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Original research article

Social health and prevention of dementia: Integration of human and mice studies

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A B S T R A C T

Objectives: Prevention of dementia is considered a healthcare priority. We aimed to identify potentially modifiable risk factors and mechanisms within the social health domain to find novel avenues to prevent cognitive decline and dementia.
Design: We integrated the results of eight sub-studies of the Social Health in Mice and Men (SHiMMy) project that were separately published in specialized journals, but not yet jointly considered. We followed the integrative methodology of Whittemore and Knafl, using the conceptual framework for social health to structure and integrate the results of human epidemiological and qualitative studies and experimental mice studies. This is a novel multi-method approach.
Participants: Participants of the population-based longitudinal cohort Rotterdam study were included in the epidemiolocal studies (ranging from N = 1259 to N = 3.720) and in the qualitative study (n = 17). Mice intervention studies were performed using a transgenic mouse model for Alzheimer's pathology and matched controls, under group and single housed conditions.
Measurements: Epidemiological studies include social health markers (loneliness, perceived social support, marital status) and magnetic resonance imaging of the brain. The semi-structured qualitative study used an interview guide. The mice study assessed behavioral and histological markers.
Results: In human and mice studies, we identified several similar potentially modifiable risk (e.g. marital status, social group size) and protective (e.g. perceived social support, behavioral responses) factors. This alignment of findings showing that social health may impact brain health lend further support to our social health hypothesis.
Conclusion: These results allow us to propose evidence-based social health targets for preventive interventions.

Introduction

Prevention of dementia is considered a healthcare priority as populations worldwide are progressively aging. Current biomedical interventions in dementia patients or those at risk are not sufficient to eliminate dementia risk fully [1,2].

Livingston et al. extended available models of risk of dementia by the identification of potentially modifiable risk factors, thus opening new entrances for risk reduction and prevention [1,2]. Here we expand on social isolation as a potentially modifiable risk factor [1,2] by broadening the scope to social health.

In considering dementia as a multifactorial syndrome, social health is increasingly recognized to play a role in the onset and development of cognitive decline and dementia. Social health has been introduced by the WHO in 1946 as the social domain of health alongside physical and mental health [3]. This term 'social health' is a relational concept in which well-being is defined as the mutual impact that an individual and the social environment have on each other [4]. Over the past two

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decades, epidemiological studies have explored associations between social health markers and cognitive decline and dementia. Markers of poor social health, such as poor social engagement and social isolation, were associated with an increased incidence of dementia [5–7]. Some markers expressing strong social health, such as maintaining social engagement, were associated with better cognitive functioning [1,8–11].

Pressing remaining questions are: what is the relationship between social health and brain health? Is there a neurobiological substrate for the relationship between social functioning and cognitive functioning? What do older adults themselves consider to be important in social health? To answer our questions, we used several approaches in an overarching research collaboration. To better understand the neurobiological mechanisms that underlie dementia, we studied associations between social health and brain health in humans; we studied the impact of the social environment on the behavioral phenotype in mice and neurobiological substrates in rodents; and we explored the social health perceptions of older adults by a qualitative approach. Brain health is an evolving concept attracting attention from both the health sector and wider society. Brain health is defined as the state of brain functioning across cognitive, sensory, social-emotional, behavioral and motor domains, allowing a person to realize their full potential over the life course, irrespective of the presence or absence of disorders [12].

This research collaboration was named the Social Health in Mice and Men (SHiMMy) project. (See Boxs 1, and 2). We based this project on the hypothesis that social health stimulates the use of cognitive reserve, thus slowing down cognitive decline or maintaining cognitive functioning in old age and that there is an underlying biological substrate to explain the relationship between social and cognitive deficits. Cognitive reserve refers to the adaptability (i.e., efficiency, capacity, flexibility) of cognitive processes that helps to explain differential susceptibility of cognitive abilities or day-to-day function to brain aging, pathology or insult [13]. Cognitive reserve is closely related to brain reserve, which refers to preexisting neurobiological capital (e.g., neurons/synapses) that may allow individuals to better cope with brain aging and pathology [13]. Results of the sub-studies in the project were separately published in specialized journals [14–21], but their outcomes were not yet jointly considered.

