The Role of Vascular-Metabolic Factors on Cognitive Impairment Workshop Report by the Campaign to Prevent Alzheimer's Disease and the Brain Watch Coalition

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Abstract

The grand challenge for healthcare systems worldwide is the escalating costs of prolonged care for older people with various chronic disabling disorders. Among these protracted brain incapacitating conditions, progressive deterioration of cognitive functions, different types of dementia, and Alzheimer's syndrome profoundly impact quality of life, economic and psycho-social, and burdens of family caregivers. This report provides an overview of the deliberations at a think-tank workshop organized by PAD2020 before the AAIC 2022 in July 2022. The participants of this forum included leading experts representing government, academia, industry, and the philanthropic sector. The overarching aim for convening this workgroup (WG) was to seek suggestions for a potential global action plan, a comprehensive public health initiative, aiming for a significant reduction in the incidence of cognitive impairment or dementia-Alzheimer syndrome. The future aim of this undertaking (specifically, the pending task of this WG) is to develop a roadmap for a coordinated large-scale effort to demonstrate the putative efficacy of reducing risks for cognitive impairment/dementia-Alzheimer syndrome via existing interventions for modifiable risks of vascular-metabolic disorders. The primary rationale for such global action plans is that a practical, broad-scale approach to this growing public health crisis problem will substantially reduce the demand and cost for prolonged personalized care of people with dementia. The proposed initiative will require a greater focus on research and investments in therapeutic strategies to delay the onset of cognitive impairment and reduce dementia-related morbidity. Such an approach would emphasize addressing modifiable risks for dementia with affordable, accessible interventions that target modifiable risks for vascular and metabolic disorders likely to result in the most tremendous success.

Keywords: **Healthcare systems, chronic disorders, personal autonomy, dementia, Alzheimer's disease, pragmatic trials, randomized group design, vascular-metabolic disorders, health equity, population public health.**

VM&E 2023;6:17-22
Published online October 27, 2023
http://dx.doi.org/10.14283/VME.2023.3

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Introduction and Context

Although the aspiration for a world without *dementia-Alzheimer syndrome*[1] is the ultimate long-range goal of public health services worldwide, a more pragmatic near-term objective is the development-validation of wide-ranging interventions to delay or prevent disabilities and chronic brain disorders such as dementia.

The primary premise for the initial formulation of a prospective public policy to promote prevention in 1992 was that *delaying the onset of disabling symptoms of dementia would substantially reduce its prevalence*. This proposal for new program initiatives at the NIA/NIH asserted that even a *modest delay of five years in the onset of disabling symptoms would cut by nearly 50% both the number of people with dementia and the related costs of care* (1, 2).

Considering burgeoning psycho-social burdens and escalating costs of long-term care,

1. In this perspective paper, dementia-Alzheimer syndrome is used as an umbrella term, a convenient proxy, for discussing a spectrum of chronic brain disorders that require prolonged, costly, and personalized care. Dementia, in various forms, is the prototype for a class of disabilities that have a profound economic impact on healthcare systems and extremely burdensome psychosocial ramifications for family caregivers. These unremitting brain conditions' most common clinical features include a) progressive functional impairments of cognition, motor skills, and affect and b) advancing function deterioration that eventually leads to total dependence on labor-intense care to sustain life. Due to increasing lifespan, the average period of disability associated with these chronic conditions is gradually being prolonged. For example, at-risk individuals now face the prospects of nearly 30–40 years of disability related to a) total dependence on personal care, b) increasing economic burden, and c) deteriorating quality of life, especially those people who are destined to survive beyond the ninth or tenth decade of life.

Received September 6, 2023
Accepted for publication September 21, 2023

the rationale for a wide-ranging global effort on prevention, precisely the public health initiatives for reducing risks and disabilities associated with chronic brain disorders, has become particularly compelling (3, 4). Even though the benefits of such notions as *prevention or delaying the onset of cognitive impairment or reducing prevalence* are widely acknowledged, these vital public health goals have remained abstract targets, needing more specific roadmap(s) to attain them.

To address the need for an actionable comprehensive plan, PAD2020 convened an international forum5 at the AAIC 2022 in July 2022 on the issue of prevention of dementia by treating vascular and metabolic disorders (5).

