Making DEEP Sense of Lifestyle Risk and Resilience

Gerd Kempermann

1 German Center for Neurodegenerative Diseases (DZNE), Dresden, Germany, 2 Center for Regenerative Therapies (CRTD) TU Dresden, Dresden, Germany

To effectively promote life-long health and resilience against – for example – neurodegenerative diseases, evidence-based recommendations must acknowledge the complex multidimensionality not only of the diseases but also of personal lifestyle. In a straightforward descriptive and heuristic framework, more than 50 potential lifestyle factors cluster around diet (D), education (E), exercise (E), and purpose (P), unveiling their many relationships across domains and scales. The resulting systematics and its visualization might be a small but helpful step toward the development of more comprehensive, interdisciplinary models of lifestyle-dependent risk and resilience and a means to explain the opportunities and limitations of preventive measures to the public and other stakeholders. Most importantly, this perspective onto the subject implies that not all lifestyle factors are created equal but that there is a hierarchy of values and needs that influences the success of lifestyle-based interventions.

Keywords: prevention, Alzheimer’s disease, neurodegeneration, public health, personal medicine

INTRODUCTION

Lifestyle-based health interventions promise solutions to pressing health problems by providing broad access to prevention and healthy aging. Preventing dementia is a prime target of these ambitions. After hundreds of failed clinical trials for treatments of neurodegenerative disease, especially of Alzheimer’s disease (AD) (Cummings et al., 2014), the insight has grown that neither conventional pharmacological targets nor immune-based strategies alone will be sufficient to conquer the problem at large. Some trials have thus reformulated their goal from curing manifest pathology to secondary prevention (Livingston et al., 2017).

This step is wise, because despite the failing therapeutic trials, within age-cohorts the risk for AD has been decreasing over the past decades (Derby et al., 2017). This “success” cannot be attributed to specific therapeutic interventions. Given that genetic factors did not change during this period, the decrease indicates that, in sum, modifiable factors must have exerted a measurable positive impact. As Fries et al. (2011) already wrote in 2011: “If we can accomplish morbidity compression without a strategy, as over the past thirty years, then we should be able to further improve if we have a plan.” How might such plan be developed?

Given the complexity of the subject, one critical prerequisite is to first systematize the available knowledge. This is necessary, because “lifestyle factors” are a category without sharp boundaries and a common definition but with many stakeholder-specific connotations.

The proposed DEEP framework is a simple way to support, yet not replace, this process across domains, disciplines, and stakeholders. It consists of common language descriptors that in the absence of a unifying theory and a comprehensive model of lifestyle-dependent risk and
resilience offer a systematic summary accessible to stakeholders across the professional disciplines and the public alike.

**Challenges of Lifestyle-Based Interventions**

“Resilience” is here defined as the comprehensive ability to deal with adversity. Resilience is here not explicitly distinguished from “resistance,” which is often used to specifically identify the ability to ward off pathology. The term “lifestyle factors for risk and resilience” is a heuristic concept to structure the large group of potentially modifiable factors with proven or face value influence on health, that at least in theory can be influenced by the individual by his or her own actions. Actions based on these factors increase or decrease risk and reduce or promote resilience. Low levels of physical activity, for example, are associated with a shorter life expectancy and the increased incidence of cardiovascular disease, cancer, neurodegeneration, and other health issues (Lee et al., 2012); being physically active in turn reduces those risks and prolongs life (Schnohr et al., 2013). This duality might suggest the existence of an equilibrium that could or should be obtained and maintained.

The general usefulness of the term “lifestyle factors” notwithstanding, the heterogeneity of such factors and the conceptual and practical difficulty of capturing what people more broadly mean by “lifestyle” endanger the concept to become either too diffuse or too narrow. While in a scientific study context, lifestyle might have to be reduced to a manageable number of variables that can be measured and that show statistically significant correlations with outcome measures of interest (as well as relevant effect sizes), be it for example longevity or disease-free years, it is not trivial to answer the question of how these variables actually contribute to subjective “lifestyle.” The term “style” refers to this “how” and to rather personal ideas of “leading a good life.” “Lifestyle” is obviously much more than the sum of identifiable “lifestyle factors.”

To understand the impact of lifestyle it is thus not advisable to restrict consideration to only those factors for which the “best” evidence (i.e., large effect sizes in population studies) exists, such as those in the SNAP scheme, which only covers smoking, nutrition, alcohol, and physical activity (Noble et al., 2015). A consensus publication in Lancet Neurology from 2017 highlighted nine factors (Livingston et al., 2017), which essentially match with other consensus lists (Deckers et al., 2015). They are also by and large identical to the set of factors that has been identified for longevity and the prevention of other, mostly age-related diseases, including cancer. The WHO lists eight such general factors plus four more specific to dementia (World Health Organization, 2017). In 2019, the WHO issued guidelines on these factors and supported its recommendations with detailed systematic reviews (World Health Organization, 2019). While this was an important step, the WHO has also been criticized for including recommendations with relatively weak evidence (management of hypertension and diabetes), while omitting other factors with potential benefit and low risks of side effects (treatment of hearing loss and depression) (Lancet, 2019). It was felt that the WHO had missed an opportunity to make even stronger statements for of public health and wake up governments to take the necessary actions. Moreover, in this domain and given the type of existing studies, it is problematic to base recommendations solely on best evidence as generated by clinical studies. The absence of evidence is also here no evidence of absence.

In addition, studies by necessity have to single out identifiable factors for the sake of design, feasibility, and statistical power. There are also first combinatorial and multi-domain studies such as the FINGERS trial (Ngandu et al., 2015) or the SMARTT trial (Yaffe et al., 2018). Even the most comprehensive multidomain study, however, will neither be able to capture the emerging qualities of actual lifestyle nor the one aspect that most people will intuitively value most: that this is their own chosen way of leading their life. The question of how to translate under such conditions from a study setting into everyday life remains extremely challenging.

