vaccination study, where lower healthcare use post-vaccination could have reduced dementia diagnoses.

Over the past decade, the use of routine healthcare data combined with quasi-experimental analytic methods has increased in LMICs, particularly in sub-Saharan Africa and South Asia, demonstrating the feasibility of this approach.[4] However, important limitations remain, including poor data quality, inaccuracies, delays in reporting, and missing or incomplete records, all of which can undermine the reliability of causal inferences.[5] Efforts to strengthen health information systems and improve data quality are currently underway across low-resource settings.[6] Also, a systematic review encompassing quasi-experimental studies from Africa, Asia, and other regions has demonstrated the effectiveness of interventions for hypertension control, such as screening, education, counseling, and management.[7] In **chapter VI**, we focus specifically on evidence generated in LMIC, to evaluate if hypertension may have a different association with future dementia risk in populations living in LMIC. We showed that the association in LMIC was comparable to known associations found in HIC.[8,9] At the same time it also highlights the great discrepancy in number of studies on this subject specifically between LMIC and HIC; in our study we identified only 26 prospective studies on the relationship between blood pressure and cognition, whereas a systematic review performed 4 years prior without geographical restrictions included 209 prospective studies.[9] We aimed to compare the association of hypertension and dementia in LMIC between different geographic regions. Due to limited number of studies from especially Africa, we were unable to formally compare pooled effect sizes between geographic regions. The majority of studies we identified in **chapter VI** were from China, in line with the fact that China produces the largest number of scientific articles worldwide, and research productivity on dementia in Asia has increased substantially.[10,11] While research output in Africa more than doubled between 2005-2016, the continent still contributes a mere 3.2% to global scientific output.[12] There

is a significant lack of geographical diversity in the evidence on many dementia risk factors, leaving key questions about the influence of ethnicity, sociocultural practices, and other societal and geographical factors unanswered.[13] This is relevant, because impact of exposure to dementia risk factors is suggested to differ between countries, and between ethnic groups within the same country.[14,15]

An inclusive perspective on those at risk and risk factor modification

This thesis offers several important starting points for developing dementia prevention strategies. According to Rose's prevention paradox, effective prevention consists of two complementary approaches. The first is the *high-risk strategy*, which focuses on identifying individuals or subgroups with an elevated risk of disease and providing targeted interventions. The second is the *population-level strategy*, which aims to reduce risk factor exposure across the entire population, thereby shifting the overall risk distribution. While the high-risk approach benefits those most at risk, the population-level strategy can yield greater overall public health impact by addressing the broader determinants of disease.[16]

Chapters III and V of this thesis could inform a 'high-risk' strategy, while **chapter VI** could guide both high-risk and population-level approaches. In **chapter III** we showed that, in the Netherlands, midlife risk scores for dementia are higher in those with a migration background as compared to the Dutch host population. An important limitation is that whilst focusing on understudied populations, and charting ethnicity specific risk profiles, we used risk scores developed and validated in predominantly white populations. However, studies comparing performance of dementia risk prediction models across ethnicities show fair predictive performance when used in non-white populations.[17] In line with our findings a systematic review showed that especially Asian and African migrants in Europe indeed have a higher risk of developing dementia.[18] **Chapter III** builds on these findings by showing during midlife, long before dementia occurs, the risk profiles of migrant populations are already less favorable. Parallel to this, fatal and non-fatal cardiovascular disease risk is elevated in migrant populations.[19] The specific cardiovascular risk factors driving ethnic differences in cardiovascular disease risk varied between the ethnic groups. Another study showed that prevalence of metabolic syndrome is higher in ethnic minority populations in HICs, indicating clustering of risk factors.[20] Interestingly, the highest overall prevalence of metabolic syndrome was identified in ethnic minority women, with pronounced differences between ethnic minority and majority women, which were not present in men. Our study showed that in native Dutch women mean risk scores were lower than in men. Globally, women face a higher risk of future dementia, with the greatest

risk observed in women from LMICs (HR 1.73, 95% CI 1.25–2.39). In contrast, mixed results from Western countries show no significant effect (HR 1.05, 95% CI 0.93–1.19).[21] Beyond genetic predispositions, the intersection of gender and ethnicity may compound disadvantages through mechanisms such as discrimination, language barriers, poverty, social exclusion, and limited access to healthcare services.[22,23]

In **chapter III** we reviewed risk scores consisting of multiple modifiable risk factors. The risk of dementia decreases with more healthy lifestyle behavior, showing that there is a cumulative effect of healthy lifestyle behaviours.[24] This could lead one to believe that a multidomain intervention addressing multiple risk factors, is best when aiming to prevent dementia. In practice, this has not been irrefutably proven, and results of intervention studies are mixed, with some studies showing modest improvements on cognition, whereas others report no effect.[25-27] This could be due to the fact that individual lifestyle change is challenging.[28] Unhealthy lifestyle behaviors are more common in those facing socioeconomic disadvantages,[29] which can further increase the barriers to adopting healthier lifestyles.

Second, in **chapter V** we focus on risk factors for dementia in individuals with symptoms of apathy, since for those individuals sustained behavior change may be extra demanding.[30] Apathy is a neuropsychiatric symptom associated with depression, characterized by reduced motivation, diminished interest, and attenuated emotional responsiveness. We aimed to identify potentially modifiable risk factors that could partially explain the higher risk of dementia that individuals with symptoms of apathy face. By investigating which risk factors mediate the largest portion of the higher risk of dementia, efforts can be steered towards interventions with the greatest expected effect. For this we performed a mediation analysis in a community dwelling cohort of older adults aged 70-78 year with a total follow up of up to 12 years. We observed that physical activity, low BMI and diabetes mellitus explain part of the association of apathy with incident dementia. Addressing these risk factors may prove to be challenging since apathy often occurs in a triad with gait slowness and executive dysfunction.[31] However, large part of the association was not explained by risk factors and therefore strengthens the concept of apathy as a risk factor independent of depression. When studying modifiable dementia risk factors, it's crucial to consider the time between exposure and the onset of dementia. However, we did not have sufficient power to perform a fully longitudinal mediation analysis, leaving ample room for reverse causality. In this context this could mean that apathy may be a prodromal sign of incipient dementia, rather than an independent risk factor. The results of this study thus only inform us on the association between apathy, dementia risk factors and incident dementia.