In this perspective paper, we aim to integrate the results of the SHiMMy sub-studies by categorizing them into the conceptual framework for social health and considering them in the context of the existing body of literature. We aim to identify potentially risk and protective factors and mechanisms in the relation between social health and brain health to identify novel targets for interventions to prevent cognitive decline and dementia.

Integration of human and mice studies into the conceptual framework for social health

We integrated the results of the human and mice studies by following the methodology of Whittemore and Knafl. This methodology allows the combination of diverse methodological approaches (in casu epidemiology, qualitative research and mice experimental studies) [22]. We used the conceptual framework for social health to structure the results.

This framework facilitates the organization of social health markers into six domains which are categorized in two levels, those of the individual and the social environmental level [4]. The conceptual framework is presented in Fig. 1.

We identified potentially risk and protective factors from the sub-studies of the SHiMMy project. Most potentially relevant factors were identified on the social environmental level.

The role of the social environment in promoting social and brain health

The role of the social environment is crucial in the personal experience of social health. The incentives and responses of the social environment can contribute to social health of the individual as well as challenge it.

The social environmental level involves its structure, function and the appraisal of the quality of relationships.

Structure refers to the social ties between persons in networks (e.g., social network size and composition) [9].The structure is the base of social health. A higher frequency of contact and larger social networks were associated with better cognitive functioning [1,8,9,23]. However, in a recent review the link between social network size and cognitive function was not consistently significant [11]. An extensive social network was not associated with reduced risk of dementia [8]. Social isolation was associated with a higher risk of dementia [2,24]. A number of studies, though not all [11,25], found a significant association between marital status and reduced risk of dementia or cognitive decline[26,27]. Evidence showing that social support reduces the risk of dementia was weak [11].

Our qualitative study (N = 17) [17] indicated that within this network structure core ties are crucial. Older adults depended on the same core player for all domains of social health, with a key role for the partner, including married and unmarried pairs [17].

Epidemiological data from the SHiMMy project revealed an association between marital status and brain structure: participants who had never been married had a smaller total brain volume compared to

Box 1
Setting and study population: Human studies.

The SHiMMy project includes data from human and rodent studies and applies a multi-method approach. The national Dutch SHiMMy project is related to the European Social Health And Reserve in the Dementia patient journey (SHARED) project[4] that also focused on the relationship between social and brain health. The SHiMMy project used the conceptual framework for social health, that has been developed in the SHARED project, to integrate the findings of its sub-projects and a systematic literature review. Human studies within SHiMMy took place within the Rotterdam Study[57], a population-based longitudinal cohort study that has been ongoing since 1990. Participants of the Rotterdam suburb of Ommoord are invited for participation when they are 40 years old or older,and are followed up every 3 to 5 years, 3720 adults participated. Social health markers (loneliness, perceived social support, marital status), were assessed repeatedly during home interviews[16,20]. Magnetic resonance imaging of the brain was performed repeatedly between 2005 −2018 for eligible participants to obtain brain volumetrics, cerebral vessel disease markers and white matter microstructural integrity as measures of brain structure[16]. Both cross-sectional and longitudinal associations between social health and brain structure were studied[20]. Two additional studies (N = 1259) explored the role of the stress system and the immune system in the link between social health and brain structure[18,21]. For the stress system, we studied whether the association between functioning of the negative feedback loop of the hypothalamic-pituitary adrenal (HPA) axis and brain structure were modified by social health markers[18]. Functioning of the negative feedback loop of the HPA-axis was measured through a very low-dose dexamethasone suppression test (DST)[18]. For the immune system, the relative balance between innate and adaptive immunity was studied using white blood cel-based-immune indices at multiple follow-up rounds[18]. The association between social health and immune system was studied, as well as the association between social health and plasma markers of neurodegeneration (amyloid-beta40, amyloid-beta42, total tau and neurofilament light chain)[21]. The COVID−19 pandemic and the accompanying lockdown provided an opportunity to learn more about social health, since it mimicked a large-scale social restrictions experiment. Social health markers (loneliness, perceived social isolation, social connectedness, living alone) and global brain volume were studies during the first months of the pandemic (N − 1720) and were associated in a subset of participants of routine Rotterdam Study follow-up (1990 −2020)[19]. For our qualitative study, Rotterdam Study participants around age 65 were invited for semi-structured in-depth interviews. A thematic analysis of interview transcripts (N = 17) was performed[17]. In this study the term partner is used, including living with a partner without being actually married. In text we use the terms used in the original articles.