The participants of this think-tank style workshop were tasked to assess the challenges for the launch of a potential demonstration project(s) to *test whether any of the readily available medications for a range of vascular-metabolic disorders might offer pragmatic public-health measures for reducing risks of cognitive impairment or delaying the onset of dementia*.

This paper is the interim report on the outcome of the PAD2020 workshop. It is a *work-in-progress* towards a final perspective paper that will critically analyze the vital perquisites for a potential comprehensive, collaborative project to *reduce the risks for cognitive impairment and dementia*, along with recommendations for a global action plan.

The present summary of the AAIC'22 think-tank proceeding outlines the major issues, challenges, and obstacles such a large-scale undertaking must address. Most importantly, it provides a brief overview of the pending tasks for future expert panels of the PAD2020 Workgroup to consider the array of open questions or issues to be resolved in a prospective collaborative project to demonstrate the effectiveness of a program to reduce risks for dementia via *interventions* for vascular-metabolic disorders; specifically, repurposing readily available medications for these conditions. Here, we cover some of the significant issues considered by the PAD2020 Workgroup (WG).

Why focus on the role of vascular-metabolic factors in dementia?

Although the putative role of vascular factors (specifically, *hardening of arteries*) was one of the earliest conventional wisdom on the origins of senile dementia and an enduring controversy due to the lack of systematic research to substantiate this longstanding theory. Now, at long last, evidence from different types of research is converging to provide compelling mechanistic explanations for the links between early risks or upstream changes in the structure-function of cerebral microvasculature and downstream loss of synaptic connectivity, cognitive impairment, and dementia-Alzheimer syndrome.

The emerging story about functional relationships of vascular-metabolic factors and clinical manifestations of dementia-Alzheimer syndrome, for example, cognitive impairment, is persuasive due to the triangulation of findings from research that include not only human studies (for example, / clinical observations/ population-based longitudinal epidemiology) but also animal research (for example, neurobiology-neurophysiology/and molecular-genetics) (6-8).

In short, converging data now provide compelling support for the proposition that disruption in *neuronal energetics* (specifically, metabolic variables), mediated by structural-functional changes in the *brain vasculature*, plays a vital role in cognitive impairment, neurodegeneration, and dementia-Alzheimer syndrome. Therefore, *vascular-metabolic* factors represent feasible targets for preventive intervention and a promising area for future therapy development for various forms of other chronic brain disorders in aging.

The discussion among the WG covers several lines of evidence that provide solid arguments for the vital role of vascular-metabolic factors in dementia, for example:

- Epidemiological findings increasingly suggest that various forms of vascular-metabolic disorders are among the most consistent precursors or comorbid factors that affect cognitive health, particularly for older adults. Virtually all forms of dementia have some vascular component, ranging from 61% in FTD to 82% in AD. Nearly 25% of aging populations have the hallmark AD pathology yet do not have symptoms of dementia. In older people with vascular pathology, the risk for cognitive impairment or dementia is doubled (9, 10).
- Since the 1980s, many prospective longitudinal studies have demonstrated a causal relationship between hypertension and the incidence of Alzheimer's disease (AD) and vascular cognitive impairment (11). Hypertension-induced vascular abnormalities, which are particularly widespread in older

adults, can lead to the development of atherosclerotic plaques in cerebral arteries that a) interfere with normal cerebral blood flow, b) compromise the structural-functional integrity of the cerebral microcirculation, and c) increase the risk for stroke and other life-threatening medical conditions (12). Approximately two-thirds of adults 60 years of age and older have hypertension, which currently is defined as systolic blood pressure (SBP) ≥ 140 mmHg and diastolic blood pressure (DBP) ≥ 90 mmHg)[2]. The prevalence of elevated blood pressure typically increases with age and currently affects approximately 1 billion individuals worldwide.