Third, in **chapter VI** we investigate the association between hypertension and dementia in LMIC on a population level. We showed that hypertension is an important risk factor for dementia, also in LMIC settings. This might provide an important cue for prevention of hypertension on a population level, as hypertension awareness and control are still significantly lower in LMIC.[32] A practical example of how this could be done using primary prevention is by taking policy measures to reduce population salt intake through processed foods, shifting the balance to diets containing less sodium and more potassium and by focusing on sodium restriction during the first years of life.[33,34] A high-risk approach could complement public health interventions for hypertension by for example active screening and medical outreach programs to identify those at risk. After identification ensuring that patients have access to medication and are actively followed over time will improve adherence. Simple protocols for treatment and education of healthcare providers will facilitate better treatment even in low resource settings.[35,36]

Alignment of health care provision with patients' needs and preferences

In **chapter IV,** we explored the specific needs of the intended end-users of an mHealth intervention, aiming to address potentially remediable differences in risk factor prevalence. The study focusses on Dutch individuals with low SES and those with a Turkish and South Asian Surinamese migration background. Ethnic minority populations are underrepresented in dementia prevention research in general,[37] but also underrepresented in co-creation studies.[38] Yet it is precisely in ethnic minority populations that co-creation during study design appears to have a stronger positive effect on mental health and health promoting behavior, potentially by enhancing self-efficacy of participants.[38] The intervention that we developed together with our target population is currently being tested for feasibility in the Mobile Health (mHealth) Intervention for Dementia Prevention through lifestyle Optimisation (MIND-PRO) trial.[39,40] Mhealth applications may be valuable tools to reach historically underserved populations, since ethnic minority populations tend to use and rely on more different sources of information than white populations.[41] Our qualitative study highlighted that mHealth interventions addressing dementia risk factors in individuals with low SES or a migration background should ideally be interactive, tailored so that it aligns with cultural needs and preferences, and respect an individuals' autonomy. Although their needs and preferences show some overlap, the extent to which cultural tailoring was deemed essential differed between the migrant groups. There are some remarkable similarities in user preferences with culturally tailored diabetes interventions for ethnic minorities. For instance, family and social support are considered crucial for success, and culturally specific preferences for physical activity often include walking,

dancing, and home-based exercises.[42] Two reviews of electronic health interventions for low SES populations highlighted barriers and facilitators that align closely with those identified in our study.[43,44] Key facilitators included the simplicity of information, often enhanced with visual or audio elements, the presence of a supportive coach, trust and credible sources, and a focus on rewards rather than obligations. Barriers identified were excessive reminder frequency, technical difficulties with device use, and challenges related to literacy or language. The importance of autonomy, that was ubiquitous in our population, is less well documented in literature.

Diagnosis of dementia

For a dementia diagnosis, clinicians often use additional tests such as imaging or invasive procedures to facilitate an early diagnosis.[45-47] Given the absence of curative treatments,[48] it remains unclear whether these ancillary tests provide meaningful clinical benefit.[49] Despite increased use, evidence is scant regarding impact on patient outcomes, suggesting the need to carefully reconsider this routine.[50] In **chapter VII** we used health care insurance data to explore whether the use of ancillary tests during the diagnostic work-up actually leads to improved patient outcomes regarding independent living and survival. Time to poor outcomes was similar for those who underwent CT/MRI, EEG, or CSF compared to those who did not, but longer for those who underwent NPE, and shorter for those who had a PET/SPECT. This suggests that additional testing generally does not improve survival or independent living, while increasing healthcare costs[51] and risks like procedural complications[52] or false positives.[53] In contrast, a study in a highly selected, younger population found that amyloid PET was linked to longer time to poor outcomes, indicating potential higher utility in rare young-onset dementia cases.[54] Nonetheless, a recent randomized study confirms that PET scanning during the diagnostic work-up is associated with higher mean healthcare costs.[55] For other ancillary tests, literature on time to poor outcome or association with health care costs is scant, potentially reflecting a similar evidence gap as identified for blood based biomarkers, where the vast majority of studies focusses on technical aspects and diagnostic accuracy, not on patient outcomes and diagnostic impact.[56]

The use of registration data for dementia research comes with inherent limitations that deserve consideration. First, despite matching, confounding by indication may have influenced results. Patients undergoing neuropsychological examinations had longer time to adverse outcomes, which may be because they are earlier in the disease course than those for whom it was deemed unnecessary. PET/SPECT imaging is often used to differentiate Alzheimer's dementia from frontotemporal dementia or

dementia with Lewy bodies, which generally have a more rapid progression, greater disability, higher costs, and shorter survival.[57-60] Second, depending on the type of data source used it has a lower sensitivity as compared to cognitive testing and diagnosis is often registered late in the disease process.[61] Time to diagnosis may be shorter in those receiving ancillary testing, since it can be used to facilitate an early diagnosis.[46,47] Contrary to our findings, this could than hypothetically lead to longer time to adverse outcome in those receiving ancillary testing. Combining registration data sources – general practitioners files, health care insurance and death certificates - may enhance diagnostic properties, but is a challenge in itself. In the Netherlands, 58% of the dementia diagnosis are established in the hospital.[62] However, when studying general practitioner's referral letters, the majority already correctly mentions one or more diagnostic criteria.[63] A systematic review examining the diagnostic accuracy of clinical judgment for all cause dementia by primary care physicians found a sensitivity of 58% and a specificity of 89%.[64] This suggests that while some cases of dementia may be missed in primary care, most diagnoses made are likely to be accurate. These findings raise important questions about the most appropriate setting for diagnosing dementia—whether it should occur in primary care or in specialized hospital settings.