Box 2
Setting and study population:Rodent studies.

The SHiMMy project includes data from human and rodent studies and applies a multi-method approach. The rodent studies were comprised of a literature study and multiple experimental mice studies. The literature study investigated the overlap between the social and cognitive domain in rodents by mapping neurobiological domains[38]. In the experimental mice studies, the influence of the social network structure (i.e. housing condition) was investigated in two different studies. These studies were performed in transgenic mouse models for Alzheimer's Disease: J20 mice (amyloid pathology model) and P301L mice (tau pathology model). In the first study, the social behavior of J20 mice and that of Wild Type healthy control mice was assessed at different ages. In addition, the composition of the group (4 J20 mice, 4 control mice, or 2 J20 + 2 control mice) on social behavior was investigated[14]. In the next experimental mouse study, mice of both AD mouse models and healthy controls were either individually housed or group housed for several months to examine the effect of the social housing condition on brain health (behavioral and histological markers)[14].

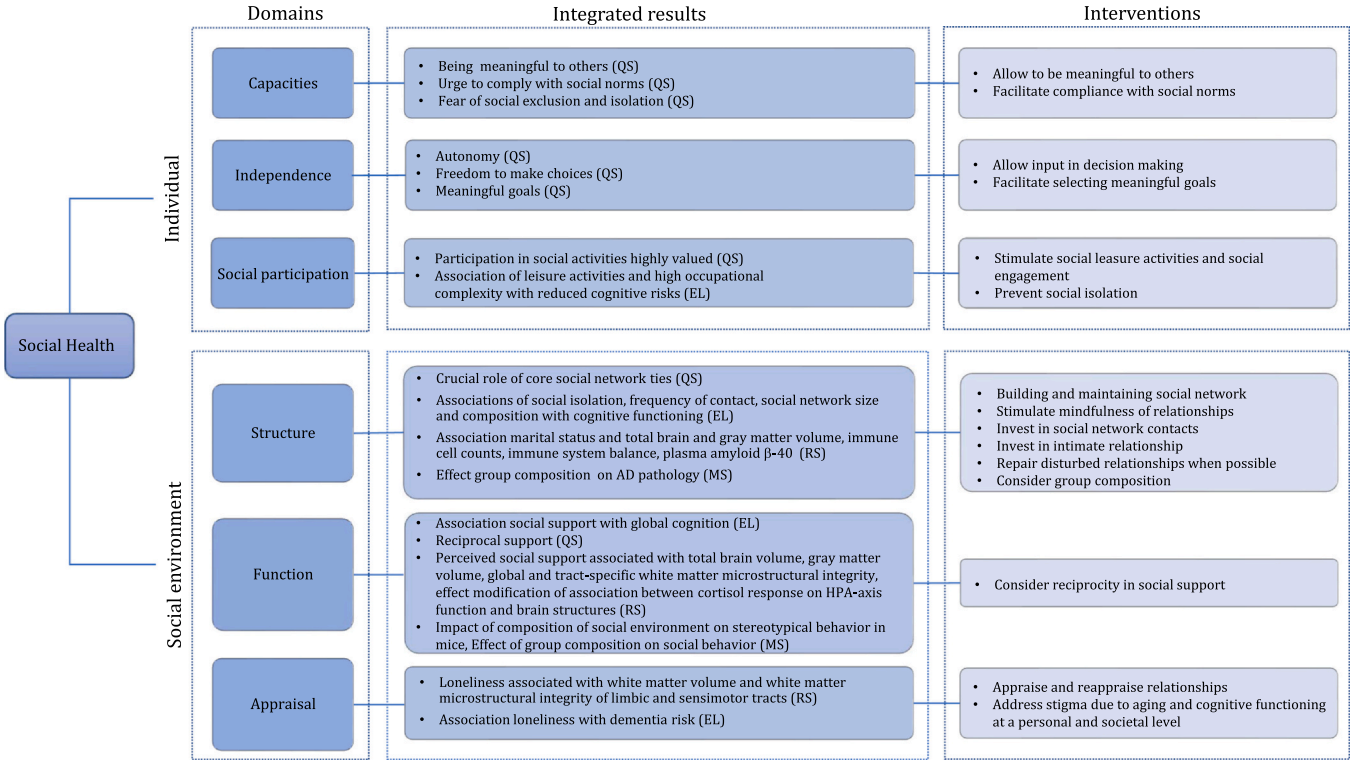

Fig. 1. Results integrated within conceptual framework for social health.

married peers, as well as a smaller gray matter volume [20]. See Box 1.

Never married older adults additionally had higher granulocyte cell counts, lower lymphocyte cells counts and an imbalance towards innate immunity [21]. They further had higher plasma levels of amyloidβ-40. Never married older males had higher plasma levels of amyloidβ-40, amyloidβ-42, neurofilament light chain, and total tau, when compared to married peers [21]. Divorced and widowed older adults had higher plasma levels of total tau [21] Social health is differently associated with immune system balance and plasma degeneration in males compared to females [21].

Together, the SHiMMy human studies indicate that marital status is a key part of the social health structure in relation to brain health and the balance in the immune system.