- Emerging evidence has now begun to pinpoint the mechanistic links between genetic-molecular variables that influence vascular physiology, specifically, changes in the intricate brain-perfusion system. Recent advances in isolating cerebrovascular cells and the technology of single-nucleus RNA sequencing analysis have enabled the study of how the complex vasculature of the brain deteriorates during dementia-Alzheimer syndrome (13). Sun et al. have uncovered nearly 2,700 differentially expressed (dysregulated) genes in vascular cells taken from six brain regions of 220 people with AD. In *APOE ε4* carriers, the cells expressed yet different transcriptomes (14). They have identified 11 subtypes of neurovascular cells and 125 genes linked to AD risk variants. In the neurovascular cells, the ramped-up genes are involved in the immune response and suppressed in those needed to maintain blood-brain barrier integrity. Overall, this study provides further credence to the need for future studies to focus on systematic investigation of vascular contribution to cognitive impairment and dementia-Alzheimer. This study explains how upstream variables might control differential genes, associate with the expression of dementia, and stress the dynamics of cell-cell communication in the neurovascular cells. The insights gained from this study may lead to a more manageable selection of therapeutic targets in the future. Lastly, these new insights should be thoroughly investigated to investigate the causal relationship further.
- The vascular component of dementia is the only known aspect that can be treated and potentially prevented. Additionally, a vascular element increases the chances of developing dementia. Thus, it is essential to detect and prevent vascular pathology to delay, mitigate, or potentially prevent several types of dementia. For instance, nearly 80% of strokes can be prevented, and there are already potential interventions that can guide stroke prevention efforts through demonstration projects, at least as a starting point (8, 12).
- Interventions and medications for various vascular and metabolic conditions are widely available at reasonable costs (15, 16). These might be good candidates for re-purposing and may be used successfully to delay dementia. However, it will be essential to identify other drugs that may be good candidates.

Why comingle vascular and metabolic factors?

In this paper, the umbrella constructs of *vascular and metabolic factors* fuse into a single entity to propose a future demonstration study to determine whether available medications for a wide range of vascular-metabolic conditions disorders might reduce the risks of cognitive impairment or delay the onset of dementia. The term terms *vascular factors* are intended to include all circulatory system conditions that affect the efficiency of brain perfusion (for example, small vessel disease, BBB, stroke, CVD, CoV, etc.). Likewise, the term *metabolic factor* is meant to include various upstream variables or physiological mechanisms that affect or disrupt neurons' need for a constant supply of energy (for example, ATP production, glucose transporter deficiencies, insulin resistance, diabetes, nutrition-diet, obesity, hypertension, and dyslipidemia, etc.).

The conceptual framework for linking these broadly defined constructs of *vascular* and *metabolic* factors into a unitary continuum is discussed in the *Berlin Manifesto* by Hachinski et al. (7, 8), where the authors outline the mechanistic details for the chain of physiological processes triggered by various upstream variables or pathologies that affect the efficiency of brain perfusion or produce multiple levels and duration of decrements in neuronal energy supply (for example, BBB, small vessel disease,

2. Note: The official definition in the US may now differ (based on SPRINT findings) from the official international cutoff, which is still 140/90---see AHA definition: https://www.heart.org/en/health-topics/high-blood-pressure

mitochondrial dysfunction, deficiencies in glucose-transporter proteins, hypoperfusion due to mineralization vessel walls or some other micro-vessel pathology, etc.)

Although this conceptual model can accommodate several alternative upstream variables leading to loss of connectivity, for a future demonstration project, the emphasis is on variables that affect brain *energetics*, specifically, alternative paths that influence metabolic, a constant supply of energy (for example, glucose), which is a requirement for peak performance of a neuron and maintaining synaptic resilience.

So, the reason for combining the umbrella constructs of vascular and metabolic factors into a single entity is that even though the initial trigger for the chain of events leading to synaptic dysfunction may start as a vascular event, its effects on neuronal performance are mediated by metabolic factors, *the final common path to neurodegeneration*.

Although the details of the mechanical relationships among various pathologies associated with metabolic disorders/syndrome[3] have not yet been fully established, insulin resistance is a core underlying cause of most metabolic and vascular disorders, including hypertension and cardiovascular disease. It is a significant risk for AD and other dementias, including vascular dementia. Insulin resistance, a causal factor in most cases of adult-onset or type 2 diabetes mellitus, may cause only mild glucose intolerance for many years before the onset of diabetes.

What are the essential steps for the launch of a potential collaborative project?