RECOMMENDATIONS FOR FUTURE RESEARCH

This thesis is grounded in epidemiology and public health and it aims for more inclusive research on dementia, by actively involving those who are often underrepresented in studies. Such as those with a low socioeconomic position, a migration background, those living in LMIC, or those with symptoms of apathy and thus not fit into the healthy sample which usually partakes in prevention research. Dementia is an illness that comes with tremendous burden and costs, and when designing studies or testing hypothesis ethical concerns should be incorporated. Following studies included in thesis I want to advocate for designing future dementia research along the lines of three principles.

1. Using a utilitarian approach for the hypothesis we test. Which preventive strategies or what interventions benefit most individuals globally in the long run? In my opinion interventions that are scalable, at low cost, easily applicable and acceptable for patients deserve priority in research. This is in line with the aforementioned population level strategy where preventive measures bring large benefit to society, but relatively little to an individual patient. Studies should focus on development and critical appraisal of effective interventions such as implementing large-scale hypertension screening programs in underserved regions, establishing systems for active patient follow-up, and developing standardized treatment protocols alongside training programs for healthcare providers. Mhealth technologies could play a role in follow-up to increase adherence and lower administrative pressure for health care providers, while at the same time providing interesting sources of data for research.
2. Ensuring that the design of the study promotes equity. Who do we hope to include in our studies? How will we make sure to include those who might be harder to reach by researchers? How can we facilitate research in low-resource settings? Research on dementia risk factors is mostly conducted in HIC, and racial and ethnic minority populations within HIC are less likely to be included in studies on risk factors for dementia.[65] By actively steering calls towards inclusive research and funding studies in LMIC more generalizable results can be obtained promoting health equity. This approach aligns with high-risk prevention strategies. While population-based preventive health may yield the greatest overall impact, efforts to improve health equity for all must also prioritize those at increased risk.
3. Warranting the clinical utility of current practices in dementia prevention, diagnosis and care. Do current practices actually benefit patients and are they aligned with personal needs and preferences? Is additional ancillary testing or a more extensive work-up actually beneficial to patients? And does this outweigh the extra burden this places on natural resources and the already overburdened healthcare system? This includes critical evaluation of our diagnostic practices, not only for accuracy but also for patient benefit, health care costs and burden it places on the health care system.

Moving beyond the cues provided by this thesis there are still some important open ends to address. In **chapter III** we used risk prediction models based on modifiable risk factors. However, they were validated nor recalibrated to the ethnically diverse sample that we used them for. Both the baseline risk as well as effect size of risk factors may be different across populations. For example, one study showed that the impact of hypertension, obesity, diabetes, low HDL and sleep disorders on dementia risk was higher in South Asian people compared to white people, and the impact of hypertension was greater in Black compared to white people.[15] Studies show that recalibrating risk models according to ethnicity improves risk classification for non-white populations.[66-69] We observed that individuals with a migration background generally have a worse dementia risk profile, although the underlying causes remain unclear. In those with disadvantaged socioeconomic status, unhealthy lifestyle

behaviors explain only a small part of the increased dementia risk.[70,71] It could be that they are other underlying factors that could mediate the risk in high-risk populations, such as socio-economic position, cognitive reserve, mental wellbeing or distance to the healthcare system. Longitudinal mediation analyses could help identify which factors drive this elevated risk.

Another interesting line of thought is the critical evaluation of current diagnostic practices. In **chapter VII**, we showed that patients who received a diagnosis supplemented with ancillary testing do not live independently for longer as compared to those diagnosed without. Due to the observational nature of this study it is impossible to deduct causal effect from the diagnostic trajectory on the outcome of the patient. This work and earlier work[45] led to the design of the PRIMED (PRImary care vs. Memory clinic Diagnostics) study.[72] In PRIMED, older people with memory complaints are randomized between a diagnostic trajectory in primary care versus referral to a memory clinic to study the effect on long term daily functioning. This is an important example of a non-inferiority trial investigating whether doing more in a specialist care setting actually brings more benefit to patients. If not, we might as well refrain from doing so. Thus, if a primary care diagnosis is on par with a memory clinic diagnosis with respect to long-term outcomes that matter to patients and caregivers, this would plead for reducing the number of referrals. This could in turn lead to downstream benefits for society as a whole, including reducing burden on healthcare systems and promoting appropriate use of resources.

CONCLUSION

In conclusion, significant disparities in dementia risk persist not only between individuals but also across different populations. By prioritizing research on those at elevated risk and tailoring preventive strategies to their specific needs and preferences, we can better target efforts to those who may benefit most. For prevention to be both effective and equitable, it is essential to integrate broad public health measures while also addressing the underlying inequalities faced by high-risk groups.

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VIII

SUMMARY

The global population is growing and aging, resulting in an increasing number of individuals living with dementia. Across populations, there are significant geographical and ethnic differences in the burden of dementia. Since no curative treatment currently exists, targeting dementia risk factors is a crucial strategy, not only to slow the rising numbers but also to reduce disparities in dementia risk among different groups. To promote equitable dementia prevention and care, this thesis aims to explore:

- What strategies can be employed to generate robust evidence on dementia risk factors, also from low-resource settings to inform preventive strategies?
- How do risk factors play a role in the increased risk of dementia in people with a migration background, those living in low- and middle income countries (LMIC) and other groups at elevated risk?
- How can diagnostic and preventive efforts benefit patients and those at risk and how should we align interventions with their needs and preferences?