The SHiMMy mice studies (see Box 2) provided more information on the impact of the social network structure (housing condition) on the brain. The first mouse study compared P301L mice (genetic tau pathology model) that were single housed (isolated) with group housed mice. Single housing was linked with the development of stereotypical behavior (i.e. somersaulting and circling behavior) but did not affect tau hyperphosphorylation in the examined brain regions [14].

The second mouse study compared single housed J20 mice (genetic amyloid pathology model) with group housed J20 mice. The single housed mice displayed fewer plaques in the hippocampus compared to the group housed mice [14]. This contrasted our expectation.

The mice studies suggest a role for both the group composition and the group size on brain health.

The *function* of the social environment refers to actual exchanges between network members, e.g., emotional support and instrumental aid [28]. The literature review of Kelly et al. described a relationship between social support and global cognition [9]. In contrast, the study of Freak-Poli et al. showed that perceived social support was not associated with cognitive decline or dementia in the Rotterdam Study and in the Swedish National Study on Aging and Care in Kungsholmen (SNAC-K) [29]. In a recent systematic review the evidence of social support reducing the risk of dementia was weak [11].

However, SHiMMy results did show associations between social support and brain health in the Rotterdam Study (N = 3720). We showed that better perceived social support was associated with larger total brain volume and gray matter volume at baseline, and with a less steep decline in total brain volume over time, compared to older adults with lower perceived social support [20]. Better perceived social support was also associated with higher global fractional anisotropy and lower mean diffusivity at baseline, indicating higher global white matter microstructural integrity [16]. Moreover, better perceived social support was associated with higher microstructural integrity of association (inferior fronto-occipital fasciculus and uncinate fasciculus) and commissural tracts (forceps minor) [16].