**The DEEP Framework**

Dependent on stringency and definitions, at least 50 lifestyle risk and resilience factors can be identified (Table A1), that to a variable extent have been discussed in the literature. In this situation of an overabundance of potentially relevant aspects, a simple conceptual framework would facilitate knowledge management, promote sense-making in face of this complexity, and stimulate the development of more sophisticated and causal models across stakeholders, domains, and disciplines. A knowledge management framework can greatly support organization of lifestyle factors in their relations to each other and to larger-scale concepts such as “quality of life,” “well-being,” “happiness,” or, of course, “lifestyle” itself. The DEEP scheme visualizes key relationships between the large number of known (as well as perceived and hypothesized) lifestyle risk and resilience factors (Figures 1A,B).

Basis of the framework is a four-field matrix with Body and Mind as columns and Input and Output as rows (Figure 1A). “Diet” (D) would stand for bodily, physical intake and “Education” (E) for sensory, cognitive, and emotional input. “Exercise” (E) represents the domain of physical activity in the broadest sense, while the “Purpose” (P) quadrant is everything that relates between individual’s inner and outer world through his or her own actions. In other words, the four quadrants are related to (Line 1) what we take in (D) physically and (E) cognitively and (Line 2) what we spend (E) physically and (P) cognitively. This captures what essentially all more or less intuitive and research-based advice in this area tells us: Eat well (D), be physically and cognitively active (E+P), and engage (P). Labels for the quadrants and their explanation are emblematic and should not be taken too narrowly: “education,” for example, here stands for mental activity and function in a much broader sense than many scholarly definitions suggest. “Purpose” stands for socially and mentally (or even spiritually) goal-directed activities. The labels are associative anchors, permitting to bring structure into the widest possible scope. It is important not to over-define these categories.

The lifestyle factors, for whose effectiveness we have the best evidence, are some with the highest level of abstraction but with good measurability such as body weight or glucose levels.
Education or physical activity cannot be measured directly but usually only be assessed via reductionist proxies (e.g., VO\textsubscript{2}max for bodily fitness or self-reporting). For some factors in the P quadrant even qualitative proxies are a problem. The P quadrant contains items that we would consider essentially human and which are determinants of well-being. To base our understanding of lifestyle solely on the relatively few quantifiable factors with “significant” effect sizes is as obviously incomplete as ascribing the genetic risk of complex disease only to the common polymorphisms with large effect sizes. Much like the “missing heritability” in the genetics of complex traits (Manolio et al., 2009), a large number of modifiable factors with small effect sizes and poor detectability will add up to explain a very large part of the total interindividual variance in lifestyle.
risk and resilience. As much as complex traits are “omnigenic” (Boyle et al., 2017), lifestyle-dependent risk and resilience will be “omni-factorial.”

Appreciating complexity is not per se an argument against pursuing lower hanging fruits, i.e., by implementing exercise programs, improving school food, and quit smoking (Norton et al., 2014). These are difficult enough. But while to reduce time spent sitting would be a valuable step forward, regularly standing up at work does not really amount to a different lifestyle. Changing one’s life requires more than working down a check-list of good arguments.

The descriptive inclusiveness is also no argument against applying rigor and the full range of reductionistic instruments of evidence-based medicine to study the individual factors! Those approaches are mandatory for understanding effect sizes, weights of factors, and interaction effects.

**THE (P) PURPOSE QUADRANT**

Descriptions of lifestyle factors that are centered on diet, exercise, and cognitive activity/education might leave a blind spot exactly where many people would intuitively focus, when asked what matters most in life. Here, social and spiritual aspects rank very high: family and friends as well as mental and religious life, purpose, and autonomy. Certain “lifestyle” risk and resilience factors correspond to this preference: remaining in charge, the role of partnership and friendship, spirituality and religion, taking responsibility for others, etc. Such factors might exert a measurable impact: for example, positive beliefs about aging more or less compensated for the increased risk for AD associated with carrying the ApoEε4 polymorphism (Levy et al., 2018).

The dimension of Purpose-related factors is nevertheless often missing from the high-level aggregation in the discussion of “healthy lifestyle,” presumably because the evidence for these factors does not match the standards (of quantification) in the other domains. But for most people “health” in the sense of the medical professions is no end in itself. They intuitively have a broader, more implicit understanding, seamlessly integrating with “quality of life”: Leading a healthy life is more than the absence of disease. The concept of “successful aging,” otherwise not without its own problems (Bowling and Dieppe, 2005), can add this missing dimension.

**RELATIONSHIPS**

In the DEEP scheme, key relationships between domains are emphasized and the communality of lifestyle factors, to which many studies have pointed (Norton et al., 2014), are visible across the entire range of factors, independent of their nature. The scheme is thereby highly interdisciplinary and generous toward different scientific cultures. This is important, because no single discipline covers the full range of contributing factors.

The four quadrants can be paired in various, non-exclusive combinations (Figure 1C). The scheme thereby not only spans out between body and mind and input and output, but at the same time self and social, energy and information, reception and action, quantity and quality, etc. The challenge is to conceptualize, model, and measure such complex relationships and avoid pitfalls (Kempermann, 2017). The secret for livable strategies for successful (cognitive) aging based on lifestyle risk and resilience factors might foremost lie in the individual manifestation of these relationships. Neither represent these ranges dichotomies nor are the tension fields they establish orthogonal to each other. They are rather exemplary forces weaving a matrix of interdependencies.

Some of such interdependencies are known better than others and a few are widely acknowledged: the most obvious might be the relationship between energy intake and physical activity. Many studies calculate communalities, but what these interdependencies ultimately mean is rarely explored, especially for factors that are not linked in a way as obvious as in the case of caloric intake and expenditure. The classical triangle of (Mediterranean) diet, physical exercise, and cognitive activity/education also emphasizes potential links, but takes only three (albeit very important ones) out of an extensive network.

The step from the mere description in the DEEP scheme to a model of the network of factors requires different sets of data than presently available in most cases. Multivariate cohort studies, observational or interventional, can generate such data sets, if they collect information across all four DEEP quadrants.

