

STUDY PROTOCOL

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Rationale, design, and methods for Canadian alliance for healthy hearts and minds cohort study (CAHHM) – a Pan Canadian cohort study

Sonia S. Anand^{1,7,8*}, Jack V. Tu^{2,16}, Philip Awadalla², Sandra Black⁴, Catherine Boileau⁵, David Busseuil¹⁵, Dipika Desai^{7,8}, Jean-Pierre Després⁹, Russell J. de Souza¹, Trevor Dummer⁵, Sébastien Jacquemont³, Bartha Knoppers¹¹, Eric Larose⁹, Scott A. Lear¹², Francois Marcotte¹⁵, Alan R. Moody⁴, Louise Parker¹⁰, Paul Poirier^{6,9}, Paula J. Robson¹³, Eric E. Smith¹⁴, John J. Spinelli¹⁷, Jean-Claude Tardif¹⁵, Koon K. Teo^{1,7}, Natasa Tusevjak¹⁶, Matthias G. Friedrich¹¹, on behalf of the CAHHM Study Investigators

Abstract

Background: The Canadian Alliance for Healthy Hearts and Minds (CAHHM) is a pan-Canadian, prospective, multi-ethnic cohort study being conducted in Canada. The overarching objective of the CAHHM is to understand the association of socio-environmental and contextual factors (such as societal structure, activity, nutrition, social and tobacco environments, and access to health services) with cardiovascular risk factors, subclinical vascular disease, and cardiovascular and other chronic disease outcomes.

Methods/Design: Participants between 35 and 69 years of age are being recruited from existing cohorts and a new First Nations Cohort to undergo a detailed assessment of health behaviours (including diet and physical activity), cognitive function, assessment of their local home and workplace environments, and their health services access and utilization. Physical measures including weight, height, waist/hip circumference, body fat percentage, and blood pressure are collected. In addition, eligible participants undergo magnetic resonance imaging (MRI) of the brain, heart, carotid artery and abdomen to detect early subclinical vascular disease and ectopic fat deposition.

Discussion: CAHHM is a prospective cohort study designed to investigate the impact of community level factors, individual health behaviours, and access to health services, on cognitive function, subclinical vascular disease, fat distribution, and the development of chronic diseases among adults living in Canada.

Background

Cardiac, vascular, and cognitive dysfunction have a tremendous impact on the quality of life, longevity and health care costs in Canada, and globally. It is of paramount importance to understand the early determinants of such dysfunction and its progression to clinical events, given the increasing prevalence of known cardiovascular (CV) risk factors, which result in organ dysfunction including heart failure, non-alcoholic fatty

liver disease (NAFLD), and dementia, which threatens the financial sustainability of health care systems. Cardiovascular Disease (CVD) is a leading cause of morbidity and mortality in Canada, and places a large burden of cost on the health care system. Each year approximately 70,000 Canadians die from CV causes and many more suffer life-threatening CV events such as myocardial infarction (MI) and stroke [1]. It has been estimated that cardiovascular diseases cost our health care system \$22 billion dollars each year in direct and indirect costs, a figure that is expected to grow over time [2]. Additionally, CV risk factors account for up to half of the attributable risk for dementia, mediated in large part by

* Correspondence: anands@mcmaster.ca

¹McMaster University, Hamilton, Canada

⁷Hamilton Health Sciences, Hamilton, Canada

Full list of author information is available at the end of the article



difficult to detect microvascular disease of the brain. The rapid increase of overweight and obesity among Canadians and its associated consequences, including hypertension and diabetes add to the problem. Importantly, CVD in Canada increasingly affects women and individuals from non-white ethnic groups [1, 3]. While the treatment of clinical events caused by CVD has improved, the effective prevention of CVD with its implications on well-being and health care costs remains a challenge, due in part to knowledge gaps regarding the impact of social and built environments in relation to individual risk factors and thus on efficient political strategies to reduce CVD burden. Furthermore, there is a lack of sensitive, early risk markers and thus information on these relationships before the onset of symptomatic organ dysfunction is limited. In order to address these gaps in our knowledge, we convened the Canadian Alliance for Healthy Hearts and Minds (CAHHM) – a prospective cohort of men and women recruited through existing cohorts in Canada and an First Nations cohort.

The specific objectives of the CAHHM are

- 1) To understand the role of socio-environmental and contextual factors (such as societal structure, activity, nutrition, social and tobacco environments, and access to health services) on CV risk factors, subclinical disease, and clinical CV events at the individual and population levels. This includes the impact of contextual factors on geographic variation in CVD (ie rural vs. urban, and east to west gradient), and their relative impact compared to individual level factors.
- 2) To characterize the unique patterns of contextual factors as well as acculturation, cultural continuity, and migration experience as related to individual CV risk factors, health service utilization (ie screening, access to diagnostics and treatments), and clinical outcomes among high risk ethnic groups including South Asian, Chinese, and African origin, as well as reserve-based First Nations people from across Canada.
- 3) To identify early subclinical dysfunction and tissue abnormalities in the brain, blood vessels and the heart, to characterize abdominal and pericardial fat distribution, and to investigate the association of dysfunction with contextual and individual determinants. Furthermore, the data will shed light on the predictive value of novel markers of subclinical abnormalities and dysfunction on the development of clinical events related to cardiac, vascular and cognitive dysfunction.