In exploring the role of the HPA-axis in brain structure in older age (N = 1259), we found that perceived social support modified the

association: a diminished cortisol response was associated with a larger total brain volume, larger gray matter volume and lower global fractional anisotropy in participants with low/moderate perceived social support, but not in those with optimal perceived social support [18].

Our qualitative study revealed the high value of reciprocity for older adults [17]. Reciprocity represents a combination of functioning and appraisal and links the individual and environmental level. People not only want to be helped when necessary, but especially desire to return on help and gifts received. They don't want to feel indebted [30]. Feelings of not being in the position to reciprocate are at the expense of dignity.

One of the mice studies revealed information on the social behavior of J20 mice in different social group compositions (same-genotype and mixed-genotype colonies). J20 mice housed with three other J20 mice (same-genotype colonies) displayed altered social behavior compared to healthy control mice (locomotor activity and social sniffing was increased, while social contact was decreased). However, when J20mice were co-housed with healthy control mice (mixed-genotype colony), their social sniffing duration was reduced and similar to that of control mice and social contact frequency increased compared to J20 mice from same-genotype colonies. Furthermore, healthy control mice housed in mixed-genotype colonies displayed increased nest hiding compared to those housed in same-genotype colonies [15]. In addition, healthy control mice housed in mixed-genotype colonies displayed increased nest hiding compared to those housed in same-genotype colonies [15]. This indicates a bi-directional relationship between brain health and social health [14,15]. They also show the complexity of group housing with the positive impact for affected mice and the potential stressfulness of their proximity for the social environment.

Not only the actual functioning of a social network is important, but also its *appraisal*. It is a basic social science premise that people are driven by their appraisals [31]. People act on the base of the meaning that things (everything they note in the world) have for them. These meanings can be revised [31]. This also goes for the appreciation of relational quality.

Appraisal of the quality of the relationship and interaction refers to perceptions and interpretations by the individual and the social network [4]. In fact, this domain relates both to the individual and the environmental level. Crucially, the appraisal of the quality of relationships can be changed by reconsidering maladaptive cognitions by both the individual and the social environment, and this domain would thus lend itself for intervention and prevention efforts.

Loneliness is a subjective appraisal measure and is defined as a perceived lack of social relationships and unfulfilled intimacy [32]. A recent systematic review on the neurobiology of loneliness reported that loneliness was associated with worse brain health [33], while associations of loneliness with dementia risk remain inconsistent [6,8]. Another review found evidence for a reverse relationship between cognitive functioning and loneliness indicating that worse cognitive functioning was a risk for loneliness [11].

In our SHiMMY project, we found that loneliness was associated with smaller white matter volumes in older adults the Rotterdam Study, compared to non-lonely peers, and this was especially true for older males [20]. Loneliness was also associated with lower microstructural integrity of limbic (parahippocampal part of the cingulum bundle) and sensorimotor tracts (superior thalamic radiation) [16].

The COVID-19 pandemic allowed us to study the effects of imposed social distancing on loneliness. We used a subset of the Rotterdam study (N = 1720). The prevalence of loneliness increased from 12.6 % pre-pandemic to 27.9 % in April 2020 [19]. However, social isolation and loneliness decreased over time during the first three months of the pandemic [19], whereas social connectedness trajectories remained stable and high during that time [19].

The role of the individual in promoting social and brain health

Individuals can influence their own social health in a positive and a negative way, as they are actors towards the immediate social network and society. Huber et al. defined three domains of action [34]. These involve: The fulfillment of social roles [35] and compliance with social norms, creating some degree of independence despite a medical condition, and social participation.

The role of the individual mainly came forward in the SHiMMy qualitative study, which was a rich source of information on social health markers relevant to older adults. They tried to *fulfill social roles and to comply with norms.* Being meaningful as an individual within the social environment was a key aspect of social life. In their wish to be socially included, participants felt judged by others and adapted their behavior to comply with social norms and to avoid negative judgements [17]. This result is in line with recent qualitative data indicating that the wish to continue to live their life as usual is a key value to older adults [36].