In **chapter II**, we explain different quasi experimental study (QES) designs that can help overcome challenges inherent to traditional dementia prevention trials. These methods can provide a useful addition because they can avoid some ethical, financial, and practical problems, especially in places with limited resources. These approaches use natural or random differences in exposure to figure out how risk factors affect dementia. They are cheaper and more flexible than standard trials but require careful design and can still be affected by hidden biases. We focus on four QES designs:

1. Instrumental variable: Uses a factor linked to the risk factor to help estimate its effect.
2. Regression discontinuity: Compares groups just above and below a cut-off point where treatment starts.
3. Interrupted time series: Looks at dementia outcomes before and after a large scale health intervention.
4. Difference-in-differences: Compares two otherwise similar groups over time, where only one group gets the intervention, to separate effects from other changes.

In **chapter III** we calculate three dementia risk scores in more than 13.000 participants aged 40-70 of the 'Healthy Life In an Urban Setting' (HELIUS) study: CAIDE, LIBRA and ANU-ADRI. We compare the three scores between six different ethnic groups; Dutch, South-Asian Surinamese, African Surinamese, Ghanaian, Turkish and Moroccan. Those with a migration background had higher dementia risk scores as compared to the native Dutch population. If we removed age from the risk scores (as this is

the strongest dementia risk factor) the discrepancy only became larger, suggesting that this higher risk score is independent of age. For the Ghanaian, Turkish and Moroccan population this association with higher risk scores was even stronger in women. Important limitation of this study is that the risk scores we used, apart from CAIDE, were neither developed, nor validated in a multi-ethnic population. Also, not all variables traditionally included in LIBRA and ANU-ADRI were available from the HELIUS cohort.

In **chapter IV** we use qualitative methods to design an mHealth application with online coach support, specifically for Dutch individuals with a low socioeconomic position and those with a Turkish or South Asian Surinamese migration background. We focused on these groups since they face an increased risk of dementia and may not always be optimally reached by traditional prevention interventions. The goal was development of the MIND-PRO app, to target dementia risk factors by providing tailored advice and educational material for self-management, goal setting, progress tracking options and coach support. We interviewed individuals from the aforementioned groups to explore their needs and preferences for such an intervention. Participants emphasized that social support and autonomy are key to making lasting lifestyle changes. Tailoring coaching and lifestyle recommendations to fit cultural traditions was deemed beneficial. Between groups, the extent to which this was deemed a necessity varied, with the South Asian Surinamese having the strongest attachment to their dietary pattern as part of their cultural identity. All groups perceived such a tailored app as a useful tool to keep them motivated and engaged.

In **chapter V** we examine if potentially modifiable risk factors may mediate the association between apathy and the increased risk of dementia using multiple mediation analysis. For this we studied 3303 community dwelling adults aged 70 -78 years old from the preDIVA study. Potential mediators in the association were systolic blood pressure, cholesterol, diabetes, body mass index(BMI), smoking and physical inactivity and outcome was incident dementia during 12 years of follow-up. The association between apathy and dementia was for 27% mediated by a composite of physical inactivity, BMI and diabetes. Among these factors, physical inactivity accounted for 28% of the mediating effect, diabetes for 9%, whereas higher BMI demonstrated a protective, counteractive influence, attenuating the effect with 12%. This shows that patients exhibiting apathy may particularly benefit from intensive prevention and care strategies. The most important limitation of this study was that apathy and presence of cardiovascular risk factors were assessed cross-sectionally, hampering any causal interpretation of our findings.

In **chapter VI** we systematically summarize the available evidence on the association between hypertension and dementia in LMIC. We included longitudinal studies (follow-up ≥6 months) from LMICs on the association between systolic blood pressure or hypertension and incident dementia or mild cognitive impairment (MCI) with a sample size of ≥500 individuals. In total 26 articles were included, of which 19 from Asia, six from Latin America and one from Africa. Hypertension was associated with increased risk of incident dementia and MCI. Due to limited number of studies from Africa and Latin America, we were unable to compare effect sizes between geographic regions. Our review confirms known associations based on studies from high income countries, but adds contextual relevance for LMIC.

In **chapter VII** we investigate the association between the use of ancillary testing during the diagnostic work-up for dementia and time to poor outcome (institutionalization or death) and healthcare costs. We used healthcare reimbursement data in the Netherlands from all Dutch hospitals, including 13,312 patients diagnosed with dementia in 2018. Ancillary testing included computed tomography or magnetic resonance imaging (CT/MRI); neuropsychological examination (NPE), nuclear imaging (PET/SPECT), electroencephalography (EEG) and cerebrospinal fluid testing (CSF). We compared those who underwent a specific test in previous years to controls, propensity-score matched for age, sex, type of hospital and comorbidity. Time to poor outcome in those who underwent CT/MRI, EEG or CSF was similar to those who did not, but was longer for those who underwent NPE. Time to poor outcome was shorter in patients who underwent PET/SPECT. Patients who underwent CSF testing or PET/SPECT had higher mean total healthcare costs as compared to controls. NPE during the diagnostic trajectory was associated with lower total healthcare cost. Better outcomes in those who underwent NPE were potentially attributable to confounding by indication. Our results underscore the pivotal role of the clinical examination, which is supported by most international guidelines. Most important limitation is that we used routinely collected health care data, which leaves room for confounding by indication.

In the general discussion **(chapter VIII),** I reflect on our findings in the context of current literature, highlight key limitations, and suggest future directions to advance dementia prevention through research and public health interventions. I address global research inequities and propose the use of QES as a complement or alternative to randomized controlled trials (RCTs), especially in settings where RCTs are not feasible. QES may improve the generalizability of findings and help overcome ethical and logistical barriers. We also conducted a systematic review on the association between

hypertension and dementia in LMICs, providing context-specific evidence often missing from studies focused on HICs.