**The Question of Perspective**

The discrepancy between lifestyle in the public-health-centered sense of recommendations and programs for prevention (mostly found in the DEE quadrants) and in what most people would see as integral parts of their personal lifestyle (represented by the P quadrant) might help to explain why the implementation of lifestyle interventions is so difficult. Recommendations based primarily on what can be measured (body weight, blood pressure, caloric intake, VO₂max, etc.) see lifestyle largely through the filter of basic needs. While these are critical foundations of lifestyle they only partly coincide with our personal hierarchy of needs.

Maslow’s hierarchy of needs, usually displayed in form of a pyramid, remains a very popular means to visualize the essential observation that we differently value the driving forces behind our actions and, by extension, our lifestyle (Maslow, 1954). Various versions exist. Figure 1D depicts a variant from the coaching literature (Loehr and Schwartz, 2005), underscoring that such concepts are widely applied in professions that aim at empowering people to master change. People tend to favor a view that moves from the fulfillment of basic needs toward personal growth, self-actualization, and self-transcendence. While the depiction as pyramid somewhat blurs the fact that motivations arising from many different layers are effective concomitantly and synergistically, its suggestive strengths lie in the identification of an order and a hierarchical value we assign to them. A pyramid of needs, tilted by 120°, superimposed on the DEEP scheme, reveals that within the scope of lifestyle factors there is a hidden hierarchy of values.

Recommendations focusing on what can be measured might hence come across as superficial and trivial (Figure 1E). Emphasizing only the P quadrant is no valid solution either, because those strategies lack the concreteness of the physical
dimension they have to build upon. But P might provide the drive to implement DEE.

DEEP Implementations
This implies that a holistic consideration of lifestyle risk and resilience factors along the DEEP scheme might help to develop causal models as basis of individualized strategies for healthy (cognitive) aging and the prevention of (neurodegenerative) disease. Interventions with large demonstrated effect sizes would obviously still be prioritized, but their practical realization and their contextual embedding would be improved by individualized multi-factorial approaches.

Physical activity, for example, remains the preventive “super factor” with massive effect sizes across many domains. Realizing its potential alone would profoundly change health and disease in any population. And most people know that they should (and actually would like to) be more physically active: there is no lack of insight and intentions. The implementation, however, of seemingly simple interventions based on reducing sedentary lifestyle and increasing physical activity is extremely difficult. Exercise-based programs often show remarkably little long-term effects on lifestyle. The same applies to nutritional recommendation, which are popular and often have high face validity. But dietary interventions are notoriously difficult to study, the underlying metabolic mechanisms to which these interventions refer show great inter-individual genetic differences, and eating food is much more than nutrition.

Measures centering only on single or few habits become isolated from the contexts of the individual’s life. New habits that were formed in the lab lack anchoring in everyday life.

Good and bad habits are context-sensitive and circumstances trigger habitual behaviors. Changing habits is difficult, if the world around us reinforces them. The question is, to which extent circumstances can be changed. While there is no general answer to this, there will be room for individual solutions that adapt lifestyle to conditions at hand and explore the available room for development. The DEEP scheme visualizes the scope of such co-factors.

What Lies at the Center?
The large cohort studies and meta-analyses indicate that the identifiable factors with large effect sizes are not independent of each other. On one side this suggests that an abstract “super factor” might be identifiable, comparable to the G factor in intelligence.

On the other hand, however, the communalities also indicate that there is more than one road to Rome. They might hide the range of options for the individual to achieve his or her goals.

The DEEP scheme might suggest that the greatest reduction in risk and the greatest level of resilience is found in individuals with a somewhat balanced nature within and between the four quadrants (Figure 1E). How would such balance relate to “quality of life”? While assessment of quality of life constitutes a major achievement in selecting appropriate, relevant “endpoints” of clinical studies, they are only surrogates for even more profound constructs such as happiness. Is a resilient individual also a happier individual? If so, what would be the direction of causality here? Positive psychology suggests that happiness can to some degree be induced. If “style” is an emerging property from the complexity of life, then so is happiness. An important question thus is, whether the assumed causality structure and interventional strategy can be put on its head. Is it possible to improve happiness and quality of life and see changes in measurable lifestyle factors as consequence or byproduct? Or, is the true center an attitude such as to “develop character in the face of the inevitable suffering,” as Peterson (2018) has put it, and thereby consider style of life in the light of giving meaning to life?

Working from the center and the intended result of “leading a good life,” including the full spectrum of our needs and values, is one way of altering contexts to our benefit. Ironically, despite being much more complex, multi-factorial changes might be more successful and ultimately easier: small steps at a time, but along different directions (as indicated in the many options of the DEEP scheme), might ultimately be more efficient and effective than focusing on one high-gain domain alone. They would lead to a diversification of the individual portfolio of lifestyle risk and resilience.

DATA AVAILABILITY
No datasets were generated or analyzed for this study.

AUTHOR CONTRIBUTIONS
GK conceived the concept presented in this article, collected the relevant information, and wrote the manuscript.

FUNDING
This work was partly funded with support of the Helmholtz Network of Excellence for writing and publication of the article. The funder did not exert any influence on the content of this article.

REFERENCES
Agli, O., Bailly, N., and Ferrand, C. (2015). Spirituality and religion in older adults with dementia: a systematic review. Int. Psychogeriatr. 27, 715–725. doi: 10.1017/S1041610214001665
Ahlskog, J. E., Geda, Y. E., Graff-Radford, N. R., and Petersen, R. C. (2011). Physical exercise as a preventive or disease-modifying treatment of dementia and brain aging. Mayo Clin. Proc. 86, 876–884. doi: 10.4065/mcp.2011.0252
Allen, M. S. (2018). Sexual activity and cognitive decline in older adults. Arch. Sex Behav. 47, 1711–1719. doi: 10.1007/s10508-018-1193-8
Anstey, K. J., Ashby-Mitchell, K., and Peters, R. (2017). Updating the evidence on the association between serum cholesterol and risk of late-life dementia: review and meta-analysis. J. Alzheimers Dis. 56, 215–228. doi: 10.3233/JAD-160826
Anstey, K. J., Cherbuin, N., Budge, M., and Young, J. (2011). Body mass index in midlife and late-life as a risk factor for dementia: a meta-analysis of prospective studies. Obes. Rev. 12, e426–e437. doi: 10.1111/j.1467-789X.2010.00825.x