On the other hand, there was a wish to *create some degree of independence despite a medical condition.* The qualitative study revealed that autonomy, having meaningful goals and freedom to make your own decisions mattered to them [17]. The latter is in agreement with a qualitative study emphasizing the importance of making own decisions [36]. Our qualitative research revealed new markers that can be used in epidemiological studies. As these markers are valued by older adults, they are feasible targets for interventions.

The *ability to actively participate in social activities* was only addressed in the qualitative SHiMMy sub-study. Active social participation was valued by the participants, even by persons in which the need for social interaction was low [17].

Other epidemiological studies have consistently indicated that social health markers such as social engagement and (social) leisure activities, were associated with better cognitive functioning [8,9,37].

Expanding the scope from social isolation identified by Livingston et al. [1] to social health led to the identification of additional social health markers representing potentially modifiable risk and protective factors for brain health. We identified marital status, perceived social support and loneliness from the Rotterdam study; social engagement, frequency of contact, social network size and composition from the literature study; being meaningful to others, autonomy and reciprocity from the qualitative study; and group composition and behavioral responses from the mice studies. See Fig. 1.

These combined results create a stronger evidence-base for the relation between social health (on the level of the social environment) and brain health and increase the preventive potential. Limitations are that not all identified social health markers are validated and evaluated in association studies. Experimental research in this area is extremely challenging due to ethical concerns surrounding the experimental conditions.

Did our hypothesis pave the way to new knowledge?

The studies within the SHiMMy project were guided by the social health hypothesis, which is only one of many hypotheses on the etiology of dementia. We delineate our ambition to this hypothesis and do not cover the full spectrum of hypotheses on the origins of dementia. While we have not addressed e.g. cardiovascular hypotheses, genetic contributions, cholinergic pathways, and many other potential biological underpinnings, these are not mutually exclusive, but may add onto the social health and cognitive reserve hypotheses.

The social health hypothesis focuses on the cognitive reserve mechanism by assuming that social health acts as a driver for stimulating the development and the use of cognitive reserve [4]. This results in maintenance of the level of cognitive function, thus postponing the clinical decline.

Cognitive reserve is not easily or directly measured, since it is not a fixed entity. Proxies to measure cognitive reserve include socio-behavioral indices and functional imaging methods [13]. While the social health hypothesis was the driver of our research projects, our results more directly apply to brain reserve than to cognitive reserve. We

assumed that social health affects brain structure [20], and that neuroendocrine and immune dysregulation may be underlying mechanisms [18].

The structure of the social environment (i.e. marital status in human studies, size and composition of the group for mice studies) seems to be related to brain health in both humans and mice. Function and appraisal of the social environment were also associated with brain structure in human studies in SHiMMy. Neuroendocrine and immune dysregulation pathways were explored in the context of social health and brain structure but require further research to pinpoint exact mechanisms.

Our findings support the hypothesis that social health affects brain structure. In combination with other literature described in this work, social health may provide a double protection for dementia pathology, by adding to brain reserve as well as driving cognitive reserve.

The mice studies contributed to our understanding of the relationship between social health and brain health by pointing at a significant effect of housing conditions at the brain and stereotype behavior, indicating that the social environment can modulate AD-related pathology [14].

To provide neurobiological understanding of brain substrates we mainly focus on rodent studies. Additional support for the relationship between social health and brain health has been found by the identification of a neurobiological substrate in rodent studies. By mapping the rodent brain regions involved in the social/and cognitive domain we found that the vast majority of brain regions involved in the cognitive domain are also involved in the social domain [38].

The relevance of combining human and rodent studies is underlined by results of both human and rodent studies indicating that modulation of social health can affect brain health and by the identified biological substrate for this relationship in rodent studies. The qualitative study provided insight into the experience of older adults themselves, and may inspire research into potentially risk and protective factors to prevent cognitive decline and dementia (i.e. reciprocity and being meaningful) [17].