The wide-ranging discussion of the PAD2020 WG provided the panoramic picture of earlier studies' successes, failures, and limitations on the association between vascular-metabolic conditions and neurodegenerative disorders. These conversations revealed the rich available data from ongoing efforts on this topic and the diversity of perspectives on framing the problem. They also exposed the consensus in this field about the *timeliness* and the *need* for a comprehensive global effort to demonstrate–whether *widely prescribed medications for various vascular-metabolic disorders may reduce the risk of cognitive impairment and dementia-Alzheimer syndrome*.

Here, we outline the major unresolved issues considered by the participants of the PAD2020 WG at the AAIC'22 think-tank workshop regarding the question of ideas on *how to proceed toward* creating a federated consortium. The deliberation of the WH covers some of the important *unresolved issues* along with the list of potential tasks that a subset of WG members with appropriate expertise or interests might undertake.

So, to move on to the next phase of this project, the plan calls for assembling several (virtual) issue-specific panels (sub-groups of the current WG) to prepare brief (500-1000 word) specific, actionable recommendations regarding the next steps necessary for further planning of proposed global initiative such as a collaborative demonstration project on the efficacy for maintaining brain health via *widely prescribed medications*[4] *for various vascular-metabolic disorders*.

The list of future WG tasks regarding *open questions* that will require further elaboration by one or more of the newly reconstituted expert panels is summarized below, followed by a more detailed discussion on some of the key unresolved issues.

Summary of open questions & potential topics-tasks for further consideration

1. How do we frame this essential question/problem?

2. How can the proposed demonstration project articulate a simple and unambiguous long-range public health objective, such as reducing the risk of cognitive impairment by 20% within ten years in populations with greater incidence-vulnerability for vascular conditions?

3. A clear consensus statement of *specific aims* for a potential pilot/demonstration project, for example, to show feasibility or test the hypothesis that widely prescribed medications for various vascular disorders that are safe, effective, and readily available at low cost may delay the onset of cognitive impairments.

3. Metabolic disorders/syndrome is defined as the co-occurrence of hypertension, diabetes, obesity, and dyslipidemia (https://pubmed.ncbi.nlm.nih.gov/19273747/ Craft 2009, Cornier 2008, REFs). (Pathogenic connection between hypertension and type 2 diabetes: how do they mutually affect each other? | Hypertension Research (nature.com)).

4. The primary goal is to accelerate the process of developing preventive interventions that are safe, effective, and readily available at low cost via repurposing existing medication in contrast to traditional approaches to demonstrate the efficacy of de novo agents.

4. Need to:

- Distinguish prospective interventions aim to treat a vascular-metabolic disorder, cognitive impairment, or dementia-Alzheimer syndrome.
- Clarify the distinction between the constructs of *treatment*, which is applied to an existing condition after it has already started, and the notion of *intervention*, which may include therapy, is a broader concept intended to block or delay the onset of the condition; it also encompasses non-pharmacological approaches (for example, lifestyle, etc.) to alter the course of the condition?
- Clarify the discrepancy between the intervention's clinical aims and the treatment medium. For example, to illustrate the need for clarification, assume the ultimate *target for intervention* is to delay or prevent cognitive decline and the medium *is a treatment* for hypertension or some other vascular-metabolic condition. In such a scenario, a particular medication may not effectively treat hypertension, yet it is a viable *intervention* to delay cognitive impairment (15).

5. Criteria-rationale for selection (inclusion-exclusion) of study subjects/cohorts/populations for testing (for example, *population with greater incidence-vulnerability* or some other well-characterized cohorts-subject).

6. The impact (specifically, the study design) of selective vulnerability in some populations (with disproportionately higher incidence and prevalence of vascular/metabolic comorbidities) on the heterogeneity and complexity of the global problem (17, 18).

7. How to take advantage of ongoing projects and get the most out of well-established resources and databases; recommendations for specific steps to link or coordinate the prospective global initiative to add value to these longstanding related projects.