Sobia, S., Fayosse, A., Dumurgier, J., Dugravot, A., Akbaraly, T., Britton, A., et al. (2018). Alcohol consumption and risk of dementia: 23 year follow-up of Whitehall II cohort study. BMJ 362, k2927. doi: 10.1136/bmj.k2927

Samieri, C., Perier, M.-C., Gaye, B., Proust-Lima, C., Helmer, C., Dartigues, J. F., et al. (2018). Association of cardiovascular health level in older age with cognitive decline and incident dementia. JAMA 320, 657–664. doi: 10.1001/jama.2018.11499

Schnohr, P., Marott, J. L., Lange, P., and Jensen, G. B. (2013). Longevity in male and female joggers: the Copenhagen city heart study. Am. J. Epidemiol. 177, 683–689. doi: 10.1093/aje/kws301

Schwarzinger, M., Pollock, B. G., Hasan, O. S. M., Dufouil, C., Rehm, J., and Sabia, S., Fayosse, A., Dumurgier, J., Dugravot, A., Akbaraly, T., Britton, A., Kempermann. The DEEP Framework

Sharp, E. S., and Gatz, M. (2011). Relationship between education and cognitive decline: a randomized clinical trial. JAMA Intern. Med. 89, 22–27. doi: 10.1001/jamainternmed.2015.008565

Terracciano, A., Stephan, Y., Luchetti, M., Albanese, E., and Sutin, A. R. (2017). Personality traits and risk of cognitive impairment and dementia. J. Psychiatr. Res. 89, 22–27. doi: 10.1016/j.jpsychires.2017.01.011

Valls-Pedret, C., Sala-Vila, A., Serra-Mir, M., Corella, D., Torre de, R., Martínez-González, M. Á., et al. (2015). Mediterranean diet and age-related cognitive decline: a randomized clinical trial. JAMA Intern. Med. 175, 1094–1103. doi: 10.1001/jamainternalmed.2015.1668

Van Ness, P. H., and Kasl, S. V. (2003). Religion and cognitive dysfunction in an elderly cohort. J. Gerontol. B Psychol. Sci. Soc. Sci. 58, S21–S29.

Verghese, J., Lipton, R. B., Katz, M. J., Hall, C. B., Derby, C. A., Kuslansky, G., et al. (2003). Leisure activities and the risk of dementia in the elderly. N. Engl. J. Med. 348, 2508–2516. doi: 10.1056/NEJMoa022252

Weng, P.-H., Chen, J.-H., Chiu, J.-M., Tu, Y.-K., Chen, T.-F., Chu, M.-J., et al. (2018). The effect of lifestyle on late-life cognitive change under different socioeconomic status. PLoS One 13:e0197676. doi: 10.1371/journal.pone.0197676

Wilson, R. S., Bennett, D. A., Bienias, J. L., Aggarwal, N. T., Mendes De Leon, C. F., Morris, M. C., et al. (2002). Cognitive activity and incident AD in a population-based sample of older persons. Neurology 59, 1910–1914. doi: 10.1212/01.wnl.0000036905.59156.a1

Wilson, R. S., Boyle, P. A., Yu, L., Barnes, L. L., Schneider, J. A., and Bennett, D. A. (2013). Life-span cognitive activity, neuropathologic burden, and cognitive aging. Neurology 81, 314–321. doi: 10.1212/WNL.0b013e31829c5e8a

World Health Organization (2017). Global Action Plan on the Public Health Response to Dementia. Geneva: World Health Organization, 2017–2025.

World Health Organization (2019). Risk Reduction of Cognitive Decline and Dementia. Geneva: World Health Organization, 1–96.

Wright, H., and Jenkins, R. A. (2016). Sex on the brain! Associations between sexual activity and cognitive function in older age. Age Ageing 45, 313–317. doi: 10.1093/ageing/afv197

Yaffe, K., Barnes, D. E., Rosenberg, D., Dublin, S., Kaup, A. R., Ludman, E. J., et al. (2018). Systematic Multi-Domain Alzheimer’s Risk Reduction Trial (SMARTT): study protocol. JAD 13, 1–14. doi: 10.3233/JAD-180634

Zammit, A. R., Robitaille, A., Piccinin, A., Muniz-Terrera, G., and Hofer, S. M. (2018). Associations between aging-related changes in grip strength and cognitive function in older adults: a systematic review. J. Alzheimers Dis. 39, 271–282. doi: 10.3233/JAD-130830

Singh-Manoux, A., Dugravot, A., Fournier, A., Abell, J., Ebmeier, K., Kivimäki, M., et al. (2017). Trajectories of depressive symptoms before diagnosis of dementia: a 28-year follow-up study. JAMA Psychiatry 74, 712–718. doi: 10.1001/jamapsychiatry.2017.0660

Stanmore, E., Stubbs, B., Vancampfort, D., de Bruin, E. D., and Firth, J. (2017). The effect of active video games on cognitive functioning in healthy adults. PLoS One 10, e0118333. doi: 10.1371/journal.pone.0118333