As a next step we propose to further use the hypothesis to gather cumulative evidence using integrated multi-method research. Based on our studies we suggest:

- Inclusion in epidemiological databases of new social health markers found in the qualitative study (i.e reciprocity).and additional research on relation between social and brain health
- Human research into an underlying neurobiological substrate in the cognitive and social domains in the brain, following the overlap found in rodent studies
- Research into the interaction between the social health hypothesis and other etiological dementia hypotheses
- Research on perception of group composition using qualitative research, following the results of our experimental mice studies
- Research into the bi-directional influence of brain and social health, following our mice studies and epidemiological studies
- Inclusion of our intervention targets into preventive interventions

Intervention targets derived from the various SHiMMy studies

The integration of SHiMMy studies provided consistent evidence on associations between social and brain health. This allows us to explore targets representing potentially risk and protective factors, which could be used for interventions to prevent dementia. There is an urgent need for translation of evidence into intervention targets.

Psychological and social interventions to prevent dementia are in its infancy [39]. When it comes to social health interventions, the only interventions that were effective for improving social health in the general population focused on loneliness and were not related to dementia prevention. These interventions included meaningful and satisfying group activities and psychological interventions to reframe maladaptive cognitions regarding loneliness [40–42]. As for interventions to prevent cognitive decline, the most well-known study is the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER). Its results indicated that multi-domain lifestyle-based intervention including stimulation of social interaction by activities could prevent cognitive and functional decline amongst at-risk older adults [43–45].

Our project suggests that intervention targets are most likely to be promising on the level of the social environment. Although we rely on associations, the integrated evidence from human and mice studies makes us confident to suggest several potentially risk and protective factors as potential intervention targets. Moreover, social heath interventions focusing on positive interactions will not cause harmful side effects. The potentially risk factors found at the environmental level included social isolation and not being married, while higher contact frequency and larger social networks are potential protective factors. They draw the attention to maintenance of the social network. The results of the mice studies indicate that grouping is not perse beneficial. The composition of the group is crucial. On the individual level, the qualitative data reveal what is important for older adults in social traffic.

We suggest the following intervention targets to maintain or improve social health (see Fig. 1):

Social environmental level:

- Building and maintaining a social network to allow social contacts
- Building and maintaining an intimate relationship
- Careful consideration of group composition
- (Re)appraisal of quality of relationships and openness to changes

Individual level.

- Consider preferences that are meaningful to individuals and allow people to be meaningful
- Include people in making decisions

- Stimulate social engagement in accordance with personal preferences.

Intervention targets can be used in daily social life by the individuals and the social environment, in clinical practice by general practitioner, nurses, case managers, social workers, geriatricians, occupational therapists and other health care professionals and in public health.

There is limited evidence on interventions using our selected targets in interventions to prevent dementia. A key finding relevant to our intervention targets is that the magnitude of the effect of complex measures of social integration on longevity was comparable with that of smoking and exceeds that of many well-known risk factors for mortality [46]. A robust conclusion from intervention studies in dementia care is that care should be personalized [1]. Considering the limited evidence of intervention studies and the recent knowledge progress in finding new targets for interventions, it is timely to focus on preventive interventions.

The adoption of social health interventions by the target audience can be impeded be the stigma associated with social stimulation programs [47] and the embarrassment and shame felt by people when their cognitive and social functioning declines [48]. Considering these issues, embedding social elements in interventions rather than framing interventions as single social stimulation programs is preferable. Including social elements in other interventions (e.g. exercise) was one of the cornerstones of the effective FINGER study [45]. Promoting social activities by referring to the benefits for brain health is a novel stimulus that might overcome shame.

Our project focused on primary prevention. However, a crucial phase for social health interventions might be when people notice that

full social and cognitive competence is diminishing. Stimulating and facilitating people to keep engaged might be effective in prevention of cognitive decline.

Conclusion

Increasing the evidence-base for the relation between social health and cognitive decline by the integration of human and mice studies is a novelty in dementia research.

