Developing a Research Agenda to Prevent Dementia:
Summary of a PHRI Workshop

January 9-10, 2019
Population Health Research Institute
Hamilton, Ontario, Canada

PHRI is developing a multi-faceted Brain Health Initiative, seeking support from the Weston Brain Institute and other sources. This Workshop was an early step in this program.

Objectives: To explore the potential for a synergistic research program as part of the PHRI Brain Health Initiative aimed at preventing cognitive decline, dementia, and functional decline, including:

a) Assessing global variations in dementia in a prospective multinational epidemiological study of high-, middle-, and low-income countries (PURE).

b) Elucidating novel environmental and lifestyle factors that predict dementia.

c) Leveraging international epidemiology and biomarker analyses to discover potential modifiable pathways to cognitive decline and dementia.

d) Mining cognitive and functional (activities of daily living) data from existing PHRI-led clinical trials of cardiovascular risk reduction, with cognitive endpoints on >20,000 participants.

e) Creating a broad registry of potential research participants for clinical trials.

This summary records selected ideas presented and discussed during the Workshop and is not comprehensive or necessarily endorsed by the Workshop organizers or participants.

Workshop sponsor: Population Health Research Institute (PHRI).

This summary was drafted by R. Hart, J. Bosch, E. Smith, W. Whiteley, S. Yusuf.

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Workshop Participants

Last	First	Institution	Expertise
Anand	Sonia	PHRI	Population health, epidemiology
Black	Sandra	Univ Toronto	Alzheimer's disease, neuroimaging
Bosch	Jackie	PHRI	Cognition, function
Bronskill	Susan	ICES	Dementia assessment
Dehgan	Mahshid	PHRI	Nutrition
Gorelick	Philip	? Health (Chicago)	Vascular cognitive decline, AHA guidelines
Hart	Robert	PHRI	Stroke, clinical trials
Leong	Darryl	PHRI	Cardiology, frailty, epidemiology
Lindsay	Patty	Heart & Stroke	Knowledge translation
Mente	Andrew	PHRI	Nutrition
O'Donnell	Martin	PHRI/ NUI-Galway	Geriatrics
Pare	Guillaume	PHRI	Genomics, fluid biomarkers
Raina	Parminder	McMaster Univ	Aging (CLSA), epidemiology
Rangarajan	Sumathy	PHRI	PURE study
Sharma	Mike	PHRI	Stroke, clinical trials
Simard	Anne	Heart & Stroke	Knowledge translation
Smith	Eric	Univ Calgary	***Workshop Co-chair***; dementia, neuroimaging
Themeles	Ellison	PHRI	Program management
Tywitt	Jessica	PHRI	Program management
Whiteley	William	Univ Edinburgh	***Workshop Co-chair***: cognition trials, outcomes
Yusuf	Salim	PHRI	Director PHRI, epidemiology & clinical trials

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Workshop Agenda

Wednesday, January 9th Day One		
8:30-8:45	Welcome/Objectives	Smith/Whiteley
8:45-9:05	Keynote address: Opportunities for promoting brain health	Gorelick
9:05-9:15	Questions/discussion	
Theme 1: Leveraging International Epidemiology to Uncover Modifiable Pathways		
9:15-9:30	PURE study overview	Rangarajan
9:30-9:45	Dementia assessment in PURE—algorithm	O'Donnell
9:45-10:00	Feedback/discussion	
10:00-10:15	Alliance study	Anand
10:15-10:30	Discussion	
10:30-10:45	Break	
10:45-11:00	Nutrition	Mente/Dehgan
11:00-11:15	Discussion	
11:15-11:30	Frailty	Leong
11:30-11:45	Discussion	
11:45-12:00	CLSA: Plans for epidemiology of age-related cognitive decline	Raina
12:15-12:30	Discussion	
Theme 2: Genomics and Biomarkers: What They Tell Us About Modifiable Pathways		
1:15-1:30	Mendelian randomization: opportunities for investigating drug-able pathways	Pare
1:30-1:45	Discussion	
1:45-2:00	Prevalence and risk factors for covert infarcts and MRI white matter changes: PURE MIND and Alliance studies	Smith
2:00-2:15	Discussion	
2:15-2:30	Alzheimer's disease markers	Smith/Pare
2:30-2:45	Discussion	
2:45-3:00	Break	
Theme 3: Trials for Age-Related Cognitive Decline and Dementia		
3:00-3:15	PHRI Experience with cognitive endpoints in clinical trials	Bosch
3:15-3:30	Discussion	
3:30-3:45	Brain imaging in PHRI trials	Sharma
3:45-4:00	Discussion	