Conflict of Interest Statement: The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright © 2019 Kempermann. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.
### APPENDIX

| Quote from the report | Type of study | References | Remarks |
|-----------------------|--------------|------------|---------|
| **D Diet**            |              |            |         |
| Smoking is associated with an increased risk of dementia. | Meta-analysis | Zhong et al., 2015 |         |
| Elderly smokers have increased risks of dementia and cognitive decline. | Meta-analysis of prospective studies | Anstey et al., 2007 |         |
| **Avoid environmental risk factors** (+) | Systematic review | Killin et al., 2016 |         |
| There is at least moderate evidence implicating the following risk factors: air pollution, aluminium, silicon, selenium, pesticides, vitamin D deficiency, and electric and magnetic fields. |            |            |         |
| **Avoid air pollution from traffic** (+) | Population-based cohort, $n = 6.6$ mio | Chen et al., 2017 |         |
| Living close to heavy traffic was associated with a higher incidence of dementia, but not with Parkinson’s disease or multiple sclerosis. |            |            |         |
| **No substance abuse** (+) | Post-mortem case–control study | Ramage et al., 2005 |         |
| Hyperphosphorylated tau and amyloid precursor protein deposition is increased in the brains of young drug abusers. | | |         |
| Former use of benzodiazepines could be a risk factor for dementia. | Nested case–control study | Lagnaux et al., 2002 |         |
| Benzodiazepine use is associated with an increased risk of Alzheimer’s disease (AD). | Case–control study | Billioti de Gage et al., 2014 |         |
| Out of the 10 studies retrieved, 9 reported an increased risk of dementia in benzodiazepine users. | Systematic review | Billioti de Gage et al., 2015 |         |
| **Moderate alcohol consumption** (+) | Systematic review | Cheng et al., 2017 |         |
| High proportion of alcohol-related dementia in early-onset dementia. | | |         |
| **Describe additional alcohol-related findings here.** | Prospective cohort study (19 years, 6500 participants) | Kuzma et al., 2014 |         |
| Middle-aged adults with a history of alcohol use disorders have increased odds of developing severe memory impairment later in life. | | |         |
| Alcohol use disorders were a major risk factor for onset of all types of dementia, and especially early-onset dementia. | Retrospective cohort study (20 years, 31 Mio. patients) | Schwarzinger et al., 2018 |         |
| The results show a greater risk of dementia in those who abstain from alcohol or consume $> 14$ units/week, with risk increasing in a linear fashion at higher levels of consumption. | Prospective cohort study (23 years, $n = 9000$) | Sabia et al., 2018 | One of the key studies supporting the idea that low alcohol consumption might be beneficial. |
| **Caffeine and tea consumption** (+) | Systematic review | Panza et al., 2015 |         |
| Several cross-sectional and longitudinal population-based studies suggested a protective effect of coffee, tea, and caffeine use against late-life cognitive impairment/decline. | | |         |