Effective and equitable dementia prevention requires both broad public health measures and targeted strategies for high-risk groups. To support a high-risk approach, we examined dementia risk profiles among Dutch individuals with a migration background. In individuals with symptoms of apathy we identified several modifiable risk factors linked to increased dementia risk. These findings can inform tailored interventions. At the same time, population-wide strategies remain essential—for example, addressing midlife hypertension, particularly in LMIC. Given the challenges of lifestyle-based prevention, interventions must align with the specific needs and preferences of target populations. Co-creating culturally and contextually appropriate strategies may enhance engagement and promote sustained behavior change. Finally, we stress the importance of critically evaluating diagnostic practices. While ancillary tests can aid clinical judgment, their benefits must be carefully weighed to avoid unnecessary healthcare resource use.

In conclusion, addressing dementia risk demands a combination of effective and scalable public health initiatives and tailored strategies for high-risk populations. Equally important is a critical evaluation of research methods to promote the global generation of evidence ánd of diagnostic practices to ensure the efficient use of resources.

SAMENVATTING

De wereldbevolking groeit en vergrijst, wat resulteert in een toenemend aantal mensen met dementie. Tussen populaties zijn er significante geografische en etnische verschillen in de kans op het krijgen van dementie. Aangezien er momenteel geen curatieve behandeling bestaat, is het aanpakken van risicofactoren voor dementie essentieel, niet alleen om de stijgende aantallen te vertragen, maar ook om ongelijkheden in het dementierisico tussen verschillende groepen te verminderen. Om rechtvaardige dementiepreventie en -zorg te bevorderen, beoogt dit proefschrift het volgende te onderzoeken:

- Hoe kunnen we onderzoek doen om robuust bewijs te genereren over dementierisicofactoren, ook in omgevingen met beperkte middelen, om preventieve strategieën te informeren?
- Hoe spelen risicofactoren een rol bij het verhoogde risico op dementie bij mensen met een migratieachtergrond, mensen die in lage- en middeninkomenslanden (LMIC) wonen en andere groepen met een verhoogd risico?
- Hoe kunnen diagnostische en preventieve inspanningen patiënten en risicogroepen ten goede komen, en hoe kunnen we interventies afstemmen op hun behoeften en voorkeuren?

In **hoofdstuk II** leggen we verschillende quasi-experimentele onderzoeksmethoden (QES) uit die kunnen helpen bij het overwinnen van uitdagingen die inherent zijn aan traditionele dementie preventie onderzoeken. Deze methoden kunnen een nuttige aanvulling zijn omdat ze bepaalde ethische, financiële en praktische problemen kunnen vermijden, en dus potentieel ook toegepast kunnen worden op plaatsen met beperkte middelen. Deze onderzoeksmethoden gebruiken natuurlijke of willekeurige variatie in blootstelling om te achterhalen hoe risicofactoren dementie beïnvloeden. Ze zijn goedkoper en flexibeler dan standaardonderzoeken, maar vereisen zorgvuldig ontwerp en kunnen nog steeds worden beïnvloed door verborgen vertekeningen van de uitkomsten. We richten ons op vier QES-ontwerpen:

1. Instrumentele variabelen: Gebruikt een factor die sterk gekoppeld is aan de risicofactor om te helpen bij het schatten van het effect ervan.
2. Regressiediscontinuïteit: Vergelijkt groepen die zich net boven en onder een afkappunt bevinden, vanaf waar behandeling geïnitieerd wordt.

3. Onderbroken tijdreeks: Bekijkt de uitkomsten van dementie vlak voor en na een grootschalige gezondheidsinterventie.
4. Verschillen-in-verschillen: Vergelijkt twee verder identieke groepen in de loop van de tijd, waarbij slechts één groep de interventie krijgt, om zo te kunnen corrigeren voor effecten die ontstaan door de tijd.

In **hoofdstuk III** berekenen we drie dementie risicoscores bij meer dan 13.000 deelnemers van 40-70 jaar oud aan de 'Healthy Life In an Urban Settin' (HELIUS) studie: CAIDE, LIBRA en ANU-ADRI. We vergelijken de drie scores tussen zes verschillende etnische groepen: Nederlanders, Hindoestanen, Creolen, Ghanezen, Turken en Marokkanen. Mensen met een migratieachtergrond hadden gemiddeld hogere risicoscores voor dementie vergeleken met de autochtone Nederlandse bevolking. Toen we leeftijd uit de risicoscores verwijderden (aangezien dit de sterkste risicofactor voor dementie is), werd het verschil alleen maar groter, wat suggereert dat deze hogere risicoscore onafhankelijk is van leeftijd. Voor de Ghanese, Turkse en Marokkaanse bevolking was deze associatie met hogere risicoscores zelfs sterker bij vrouwen. Een belangrijke beperking van dit onderzoek is dat de risicoscores die we gebruikten, afgezien van CAIDE, noch ontwikkeld, noch gevalideerd zijn in een multi-etnische populatie. Ook waren niet alle variabelen die officieel in LIBRA en ANU-ADRI worden opgenomen, beschikbaar uit het HELIUS-cohort.

In **hoofdstuk IV** gebruiken we kwalitatieve methoden om een mHealth-applicatie te ontwerpen met online coaching, specifiek voor Nederlanders met een lage sociaaleconomische positie en mensen met een Turkse of Hindoestaanse migratieachtergrond. We richtten ons op deze groepen omdat ze een verhoogd risico lopen op dementie en mogelijk niet altijd optimaal bereikt worden door traditionele preventie-interventies. Het doel was ontwikkeling van de MIND-PRO app, om risicofactoren voor dementie aan te pakken door passend advies en educatiemateriaal te bieden voor leefstijlverandering door middel van zelfmanagement, doelen stellen, voortgang bijhouden en ondersteuning door een online coach. We hielden interviews met individuen uit onze doelgroepen om behoeften en voorkeuren voor zo'n interventie te verkennen. Deelnemers benadrukten dat sociale steun en autonomie cruciaal zijn voor het duurzaam veranderen van hun leefstijl. Het aanpassen van coaching en leefstijladviezen aan de eigen cultuur werd als bevorderlijk ervaren. Tussen groepen varieerde de mate waarin dit als noodzakelijk werd beschouwd, waarbij Hindoestanen als onderdeel van hun culturele identiteit een sterkere gehechtheid aan hun voedingspatroon hadden. Alle groepen beschouwden zo'n op maat gemaakte app als een nuttig hulpmiddel om hen gemotiveerd en betrokken te houden.