4:00-4:15	Selecting the population for trials: Incidence of cognitive decline & dementia in general population	Smith
4:15-4:30	Discussion	
4:30-4:45	Outcomes: dementia, function, or cognitive test scores?	Bosch
4:45-5:00	Discussion	
5:00-5:15	Approaches to evaluating interventions for suitability for dementia prevention trials	Whiteley
5:15-5:30	Wrap-up	Whiteley/Smith
Dinner – 7:30 pm Nique Restaurant		
Thursday, January 10th		
Day 2 Planning a Pilot Trial for Preventing Age-Related Cognitive Decline and Dementia		
8:30-9:00	Reflections on Day 1 Discussion of potential interventions for dementia prevention	Smith/Whiteley
9:00-9:15	Keynote address: The Landscape of Alzheimer's Disease-focused Trials	Black
9:15-9:30	Discussion	
9:30-9:45	Why have so many trials been unsuccessful?	
9:45-10:00	Discussion	Whiteley
10:00-10:15	Break	
Theme 4: Achieving Efficiencies in Dementia Prevention Trials		
10:15-10:30	Innovative efficient approaches for epidemiological studies and registries	Smith
10:30-10:45	Discussion	
10:45-11:00	Assessing dementia using Canadian health data	Bronskill
11:00-11:15	Discussion	
11:15-11:30	Web-based cognitive assessment	Whiteley
11:30-11:45	Discussion	
11:45-12:00	Wrap up and next steps	
12:00	Adjourn	

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Selected Highlights

Cognition and functional status have been measured in several large clinical trials and epidemiological studies carried-out by PHRI over the past decade. These data have not been thoroughly analyzed or published. The ongoing COGWHEEL project will analyze these data and including assessment of the slope of cognitive and functional decline using different instruments and in different populations to allow sample size estimates to be refined for future studies. Preliminary analysis indicates that decline in cognitive and functional outcomes over time can be measured using brief assessment tools that can be applied to global clinical trials.

Age-related cognitive and functional decline should be considered in the broader context of a life pathway in which "a dimmer switch is flipped on" in midlife that leads to clinically manifest disease decades later. Alzheimer's pathology may be the result of several metabolic perturbations that begin in midlife, accumulating slowly over many years. A "web of causation" that begins long before clinical disease is postulated. Hence, intervening in young and middle age may be critical to preventing cognitive decline and dementia in late life.

The American Heart Association (AHA) recommends "Life's Simple 7" to achieve optimal cardiovascular health. Support for the recommendations are based mainly on observational data, and controversy exists about the strength of evidence. Importantly, interventions and lifestyles advocated to achieve optimal cardiovascular health correlates strongly with optimal brain health, and these recommendations have been extended to preserving cognition (Gorelick PB et al., Smith EE et al. Defining optimal brain health in adults. A presidential advisory form the AHA/ASA. *Stroke* 2017; 48: e284-e303).

The large, international Population Urban Rural Epidemiology (PURE) study involving nearly 200,000 participants from high-, middle- and low-income countries will assess cognition during the next follow-up visit that will occur after about nine years of observation. These data will offer unique and exciting information about prevalence and new risk factors for cognitive impairment and dementia. In the subset of PURE participants with biomarker samples available, discovery of novel etiological pathways using comprehensive, multi-panel "agnostic" testing of hundreds of biomarkers will be undertaken. The brief "mini-cog" screening test will be used in PURE: participants with objective abnormalities on cognitive testing will be considered as mild cognitive impairment unless accompanied by loss of activities of daily living, leading to a diagnosis of dementia. It was noted that existing cognitive screening tests tend to misclassify mild cognitive impairment yet identifying cases early in the process of dementia may be critical for interventions. Insights from the PURE cognition assessment should provide blockbuster new evidence.

The Alliance project is obtaining brain MRIs and carotid artery wall thickness on ~9000 Canadians, including ~1300 First-Nations people, along with cognitive testing. The mean age is 59 years, and the sample is more highly educated and affluent that average Canadians. This will be a valuable resource, particularly for neuroimaging correlations.

Based on cross-sectional data from the PURE MIND study, it was noted that measurable impairment on the digital symbol substitution test (DSST) and Montreal Cognitive Assessment (MoCA) battery can be demonstrated in the people in their 40s. Three percent of a population-based sample of Canadians between the ages of 30 and 40 years had covert brain infarcts on MRI. Hence, brain health issues are not restricted to old age.