(Continued)
| Quote from the report                                                                 | Type of study                                | References                   | Remarks                                                                 |
|-------------------------------------------------------------------------------------|----------------------------------------------|------------------------------|------------------------------------------------------------------------|
| (+) Daily tea drinking is associated with decreased risk of cognitive impairment, MCI, and cognitive decline in the elderly. However, the association between tea intake and AD remains elusive | Meta-analysis, 52,503 participants           | Ma et al., 2016              |                                                                          |
| Sufficient hydration*                                                                | Review                                       | Masento et al., 2014         | Drinking sufficient amounts of water is a popular advice, but backed by limited evidence. Because dehydration promotes delirium and thus can aggravate dementia, especially in care settings, this factor nevertheless has good face validity. |
| Vitamins, trace elements, antioxidants                                               | Systematic literature research and meta-analysis | Etgen et al., 2011           |                                                                          |
| + Within the range of a habitual dietary intake, higher intake of lignans is associated with less cognitive decline at middle age. | Retrospective cohort study                   | Nooyens et al., 2015         | Example of the large class of polyphenols.                             |
| ? Findings do not consistently show habitual intakes of dietary antioxidants and are associated with better cognitive performance or a reduced risk for dementia. | Systematic review                            | Crichton et al., 2013        | The WHO found the available evidence sufficient to recommend against the use of vitamin substitution in its 2019 guidelines. |
| + Vitamin E intake, from foods or supplements, is associated with less cognitive decline with age. There was little evidence of association with vitamin C or carotene intake. | Longitudinal population-based study          | Morris et al., 2002          |                                                                          |
| Medit./balanced diet                                                                 | Randomized clinical trial                    | Valls-Pedret et al., 2015    |                                                                          |
| + In an older population, a Mediterranean diet supplemented with olive oil or nuts is associated with improved cognitive function. | Systematic review                            | Singh et al., 2014           |                                                                          |
| Controlled blood lipids                                                              | Meta-analysis, \( n = 23,338 \)              | Anstey et al., 2017          |                                                                          |
| + Significant gaps in the literature regarding total cholesterol and late-life dementia remain. Evidence suggests that high midlife total cholesterol increases risk of late-life AD, and may correlate with the onset of AD pathology. |                                                                                   |                              |                                                                          |
| Controlled glucose metabolism                                                        | Prospective study                            | Crane et al., 2013           |                                                                          |
| + Higher glucose levels may be a risk factor for dementia, even among persons without diabetes. |                                                                                   |                              |                                                                          |
| Controlled body weight                                                               | Meta-analysis of 15 prospective studies, \( n = 15,435 \) | Anstey et al., 2011          |                                                                          |
| + Underweight, overweight, and obesity in midlife increase dementia risk.             | Review                                       | Emmerzaal et al., 2015       |                                                                          |
| + Studies investigating the association between midlife BMI and risk for dementia demonstrated generally an increased risk among overweight and obese adults. When measured in late-life, elevated BMI has been associated with lower risk. In addition, being underweight and/or having a decrease in BMI in late-life are associated with higher dementia risk compared to BMI in the normal range or stable BMI. |                                                                                   |                              |                                                                          |
| Quote from the report | Type of study | References | Remarks |
|-----------------------|--------------|------------|---------|
| + Being underweight in middle age and old age carries an increased risk of dementia over two decades. | Retrospective cohort study, \( n = 2 \) million | Qizilbash et al., 2015 | Controversial study that contradicts some conclusions from other studies in that no effect of overweight was reported. |
| Hormone replacement | - Estrogen plus progestin therapy increased the risk for probable dementia in postmenopausal women aged 65 years or older. In addition, estrogen plus progestin therapy did not prevent mild cognitive impairment in these women. These findings, coupled with previously reported WHI data, support the conclusion that the risks of estrogen plus progestin outweigh the benefits. | Shumaker et al., 2003 | There is still considerable controversy regarding this conclusion, but there is no clear evidence in favor of the idea that hormone therapy lowers the risk for dementia. |
| **Exercise** | | | |
| **Controlled blood pressure** | +/− There is no convincing evidence from the trials identified that blood pressure lowering in late-life prevents the development of dementia or cognitive impairment in hypertensive patients with no apparent prior cerebrovascular disease. | Meta-analysis (Cochrane), \( n = 15,936 \) | McGuinness et al., 2009 | No clear case can yet be made for interventions at older age. |
| | + Elevated blood pressure during midlife, persistence of elevated blood pressure into late life, and, among non-hypertensives, a steep decline in blood pressure during mid- to late-life were associated with an increased dementia risk in a community-based cohort. Our data highlight the potential sustained cognitive benefits of lower blood pressures in mid-life and also suggest that declining blood pressure in older adults with prehypertension or normotension, but not in those with hypertension, may be a risk marker for dementia. | Retrospective study, \( n = 1440 \) | McGrath et al., 2017 | This study highlights the complex relationship between control of blood pressure and the risk of dementia. |
| | + In this cohort of older adults, increased numbers of optimal cardiovascular health metrics and a higher cardiovascular health score were associated with a lower risk of dementia and lower rates of cognitive decline. These findings may support the promotion of cardiovascular health to prevent risk factors associated with cognitive decline and dementia. | Population-based cohort study; \( n = 6626 \) | Samieri et al., 2018 | |
| Reduce TV consumption | + High television viewing and low physical activity in early adulthood were associated with worse midlife executive function and processing speed. | Prospective 25-year study | Hoang et al., 2016 | TV consumption represents the largest part of average sedentary behaviors. |
| Non-exercise activity thermogenesis (NEAT)* | (+) NEAT is a highly variable component of daily total energy expenditure and a low level of NEAT is associated with obesity. NEAT enhances lifestyle, and variations in individual and environmental factors can significantly affect daily energy expenditure. | Review | Chung et al., 2018 | No data directly related to neurodegeneration and brain function exist. |
| Avoid head injury | + Although further research is needed, these 10 findings suggest that dose-dependent effects of violent head displacement in vulnerable brains predispose to dementia. | Review | Mendez, 2017 | (Continued) |
| Quote from the report | Type of study | References | Remarks |
|-----------------------|--------------|------------|---------|
| (+) Meta-analysis revealed a significant association of prior TBI with subsequent dementia. | Meta-analysis, n = 3,263,207 | Huang et al., 2018 | The authors come to the opposite conclusion because the effect here disappeared for individual neurodegenerative diseases (Simpson's paradox). |
| + History of TBI, including mild TBI, is associated with the development of neurological and psychiatric illness. This finding indicates that either TBI is a risk factor for heterogeneous pathological processes or that TBI may contribute to a common pathological mechanism. | Meta-analysis | Perry et al., 2016 | Increased pooled odds ratios for “dementia,” Parkinson’s disease, AD, and other disorders. |
| Prevent falls* (+) n/a n/a n/a | Preventing the disabling consequences of falls supports the positive effects of physical activity. Currently no studies exist on falls as modifiable risk factor for neurodegeneration. |
| Balance training (+) Balance training intervention […] was effective in improving balance and mobility, […] Cognition did not decline during the course of the intervention but did decline following the intervention, suggesting a possible protective effect. | Prospective study | Ries et al., 2015 |
| Physical activity + Meta-analyses of prospective studies documented a significantly reduced risk of dementia associated with midlife exercise; similarly, midlife exercise significantly reduced later risks of mild cognitive impairment in several studies. | Review of meta-analyses and other reports | Ahlskog et al., 2011 |
| + We found a higher level of physical activity to be associated with a lower risk of dementia. | Prospective, population-based study (Rotterdam Study), n = 4406 | de Bruijn et al., 2013 | One of the key long-term population studies, supporting the claim. |
| + This meta-analysis suggests that physical activity interventions positively influence cognitive function in patients with dementia. | Meta-analysis, n = 802 | Groot et al., 2016 |
| Muscular strength training (+) All studies concluded that cognitive function and grip strength declined, on average, with increasing age, although with little to no evidence for longitudinal associations among rates of change. | Systematic review | Zammit et al., 2018 |
| + High-intensity progressive resistance training results in significant improvements in cognitive function, muscle strength, and aerobic capacity in older adults with MCI. Strength gains, but not aerobic capacity changes, mediate the cognitive benefits of progressive resistance training. | Randomized, double-blind, double-sham controlled trial; n = 100 | Mavros et al., 2017 |
| + Resistance training significantly improved global cognitive function, with maintenance of executive and global benefits over 18 months. | Randomized, double-blind, double-sham controlled trial; n = 100 | Fiatarone Singh et al., 2014 |