In **hoofdstuk V** onderzoeken we of potentieel modificeerbare risicofactoren de associatie tussen apathie en het verhoogde risico op dementie kunnen mediëren met behulp van multipele mediatieanalyse. Hiervoor bestudeerden we 3303 thuiswonende volwassenen die tussen de 70 en 78 jaar oud waren, afkomstig uit de preDIVA-studie. Mogelijke mediatoren in de associatie waren systolische bloeddruk, cholesterol, diabetes, body mass index (BMI), roken en lichamelijke inactiviteit, en de uitkomst was incidente dementie gedurende 12 jaar follow-up. De associatie tussen apathie en dementie werd voor 27% gemedieerd door een combinatie van fysieke inactiviteit, BMI en diabetes. Van deze factoren was fysieke inactiviteit verantwoordelijk voor 28% van het mediërend effect, diabetes voor 9%, terwijl een hogere BMI een beschermende invloed had, hetgeen het effect met 12% afzwakte. Dit toont aan dat patiënten met apathie extra baat kunnen hebben bij intensieve preventie- en zorgstrategieën. De belangrijkste beperking van deze studie was dat apathie en de aanwezigheid van cardiovasculaire risicofactoren cross-sectioneel werden beoordeeld, wat een causale interpretatie van onze bevindingen belemmerd.

In **hoofdstuk VI** vatten we systematisch de beschikbare literatuur samen over de associatie tussen hypertensie en incidente dementie in lage- en middeninkomenslanden. We includeerden longitudinale studies (follow-up ≥6 maanden) uit lage- en middeninkomenslanden over de associatie tussen systolische bloeddruk of hypertensie en incidentie van dementie of milde cognitieve stoornissen (MCI) met een steekproefgrootte van ≥500 individuen. In totaal werden 26 artikelen geincludeerd, waarvan 19 uit Azië, zes uit Latijns-Amerika en één uit Afrika. Hypertensie was geassocieerd met een verhoogd risico op incidente dementie en MCI. Vanwege het beperkte aantal studies uit Afrika en Latijns-Amerika konden we de effectgroottes niet vergelijken tussen geografische regio's. Onze review bevestigt bekende associaties op basis van studies uit landen met hoge inkomens, maar voegt context toe voor lage en middeninkomenslanden.

In **hoofdstuk VII** onderzoeken we de associatie tussen het gebruik van aanvullend onderzoek tijdens het diagnostische proces voorafgaand aan de diagnose dementie en de tijd tot slechte uitkomst (opname in een instelling of overlijden) en de zorgkosten. We gebruikten gegevens over vergoeding van zorgkosten in Nederland van alle Nederlandse ziekenhuizen, van 13,312 patiënten die in 2018 de diagnose dementie kregen. Aanvullend onderzoek omvatte computertomografie of magnetische resonantie beeldvorming (CT/MRI); neuropsychologisch onderzoek (NPO), nucleaire beeldvorming (PET/SPECT), elektro-encefalografie (EEG) en onderzoek van het hersenvocht (ruggenprik). We vergeleken degenen die in voorgaande jaren een specifieke test ondergingen met controles, gematcht op basis van propensity score

voor leeftijd, geslacht, type ziekenhuis en comorbiditeit. De tijd tot een slechte uitkomst bij degenen die een CT-scan/MRI, EEG of ruggenprik ondergingen, was vergelijkbaar met die bij degenen die dit niet deden, maar was langer voor degenen die een NPO ondergingen. De tijd tot slechte uitkomst was korter bij patiënten die een PET/SPECT-scan ondergingen. Patiënten die een ruggenprik of PET/SPECT ondergingen, hadden hogere gemiddelde totale zorgkosten vergeleken met de controlegroep. NPO tijdens het diagnostische traject was geassocieerd met lagere totale zorgkosten. Betere uitkomsten bij degenen die een NPO ondergingen, waren mogelijk toe te schrijven aan vertekening door indicatiestelling. Onze resultaten onderstrepen de cruciale rol van het klinisch onderzoek. Dit wordt ook ondersteund door de meeste internationale richtlijnen. De belangrijkste beperking is dat we routinematig verzamelde gezondheidszorggegevens hebben gebruikt, wat ruimte laat voor vertekening door indicatiestelling.

In de algemene discussie (**hoofdstuk VIII**) reflecteer ik op onze bevindingen in de context van de huidige literatuur, belicht ik belangrijke beperkingen en werp ik een blik op de toekomst om dementiepreventie te bevorderen door middel van onderzoek met aandacht voor kwetsbare groepen en effectieve volksgezondheidsinterventies. Ik behandel mondiale ongelijkheden in onderzoek en stel het gebruik van QES voor als aanvulling op of alternatief voor gerandomiseerde gecontroleerde studies (RCT's), vooral in omgevingen waar RCT's niet haalbaar zijn. QES kan de generaliseerbaarheid van bevindingen verbeteren en helpen ethische en logistieke barrières te overwinnen. We hebben ook een systematische review uitgevoerd naar de associatie tussen hypertensie en dementie in lage- en middeninkomenslanden, waarbij we context specifiek bewijs leverden dat vaak ontbreekt in studies die zich alleen richten op hoge inkomenslanden. Effectieve en rechtvaardige dementiepreventie vereist zowel brede volksgezondheidsmaatregelen als gerichte strategieën voor groepen met een hoog risico. Om een risicovolle aanpak te ondersteunen, hebben we dementierisicoprofielen onderzocht bij Nederlanders met een migratieachtergrond. Bij personen met symptomen van apathie identificeerden we verschillende aanpasbare risicofactoren die verband houden met een verhoogd risico op dementie. Deze bevindingen kunnen als basis dienen voor op maat gemaakte interventies. Tegelijkertijd blijven strategieën voor de hele bevolking essentieel – bijvoorbeeld het aanpakken van hypertensie op middelbare leeftijd, met name in lage- en middeninkomenslanden. Gezien de uitdagingen van leefstijlpreventie, moeten interventies aansluiten bij de specifieke behoeften en voorkeuren van de doelgroepen. Het samen bedenken van cultureel en contextueel passende strategieën kan de betrokkenheid vergroten en duurzame gedragsverandering bevorderen. Tot slot benadrukken we het belang van het kritisch evalueren van diagnostische praktijken. Hoewel aanvullende tests kunnen helpen