8. Among the several approaches to explore the validity of the assertion that early intervention of various vascular-metabolic system-related dysfunctions will reduce the risk or delay cognitive impairment, the WG should assess the merits, limitations, and cost-effectiveness/practicality of multiple approaches to tackle the central question. For example, one option for study design might be a pragmatic clinical trial based on the model of a traditional clinical trial to demonstrate effectiveness. Another possibility is a public health approach using a risk cohort for a population-based prospective longitudinal study on the putative preventive effects of meditation. A third alternative is a data-mining epidemiological study on existing populations/databases to determine the impact of such intervention on the incidence or prevalence of cognitive impairment.

9. Specification of risk, comorbid conditions, upstream variables, etc., for consideration-inclusion.

10. What should be the precise operational definition(s) for a) independent variable(s) (for example, better definition of current for umbrella construct of vascular-metabolic factors/conditions); b) intermediate or mechanistic variables (for example, hypoperfusion due to vascular changes and energy crisis due to reduced energy supply to neurons); and c) dependent variable (for example, specification of clinically meaning outcome(s) such as cognitive functioning/impairment)?

11. What should be the index for the effectiveness of the intervention, a) clinically meaningful outcome (for example, delay in onset, slowing of progression, prevention) and b) public health success (for example, risk reduction, lowering incidence, reducing prevalence) and c) recommendations for instrument(s)-measure(s) to be used?

12. Recommendations are needed regarding the selection of biomarkers for a) early detection-identification of subjects at elevated risk in asymptomatic cohorts; b) monitoring disease progression and tracking drug-effect regarding the effectiveness of the intervention; and c) prognostic use, specifically, a validated surrogate marker that can accurately-precisely predict putative outcome that is clinically meaningful (19).

13. The WG should consider the most promising options among safe, effective, and readily available at low cost for an initial demonstration of effective interventions initially developed for various vascular-metabolic conditions (7, 8). This task should include wider-ranging interventions (beyond medication) to fit lifestyle and behavioral approaches, for example, the FINGER Study (20, 21).

14. There is a need to increase the availability and access to low-cost and effective intervention, particularly in low-middle-income countries, to widen the participation of people at elevated risk or under-served populations (17, 18, 22).

15. How do we build R&D capacity and resources for clinical studies in low-middle-

income countries to widen the participation base of people at elevated risk or under-served populations?

16. There is a great need for novel approaches to overcome many of the failures and limitations of earlier studies for example, WGs should pinpoint barriers (psycho-social, resources, etc.) unique to different populations that are preventing adherence to medication/lifestyle changes to lower vascular/dementia risk and (especially on a global scale) to understand better the current sentiment in various populations towards dementia prevention to help design trials, guide policy changes - specifically, beliefs and attitudes towards the connections between dementia risk and certain lifestyle factors? For example, one such prevailing view is that dementia-Alzheimer syndrome is simply a normal part of aging).

17. Evaluate various models for the governance of a global alliance of stakeholders to sponsor such an initiative.

Ethical standards

Ara S. khachaturian is editor-in-chief of *Vitality, Medicine & Engineering*; he has recused himself from any editorial decision on this manuscript. Dr. Bruno Vellas was responsible for the editorial peer-review process.

Acknowledgments

PAD2020 Workgroup on: "Prevention of dementia by treating vascular & metabolic disorders". AAIC 2022 Pre-Conference Workshop. // The think-tank format of the symposium is designed to promote critical analysis and thoughtful discussion by KOLs regarding their assessments and recommendations. // The was convened by Prevent Alzheimer's Disease 2020 (PAD2020). The steering committee members include Vladimir Hachinski, Bill Potter, Walter Kukull, Ara Khachaturian and Zaven Khachaturian.

Developing strategic solutions to the medical, scientific, economic, and policy challenges related to cognitive impairment in an aging society is the primary mission of Prevent Alzheimer's Disease 2020 (PAD2020), a Maryland-based non-profit organization established in (___). In recent years we have begun to mobilize (many of the) the scientific and intellectual resources of the neuroscience community with the goal of establishing a scientific consensus on recommendations for (national and global) initiatives that aim to maintain brain health and extend independent functioning among adult populations at risk for dementia. Planning, assembling and coordinating issue-specific workgroups for the purpose of arriving at actionable expert recommendations have been among our core capabilities, along with providing unique scientific forums for exploring solutions to the large global challenge of reducing dementia-related morbidity.

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