(Continued)
| **Type of study** | **References** | **Remarks** |
|------------------|----------------|-------------|
| **Exergames (physically active video games)** | Exergames significantly improved global cognition. | Meta-analysis of 17 randomized controlled trials, n = 926 | Stanmore et al., 2017 | Control groups are physically active. |
| **Walking groups** | Walking groups are effective and safe with good adherence and wide-ranging health benefits. | Systematic review and meta-analysis, 1843 patients, including PD patients | Hanson and Jones, 2015 | Outcome measure: general health, depression score, VO2max. It is unclear, at present, how much of the observed effect can be attributed to physical activity per se rather than the social aspect of this activity. |
| **Flexibility training** | n/a | n/a | n/a | Flexibility is one of the three pillars of physical activity (besides endurance and strength), but its contribution to prevention of dementia and neurodegeneration has not yet been studied. |
| **Tai Chi** | Compared with usual physical activities, Tai Chi shows potential protective effects on healthy adults’ cognitive ability. | Systematic review of prospective controlled trials, n = 632 | Zheng et al., 2015 | |
| **Sexual activity** | There were significant associations between sexual activity and number sequencing and recall in men. | Cross-sectional study, n = 6833, two tests of cognitive functioning | Wright and Jenks, 2016 | Protective effects of sexual activity are a popular assertion in the media with a certain face validity and some evidence from studies, but currently still backed by insufficient data. |
| **Meditation and mindfulness** | All studies reported significant increases in gray matter volume in the meditators/intervention group, albeit in assorted regions of the brain. Limited research exists on the mechanisms through which meditation affects disease-related neurodegeneration, but preliminary evidence suggests that it may offset gray matter atrophy. | Review | Last et al., 2017 | |
| **Avoid stressors** | Higher event-based stress ratings collected over the follow-up period were associated with faster cognitive decline in subjects with mild cognitive impairment but not in cognitively normal subjects. | Prospective study, n = 52 | Peavy et al., 2009 | |
| **Yoga** | Based on the available literature, it could be concluded that yoga might be considered as an effective adjuvant for the patients with various neurological disorders. | Review | Mooventhan and Nivethitha, 2017 | |
| **Music and dance** | Playing a musical instrument was significantly associated with less likelihood of dementia and cognitive impairment. | Twin study, n = 157 twins | Balbag et al., 2014 | |
| Type of study                                      | References                      | Remarks                                                                 |
|--------------------------------------------------|---------------------------------|-------------------------------------------------------------------------|
| + Recent and past musical activity, but not general lifestyle activities, predicted variability across both verbal and visuospatial domains in aging. Early age of musical acquisition, sustained and maintained during advanced age, may enhance cognitive functions and buffer age and education influences. | Cross-sectional case control study, n = 70 | Hanna-Pladdy and Gajewski, 2012                                           |
| + Among leisure activities, reading, playing board games, playing musical instruments, and dancing were associated with a reduced risk of dementia. | Prospective cohort, n = 469 | Verghese et al., 2003                                                   |
| + Sleep disturbances may predict the risk of incident dementia. | Systematic review and meta-analysis, n = 246,786 | Shi et al., 2018                                                        |
| (+) Increases in dementia risk were also observed with [...] night-time noise levels. | Retrospective cohort study, n = 130,978 | Carey et al., 2018                                                      |
| ? When completed in 2022, Aging and cognitive health evaluation in elders study should provide definitive evidence of the effect of hearing treatment versus education control on cognitive decline in community-dwelling older adults with mild-to-moderate hearing impairment. | Multicenter randomized controlled trial, n = 850 | Deal et al., 2018                                                      |
| + Hearing loss is independently associated with accelerated cognitive decline and incident cognitive impairment in community-dwelling older adults. | Prospective observational study, n = 1984 | Lin et al., 2013                                                       |
| + Comparing participants with moderate/severe hearing impairment to participants with no hearing impairment, 20-year rates of decline in memory and global function differed by −0.47 standard deviations (P = 0.02) and −0.29 standard deviations (P = 0.02), respectively. Estimated declines were greatest in participants who did not wear a hearing aid. | Cross-sectional and longitudinal analysis in a prospective study, n = 253 | Deal et al., 2015                                                      |
| (+) Lower education was associated with a greater risk for dementia in many but not all studies. The level of education associated with risk for dementia varied by study population and more years of education did not uniformly attenuate the risk for dementia. It appeared that a more consistent relationship with dementia occurred when years of education reflected cognitive capacity, suggesting that the effect of education on risk for dementia may be best evaluated within the context of a lifespan developmental model. | Systematic review | Sharp and Gatz, 2011                                                   |
| (+) Lifelong bilingualism confers protection against the onset of AD. | Retrospective study on AD patients, n = 211 | Craik et al., 2010                                                      |
| Childhood bilingualism, which has been assessed here, is not identical to the popular assertion that learning a new language later in life is protective! | | (Continued) |
| Quote from the report | Type of study | References | Remarks |
|----------------------|---------------|------------|---------|
| + Our results suggest a positive effect of bilingualism on later-life cognition, including in those who acquired their second language in adulthood. | Population-based cohort study, n = 853 | Bak et al., 2014 | Sixty-five participants learned the second language after the age of 18 years. |
| (+) We did not find that bilingualism protects from cognitive decline or dementia from prospective studies. | Systematic review and meta-analysis | Mukadam et al., 2017 | The conclusion is controversial, because the retrospective studies in the analysis did not show the association. |
| Reading | + Among leisure activities, reading, playing board games, playing musical instruments, and dancing were associated with a reduced risk of dementia. | Prospective cohort, n = 469 | Verghese et al., 2003 |
| Lifelong learning | + More frequent cognitive activity across the life span has an association with slower late-life cognitive decline. | Longitudinal cohort study, n = 294 | Wilson et al., 2013 |
| Cognitive stimulation | + Frequent participation in cognitively stimulating activities is associated with reduced risk of AD | Longitudinal cohort study (“Nun study”), n = 801 | Wilson et al., 2002 |
| Environmental enrichment | + The longitudinal evidence consistently shows that engaging in intellectually stimulating activities is associated with better cognitive functioning at later points in time. | Review | Hertzog et al., 2008 |
| Playing board games | + Among leisure activities, reading, playing board games, playing musical instruments, and dancing were associated with a reduced risk of dementia. | Prospective cohort, n = 469 | Verghese et al., 2003 |
| P Purpose | Volunteering | Systematic review | Jenkinson et al., 2013 |
| (+) Cohort studies showed volunteering had favorable effects on depression, life satisfaction, wellbeing but not on physical health. These findings were not confirmed by experimental studies. Meta-analysis of five cohort studies found volunteers to be at lower risk of mortality. | Population-based cohort study (registry study), n = 1001 | Griepp et al., 2017 |
| (+) Our results largely support the assumptions that voluntary work in later life is associated with lower self-reported cognitive complaints and a lower risk for dementia, relative to those who do not engage, or only engage episodically in voluntary work. | Panel survey, n = 13,262 | Infurna et al., 2016 |