bij klinische beoordeling, moeten hun voordelen zorgvuldig worden afgewogen om onnodig gebruik van gezondheidszorgmiddelen te voorkomen.

Concluderend vereist het aanpakken van het risico op dementie een combinatie van effectieve en schaalbare volksgezondheidsinitiatieven en op maat gemaakte strategieën voor risicogroepen. Even belangrijk is een kritische beoordeling van onderzoeksmethoden om de wereldwijde generatie van bewijs te bevorderen én van diagnostische praktijken om het doelmatig gebruik van middelen te waarborgen.

PHD PORTFOLIO

Name PhD student: Josephine Emma Lindhout
PhD period: 15th of June 2022 – 10th of October 2025
Names of PhD supervisor(s) & co-supervisor(s): prof. E. Richard, prof. E. P. Moll van Charante, dr. M.P. Hoevenaar-Blom, dr. J. van Dalen

	Year	ECTS
1. PhD training		
General courses		
Systematic review, Doctoral school	'22	0.7
Scientific writing, Doctoral school	'22	1.5
eBROK, Doctoral school	'22	1.5
Presentatievaardigheden, Spies en Spreken	'23	0.4
Didactical Skills, Doctoral school	'23	0.4
Weekly PhD education	'22-'25	5
Research meetings department of General Practice	'22-'24	2
Specific courses		
Msc Epidemiology	'22-'24	
V10 Epidemiologisch onderzoek: basisprincipes		4
V20 Principes van de epidemiologische data-analyse		4
V30 Regressietechnieken		4
V40 Klinimetrie: het ontwikkelen en evalueren van meetinstrumenten		3
V51 Epidemiologisch onderzoek: verdieping		4
V55 Methodologische advisering		3
V81 Missing data: consequenties en oplossingen		2
K75 Multilevel modellen en longitudinale data-analyse		4
K82 Mediatie analyse		2
WK87 Causal Inference and Propensity Score Methods		2
Onderzoeksstage		30
Presentations		
Global equity in dementia research, public and occupational health meeting	'22	0.3
Ancillary testing in dementia diagnosis, Vasculaire wetenschapsbespreking, RadboudUMC	'23	0.3
Ancillary testing in dementia diagnosis, Europrev, best oral presentation	'23	0.8
Quasi experimental study designs, poster presentation Alzheimer's Association International Conference	'23	0.5
Dementia risk scores, public and occupational health meeting	'24	0.3
Dementia risk scores, poster presentation, Amsterdam Public Health conference	'24	0.5
Multiple mediation analysis of apathy and dementia with dementia risk factors, final master presentation for Msc Epidemiology	'24	0.5
The association of ancillary diagnostic tests with outcome in dementia, poster presentation, Dutch Dementia Research Conference	'24	0.5

(Inter)national conferences		
European public health conference, Berlijn, attendance	'22	0.3
European Forum on Prevention and Primary Care – Porto, oral presentation	'23	1
NHG-wetenschapsdag, Rotterdam, attendance		
Alzheimer's Association International Conference, Amsterdam, poster	'23	0.3
presentation	'23	0.3
Amsterdam Public health conference, poster presentation ('23), attendance		
('22,'24)	'22-'24	1.2
Dutch Dementia Research conference, poster presentation	'24	0.5
2. Teaching		
Lecturing		
WG AV Journal club 1,2,3	'23-'24	1
WG AV Klimaatverandering in de grote stad	'23-'24	0.3
WG AV Communiceren met kinderen	'23-'24	0.3
Supervising		
Adnane el Marini, Master Medicine	'23	1
Richler Amponsah, Master Personalized Medicine	'24	1
3. Parameters of Esteem		
Grants		
Travelgrant 2500 euro, Aging and Later Life, Amsterdam Public Health	'23	
OKE fonds 6750 euro, Epidemiology & Data Science	'23	
Awards and Prizes		
Best oral presentation, Europrev	'23	

LIST OF PUBLICATIONS & AUTHOR CONTRIBUTIONS

1. **Lindhout, J. E.,** van Dalen, J. W., van Gool, W. A., & Richard, E. (2023). The challenge of dementia prevention trials and the role of quasi-experimental studies. *Alzheimer's & Dementia*, *19*(8), 3722-3730.

Author contributions: JL, JvD, WvG, ER study concept and design; JL drafting the manuscript; JvD, WvG, ER critical revision of the manuscript.

2. **Lindhout, J.E.,** van der Endt, J. R., Hoevenaar-Blom, M. P., van Dalen, J. W., Deckers, K., Geerlings, M. I., Galenkamp, H., Richard, E. & Moll van Charante, E. P. (2025). Midlife dementia risk scores in a multi-ethnic population in the Netherlands: the HELIUS study. *Journal of Public Health*, *47*(2), 194-202.