Information about covert brain infarcts detected by neuroimaging in people without a history of clinical stroke has been largely confined to North American and Western European countries. PURE MIND is comparing the frequency, risk factors, and cognitive effects of covert brain infarction in Canada, China, and Poland. The presence of covert brain infarcts is associated with 3.4 to 7.4 years of aging based on multivariable linear regression analysis of the DSST and MoCA in models that include age, sex, and education. Based on repeat MRIs in PURE MIND, the incidence of covert brain infarction was 4.3% during a mean interval of 6 years in people of a mean age of about 60 years, higher than incident clinical strokes. In short, PURE MIND offers important evidence that covert brain infarcts are more frequent than clinical strokes and are associated with cognitive impairment. Covert brain infarcts as an outcome in randomized clinical trials has been a special interest of several PHRI investigators (COMPASS, NAVIGATE ESUS, DATAS II).

Are brain beta-amyloid and tau vascular biomarkers rather than underlying causes of dementia? Their detection requires positron emission tomography (PET) imaging that is expensive, limited in availability, and involves radiation exposure or CSF that is impractical to obtain for large-scale clinical studies. Current dementia risk scores are inadequate for identifying those at high-risk of dementia for clinical trials. Novel blood biomarkers that would allow more accurate diagnosis of subtypes of dementia are urgently needed for clinical trials of prevention of dementia to refine patient selection. Misdiagnosis of trial participants as mind cognitive impairment likely contributes to neutral trial results. Consistent results of observational studies demonstrate that education is protective against development of Alzheimer's disease. Genetic and biomarker studies offer the opportunity to understand the mechanistic underpinnings of this important association. The biomarker studies planned at PHRI should be revealing.

A rational, systematic approach to identifying and assessing new interventions to reduce cognitive and functional decline was discussed. This could include a systematic synthesis of existing systematic reviews (at least 314 published to date) based on presumed mechanisms, on epidemiologic associations, and/or on animal studies. In addition, critical review of previous randomized trials to identify interventions that were prematurely abandoned due to poor trial design or commercial reasons, yet that showed a signal of potential efficacy (e.g. propentofylline and desferrioxamine) should be considered. It was noted that while several recent trials targeting amyloid and tau have been neutral, it may be too soon to abandon these targets, particularly considering the ongoing trials of adacanumab, a potent anti-amyloid antibody.

Potential design flaws of previous randomized trials testing interventions that could contribute to the neutral outcomes was discussed. These vagaries include too few participants (i.e. underpowered), expectation of large treatment effects (i.e. missing smaller, but still clinically important treatment

effects), involvement of patients too far into the disease, inclusion of low-risk patients / those without the disease (i.e. poor participant selection), insufficient follow-up (i.e. the intervention may require extended time), and insensitive instruments to measure outcome.

The Institute of Clinical Evaluative Sciences (ICES) based in Toronto, but with an outreach site at McMaster University, has considerable experience with dementia assessment in this large, population-based administrative database. The ICES definition of dementia, for example, has been shown to have 99% specificity and 80% positive predictive value. Collaboration with the PHRI Brain Health Initiative is eagerly anticipated.

There are several registries in the Europe, U.S. and Canada have been developed by lay societies and governmental funding agencies to facilitate rapid recruitment into randomized trials aimed at prevention and treatment of cognitive decline and dementia. Some web-based registries include scores of thousands of people.

As the PHRI Brain Health Initiative goes forward, the issue was discussed *"what does PHRI add to the existing dementia research landscape?"*

1. PHRI's track record of large, streamlined randomized clinical trials carried-out in high-, middle-, and low-income countries done at relatively low cost.

2. Dementia assessment in the PURE study to assess prevalence and risk factors for dementia and mild cognitive impairment in high-, middle-, and low-income countries.

3. Biomarker-based discovery of novel mechanisms through OLINK application involving PURE participants.

4. PURE MIND assessment of covert brain ischemia and its implications.

5. Validation of covert brain infarcts as a treatment-responsive, clinically-relevant clinical trial outcome.

6. Additional collaboration with ICES, including extended follow-up of trial participants.

7. PHRI experience with cognitive assessment in multiple, global clinical trials. The COGWHEEL project will assess cognitive instruments that can be applied on a global scale.

8. Potential collaboration with Alliance taking advantage of the large number of brain MRI on a population-based cohort sample.