Our approach validates and supports results presented in a series of recent International Psychogeriatrics (IPG) publications by its contributions across several fields of social health and dementia research. First, it enhances the conceptual development of social health as indicated by Steffens [49]. Second, it expands the knowledge on associations between social connectedness and mental health resilience [50], network composition and cognitive decline [51], network composition and executive functioning [52], marital status and risk of cognitive decline and dementia [11] and social health and brain volume [49] Third, it adds to models on social health and dementia such as a model on loneliness and dementia [53]. Additionally, it contributes to research leveraging the COVID-19 epidemic as an opportunity to explore the effects of social isolation on cognitive functioning [54,55]. The paper also adds by identifying new social health markers relevant to cognition and dementia such as purpose in life [56]. Finally, it provides potential targets for interventions in the social health domain.

Our main conclusion is that better social health was associated with better brain structure in older adults. Integrated with the qualitative studies, these findings confirmed the key role of a partner in life as well as the value attached to being meaningful and the reciprocity in social support. The mice studies provided insight into the bi-directional impact of co-housing of healthy Wild Type mice and Alzheimer Disease modeled mice on behavior and the brain. Results of rodent and human studies are in line with each other.

Expanding the scope from the negative marker 'social isolation' identified by Livingston et al. [1] to the more positive concept of social health led to the identification of more social health markers related to cognitive decline representing potentially modifiable risk and protective factors. Consequently, we identified several positive social health markers, giving more feasible direction to action. The rodent studies enriched our understanding by the identification of a neurobiological substrate underlying the overlap between the social and cognitive domain. Since the social brain is highly conserved across species, this overlap might persist in the human brain [38].

The results lend support to our social health hypothesis but leave important questions for future research: while we found that social health is linked to brain structure, further research is needed to parse out the contribution of social health to cognitive reserve on the pathway from social relationships to cognitive impairment and dementia.

In our research here, we theorized about the roles of functioning of the HPA-axis and the immune system, but more work is needed to untangle causal relationships between these complex systems. The studies in mice and humans encourage to investigate a bidirectional link between social behavior and the brain. As a next step we encourage cumulative evidence building using integrated multi-method research as we did [52].

Our sub-studies identified several potentially risk and protective factors that may offer entrances for social health interventions with loneliness and perceived social support as key targets.

Interventions should focus on the improvement of social competencies and on the stimulation a person-centered approach. Social heath interventions should be included in other preventive interventions and its principles, like reciprocity and social engagement, can be applied in daily life.

Interventions should raise awareness of the importance of social engagement, not only for the sake of the Dutch untranslatable "gezelligheid" (i.e. conviviality, coziness, or fun in a social context), but for the potential benefit for cognitive and brain health.

CRediT authorship contribution statement

Costanzo Andrea: Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Drinkenburg Wilhelmus H.I.M.:** Conceptualization, Funding acquisition, Supervision, Writing – original draft, Writing – review & editing. **Ikram M. Arfan:** Conceptualization, Formal analysis, Funding acquisition, Supervision, Writing – original draft, Writing – review & editing. **van der Zee Eddy A.:** Investigation, Supervision, Writing – original draft, Writing – review & editing. **Lanooij Suzanne D.:** Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **van der Velpen Isabelle F.:** Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Perry Marieke:** Conceptualization, Formal analysis, Methodology, Supervision, Writing – original draft, Writing – review & editing. **Vernooij-Dassen Myrra:** Conceptualization, Funding acquisition, Methodology, Supervision, Writing – original draft, Writing – review & editing, Formal analysis. **Kas Martien J.H.:** Conceptualization, Formal analysis, Funding acquisition, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing. **Melis René:** Formal analysis, Methodology, Supervision, Writing – original draft, Writing – review & editing. **Eisel Ulrich L.M.:** Formal analysis, Investigation, Supervision, Writing – original draft, Writing – review & editing. **Vernooij Meike W.:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

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