(Continued)
| Quote from the report                                                                 | Type of study                        | References                        | Remarks                                                                 |
|--------------------------------------------------------------------------------------|--------------------------------------|-----------------------------------|-------------------------------------------------------------------------|
| Socio-economic status + Significant interactions were found between a healthful lifestyle (defined as having more than or equal to three healthful lifestyle factors) and income on changes of global cognition and verbal fluency [...]. The protective effect of a healthful lifestyle was observed only among participants with lower income in global cognition and logical memory [...]. | Prospective cohort study, \( n = 603 \) | Weng et al., 2018                                                      |                                                                 |
| +/- Occupational social class was not statistically significantly associated with dementia death in men or women. | Meta-analysis, of 11 prospective cohort studies, \( n = 86,508 \) | Russ et al., 2013                |                                                                 |
| Artistic and craft activities + The risk [of MCI] was reduced with engagement in artistic, craft, and social activities in both midlife and late life. | Population-based prospective cohort study, \( n = 256 \) | Roberts et al., 2015            |                                                                 |
| Spiritual life and religion (+) Study results show an inverse association between religious attendance in 1982 and cognitive dysfunction in 1985. | Population-based cohort study, \( n = 2812 \) | Van Ness and Kasl, 2003           |                                                                 |
| (+) Religious attendance may offer mental stimulation that helps to maintain cognitive functioning in later life, particularly among older depressed women. | Population-based cohort study, \( n = 2938 \) | Consentino et al., 2009          |                                                                 |
| (+) Spirituality and religion appear to slow cognitive decline, and help people use coping strategies to deal their disease and have a better quality of life. | Systematic review                      | Agli et al., 2015                |                                                                 |
| Spiritual life and religion (-) The prevalence of dementia was increased among men with exclusively religious education and among those with the most strict observance. In both cases, these associations were not altered appreciably after controlling for sociodemographic confounders. | Longitudinal cohort study (Israeli Ischemic Heart Disease study), \( n = 1628 \) | Beeri et al., 2008              | Personality traits are to some extent amenable to volitional change (Roberts et al., 2017). |
| Religious life-style (-) Using brief assessments of personality and cognition, we found robust evidence that personality is associated with risk of cognitive impairment and dementia in a large national sample. | Population-based, longitudinal study, \( n = 10,000 \) | Terracciano et al., 2017          |                                                                 |
| (+) Neuroticism increased risk for dementia, and conscientiousness reduced risk. The protective effect of openness was tentative. Extraversion and agreeableness were not associated with dementia. | Systematic review and meta-analysis, \( n = 3285 \) | Low et al., 2013                 | Relevance of intelligence as modifiable risk and resilience factor relies on the question, whether intelligence can be improved, which despite many claims to the contrary remains questionable (Haier, 2014). |
| Intelligence + Compared to the highest intelligence group \((\geq 115)\), dementia risk was raised in the lowest-scoring category \((<85)\) and these associations were stronger for women [...]. There was evidence of a dose–response association between childhood IQ and dementia in women [... but not in men [...]. | Population-based cohort study (1932 Scottish Mental Survey), \( n = 32,000 \) | Russ et al., 2017               |                                                                 |

(Continued)
TABLE A1 | Continued

| Quote from the report                                                                 | Type of study                     | References                          | Remarks                                             |
|--------------------------------------------------------------------------------------|-----------------------------------|-------------------------------------|-----------------------------------------------------|
| Positive attitudes toward aging                                                     | +                                 | Prospective cohort study            | Levy et al., 2018                                   |
|                                                                                      | In the total sample those with positive age beliefs at baseline were significantly less likely to develop dementia, after adjusting for relevant covariates. Among those with APOE ε4, those with positive age beliefs were 49.8% less likely to develop dementia than those with negative age beliefs. |                                                    |                                                     |
| Optimism                                                                             | +                                 | Prospective cohort study, n = 9568  | Gawronski et al., 2016                              |
|                                                                                      | Optimism was prospectively associated with a reduced likelihood of becoming cognitively impaired. |                                                    |                                                     |
| No or treated depression                                                             | +                                 | Review                              | Byers and Yaffe, 2011                               | The WHO found the available evidence insufficient to recommend treating depression in its 2019 guidelines. |
|                                                                                      | The literature suggests an association between depression and dementia, and growing evidence implies that timing of depression may be important to defining the nature of the association. |                                                    |                                                     |
|                                                                                      | Depressive symptoms in the early phase of the study corresponding to midlife, even when chronic/recurring, do not increase the risk for dementia. Along with our analysis of depressive trajectories over 28 years, these results suggest that depressive symptoms are a prodromal feature of dementia or that the two share common causes. The findings do not support the hypothesis that depressive symptoms increase the risk for dementia. | Singh-Manoux et al., 2017                       |                                                     |
|                                                                                      | Cross-sectional study, n = 779     | Poey et al., 2017                   | The WHO found the available evidence insufficient to recommend social activity in its 2019 guidelines. |
|                                                                                      | Feeling lonely rather than being alone is associated with an increased risk of clinical dementia in later life and can be considered a major risk factor. |                                                   |                                                     |
| Marital status                                                                       | +                                 | Population-based cohort study        | Helmer et al., 1999                                 |
|                                                                                      | We confirmed an association between marital status and AD, with an excess risk observed among never-married individuals. |                                               |                                                     |
|                                                                                      | Prosp ective cohort study, n = 2173 | Holwerda et al., 2014               |                                                      |
|                                                                                      | Those living alone as non-marrieds may be at risk for early-onset and late-onset dementia. | Sundström et al., 2016                |                                                      |
|                                                                                      | Prospective population-based study, n = 31,572 |                                               |                                                      |

In a few cases, references have been included that do not specifically deal with neurodegeneration, if the factor has been suggested in the context but no published study exists. The table provides an annotated reference list to the DEEP scheme and does not represent a systematic review of the subject. Bold text: modifiable risk factors according to WHO guideline (2019). The WHO publication also contains a systematic review of the evidence for these factors. *, factors with face validity that are found in popular media or are suggested by context; +, the literature supports a positive association; −, the literature supports a negative association; +/-, the literature indicates a variable association or neutrality; ?, evidence cannot be conclusively judged at this time.