Author contributions: JL, JvdE, MHB, ER, EMvC study concept and design; HG, EMvC data acquisition and preparation; JL, JvdE, MHB, JvD data cleaning and analysis; JL, JvdE, MHB, JvD, ER, EMvC interpretation of results; JL, JvdE drafting manuscript; JL figures; MHB, JvD, KD, MG, HG, ER, EMvC critical revision of the manuscript.

3. Van der Endt, J.R.*, **Lindhout, J.E.*,** van Apeldoorn, J.A.N., Amponsah, R., Ramkishun, R., Sert, E., Craamer, C., Richard, E., Hoevenaar-Blom, M.P., Moll van Charante, E.P. (2025). A coach-supported mHealth lifestyle intervention to reduce dementia risk in persons with low SES or a migration background -a qualitative co-design study. accepted to: *Journal of Participatory Medicine 17(1), e76094.*

Author contributions: JvdE, JL, ES, ER, MHB, EMvC study concept and design; JvdE, ES, contact with participants, JvdE, JL, RA, RR, ES, CC, data collection and transcription of interviews; CC live adaption of the MIND-PRO demo app during focus interviews; JvdE, JL, JvA, ES, MHB, EMvC thematization and interpretation of interviews; JvdE, JL drafting of the manuscript; JvA, ES, ER, MHB, EMvC critical revision of the manuscript.

4. **Lindhout, J. E.,** van Dalen, J. W., van Gool, W. A., Richard, E., & Hoevenaar-Blom, M. P. (2025). The Association of Apathy With Incident Dementia: A Multiple Mediation Analysis of Cardiovascular Risk Factors. *International Journal of Geriatric Psychiatry*, *40*(5), e70092.

Author contributions: JL, JvD, WvG, ER, MHB study concept and design; JL, JvD, MHB data preparation and analysis; JL, JvD, WvG, ER, MHB interpretations of results; JL, JvD drafting of the manuscript; JvD, WvG, ER, MHB critical revision of the manuscript.

5. **Lindhout, J.E.,** Hoevenaar-Blom, M.P., van Dalen, JW., Song, M., Lin, D., Wang, W., Richard, E., Moll van Charante, E.P., van Middelaar, T. (2025). Association between hypertension and dementia risk in low-and middle-income countries: A systematic review. *The Journal of Aging Research & Lifestyle*, *14*, 100027.

Author contributions: JL, MHB, ER, EMvC, TvM study concept and design; JL, MHB, TvM systematic search and selection of articles; JL, MHB, MS, DL, WW data-extraction; MS, DL, WW translation and verification of data from articles written in Chinese; JL, MHB, JvD, TvM data preparation and analysis; JL, MHB, TvM drafting of manuscript; MHB, JvD, MS, DL, WW, ER, EMvC critical revision of the manuscript.

6. **Lindhout, J. E.,** Richard, E., Hafdi, M., Perry, M., Moll van Charante, E. P., & van Gool, W. A. (2024). The Association of Ancillary Diagnostic Tests With Outcome in Dementia. *Journal of the American Medical Directors Association*, *25*(7), 105040.

Author contributions: ER, MH, WvG study concept and design; ER, WvG acquisition of data; JL, MH, WvG analysis and interpretation of data; JL, WvG drafting manuscript; ER, MH, MP, EMvC, WvG critical revision of the manuscript.

NOT INCLUDED IN THIS THESIS

7. Arends, C. R., **Lindhout, J. E.,** van der Molen, L., Wilthagen, E. A., van den Brekel, M. W., & Stuiver, M. M. (2023). A systematic review of validated assessments methods for head and neck lymphedema. *European Archives of Oto-Rhino-Laryngology*, *280*(6), 2653-2661.

Author contributions: CA, LvdM, MvdB, MS study concept and design; CA, JL, EW systematic search; CA, JL data-extraction, preparation and analysis; CA, JL drafting of manuscript; LvdM, EW, MvdB, MS critical revision of the manuscript.

8. Arends, C. R., van der Molen, L., **Lindhout, J. E.,** Bragante, K., Navran, A., van den Brekel, M. W., & Stuiver, M. M. (2024). Lymphedema and trismus after head and neck cancer, and the impact on body image and quality of life. *Cancers*, *16*(3), 653.

Author contributions: CA, LvdM, KB, AN, MvdB, MS study concept and design; JL, KB data collection; CA, JL data preparation and analysis; CA drafting manuscript; LvdM, JL, AN, MvdB, MS critical revision of the manuscript.

ABOUT THE AUTHOR

Josephine Emma Lindhout was born on 13 August 1994 in Amsterdam, the Netherlands. Her interest in medicine and global health began at the age of sixteen, when she took part in a voluntary internship at a hospital in Ghana. This experience left a lasting impression and shaped her ambition to combine clinical care with a broader, global perspective on health.

She completed her secondary education at the Murmellius Gymnasium in Alkmaar in 2012, after which she moved to Maastricht to study Medicine in the international track at Maastricht University. Alongside her medical training, she participated in the honours programme, where she focused on human resources for health in India. Driven by her growing interest in global health, she pursued a Master's degree in Global Health before starting her clinical rotations, studying in Maastricht and at Thammasat University in Bangkok, Thailand.

Josephine graduated as a medical doctor in 2020. She subsequently worked in surgical oncology at the Antoni van Leeuwenhoek Hospital, and later in elderly care, where her interest in ageing and prevention of chronic disease further deepened. Wanting to integrate her clinical experiences with her interest in population health, she started her PhD at the Department of General Practice in 2022. During this time, she also completed a Master's degree in Epidemiology at Vrije Universiteit Amsterdam.

Josephine currently works as a general practitioner in training. She hopes to build a career that combines clinical work in primary care with contributions to public health, aiming to improve health both within and beyond the consultation room.

Outside of her professional life, Josephine enjoys being outdoors and challenging herself physically, whether through running, cycling, ice skating, climbing or hiking. She especially values sharing these experiences with her partner, family, and friends.

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