Methods/Design

CAHHM is a ‘cohort of cohorts’ as the majority of participants (>80 %) will be recruited through existing

cohorts: 1) Canadian Partnership for Tomorrow Project (CPTP), a harmonized longitudinal population study capturing health data, physical measures and biologics of over 300,000 Canadians (www.partnershipfortomorrow.ca). CPTP participants provide broad consent to research by internal and external scientists, and linkage to administrative health data. CPTP is a federation of five regional cohorts: the BC Generations Projects, Alberta’s Tomorrow Project, the Ontario Health Study, CARTaGENE, and Atlantic PATH (Atlantic Partnership for Tomorrow’s Health), 2) the Prospective Urban Rural Evaluation (PURE)-Canada cohort, 3) the Montreal Heart Institute (MHI) Biobank, and 4) a newly formed First Nations Cohort study. The details of the separate cohorts are found in the Additional file 1.

Eligibility and recruitment of participants into CAHHM

Participants are eligible for CAHHM if they were between ages 35 and 69 years (inclusively) at time of screening [or for First Nations participants ≥ 18 years] and willing to undergo an MRI scan and all other required study procedures. In order to recruit the majority of participants without existing CVD we asked each cohort to include participants of whom less than 20 % have known CVD, and about 50 % are women, all balanced across age strata 35–45, 46–55, 56–69 years. Some variations exist between cohorts given their differences in feasibility of recruitment and access to MRI centres. (Table 1) Details on the new First Nations cohort will be published in a separate manuscript.

Clinical assessment

The clinical assessment for CAHHM participants consisted of: a) completion of questionnaires, b) physical measurements, c) collection of blood samples in some participants (stored blood samples will be used for others), and d) a MRI scan of brain, heart, carotid artery and abdomen, details of each component are provided below.

Health questionnaires

Personal and Medical History were collected using standardized questions including family history, and health behaviors. Diet and physical activity were collected using a food frequency questionnaire (FFQ) and the short form International Physical activity Questionnaire (IPAQ). (Table 2)

Cognitive function

Cognitive function measures in CAHHM were selected balancing the need for a brief, cost effective, and sensitive measure appropriate for use in a 35–69 year age group. Two assessments were chosen, first the Digit Symbol Substitution (DSS) test (Wechsler Adult Intelligence Scale IV version) was chosen because it displayed age-related effects over the age range of 40–70

Table 1 Participant Selection Criteria for Alliance Recruitment – By Cohort

	CARTaGENE	OHS	BCGP	APATH	Alberta's tomorrow project	PURE	MHI	First Nations
Preliminary Selection Criteria of Participants								
Email	Yes	Yes	Yes	NA	Yes	NA	NA	NA
Blood Sample previously collected	Yes – also new sample	Yes	Yes – also new sample collected	Yes – also new sample collected	NA – obtaining new blood sample	Yes – new sample for Hamilton only	Yes – also new sample	NA – new sample
Geographic Criteria	Metropolitan Montreal and Quebec City	Greater Toronto Area, London, Hamilton, Ottawa	Metro Vancouver	Halifax and surrounding area	Calgary and Edmonton	Hamilton, Vancouver, Quebec City	Montreal	Hazelton, Maskwacis, Lac La Ronge, Sandy Bay, Fort MacKay, Thunder Bay, Six Nations, Oneida, Wendat, Pictou Landing
Prioritized Ethnic	African	South Asian, Chinese, African	East Asian, South Asian, Black	NA	NA	NA	NA	First Nations
CVD (–)	Max 20 % can have history of: MI, stroke or cancer – if not then expand	Exclude: MI, stroke, CABG, PTCA, CHF, cancer	Max 20 % can have history of: MI, stroke, CABG, PTCA, CHF or cancer	Max 20 % can have history of: MI, stroke, CABG, PTCA, CHF or cancer	Max 20 % can have history of: MI, stroke, CABG, PTCA, CHF or cancer	Max 20 % can have history of: MI, stroke, CABG, PTCA, CHF or cancer	Max 20 % can have history of: MI, stroke, CABG, PTCA, CHF or cancer	Max 20 % can have history of: MI, stroke, CABG, PTCA, CHF or cancer
Age	35–69 years at time of entry	35–69 years at time of entry	35–69 years at time of entry	35–69 years at time of entry	35–69 years at time of entry	35–69 years at time of entry	35–69 years at time of entry	18 years and up
Additional Sampling after above criteria considered								
Participant Selection	Random	Random	Random	Random	Random	Consecutive	Consecutive	Volunteer
Cohort specific selection criteria	Prioritized for existing RNA sample and genomic information					Approach participants coming for in-person follow up visit		
Exclusions	Participants in the Diabetes/Depression substudy or with pacemaker				Recently invited to participate in other sub-studies			
Log of participant kept or available	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA

Table 2 List of Measures/Questionnaires of Baseline Visit

Questionnaire/Measure	Source	Time to complete (minutes)	Method
Physical Activity	IPAQ-S [71]	4	Self Administered
Dietary Intake (Macro and Micro Nutrients)	SHARE-FFQ [72] and DHQ II	22	Self Administered
Cognitive Function: Digital Symbol Substitution	DSS [73]	5	Administered by RA
Montréal Cognitive Assessment	MoCA [9]	8	Administered by RA
Community Factors (Individual Perception)	EPOCH-2 [58]	21	Self Administered
Immigrant Questionnaire	Longitudinal Survey of Immigrants in Canada [60]	3	Self Administered
Acculturation	Vancouver Inventory of Acculturation [61]	3	Self Administered
CVD related Health Services Questionnaire	Multi-source: Canadian Community Health Survey, Ontario Health Study	7	Self Administered
General CVD Questionnaire	Prior Longitudinal Studies (SHARE, PURE)	7	Self Administered
CPTP Core Baseline Health and Lifestyle Questionnaire	CPTP Study [74]	14	Self Administered
Physical Measures (blood pressure and heart rate via OMRON cuff, Body Fat & Weight via Tanita BIA)		10	Clinic

RA: Research Assistant

years in participants in the PURE-MIND study, a contemporary Canadian-based prospective cohort study of 800 participants with similar entry criteria to the Canadian Alliance for Healthy Hearts and Minds [4]. In the DSS, the participant transcribes as many coded symbols as possible within a given time (in this case, two minutes). Lower scores indicate worse performance. The DSS is sensitive to change over time [5], is lower in persons with silent brain infarct, is independent of language, is sensitive to mildly impaired cognition [6], and predicts clinically important events such as falls and mortality [7, 8]. Second, the Montréal Cognitive Assessment (MoCA) was used as a global cognitive screening test. The MoCA takes 10–15 min to administer and briefly evaluates the following domains: delayed recall, verbal fluency, visuospatial skills, clock drawing, executive functions, calculation, abstraction, language, orientation, attention and concentration [9]. The test has a sensitivity of 90 % and specificity of 87 % to detect mild cognitive impairment in patients and distinguish them from normal controls [10]. The MoCA has been validated in memory clinic settings for diagnosis of mild cognitive impairment or dementia [9–13]. The MoCA tests domains including executive function and therefore should be more sensitive to vascular cognitive impairment than the Folstein Mini mental status examination [14–18], is more sensitive to milder forms of impairment [9, 15, 19] and shows less ceiling effect [19, 20].

Physical measurements

Participants height, weight, percent body fat using the Tanita BIA machine, waist circumference, hip circumference, resting heart rate, and blood pressure using an

automated OMRON cuff are collected. All measurements are taken using a standardized protocol.

Blood collection

New blood samples are collected from cohorts in which blood had not previously been collected from their parent cohort. A new blood sample will be collected from First Nations participants, the Alberta's Tomorrow Project, BC Generations, CARTaGENE, Atlantic PATH, MHI Biobank, and PURE (Hamilton site only).

Rationale for MRI imaging

Imaging-derived markers can be acquired non-invasively and include focal tissue, thereby increasing the sensitivity to detect vascular lesions and tissue pathology with prognostic impact. Among the available imaging tools, MR imaging combines an outstanding safety profile with excellent accuracy and reproducibility. Its advantages also include a high spatial resolution, a small observer dependence, and excellent. Moreover, it allows for a comprehensive, multi-target approach including morphology, mass, function, flow, vessel lumen, tissue composition, and metabolism. It can be considered the most efficient imaging tool for clinical or cohort studies in healthy individuals. Several existing and conceptualized population-based cohorts utilize either cardiac or brain MRI, including the UK BioBank [21], The German National Cohort study [22], the Dallas Heart Study [23] the MESA study [24], Age, Gene/Environment Susceptibility –Reykjavik Study [25, 26], Framingham study [27, 28] and Rotterdam study [29, 30]. However, few studies have comprehensively assessed the cardiovascular system using MRI, including arterial imaging. In CAHHM,

participants will undergo a comprehensive MR examination of the brain, heart, carotid artery and abdomen (for visceral and liver adiposity). Of note, the CAHHM not only uses markers with demonstrated value, but also novel candidates related to coronary plaque stability and microvascular function.

MRI Protocol

Details of the CAHHM MRI protocol are found in Tables 3 and 4. The protocol was developed in collaboration with a multi-disciplinary expert group (see working groups listed at the end of the conclusion section) balancing the scientific objectives with time efficiency. The protocol uses validated standard techniques and provides information on

Table 3 MRI key measures in Heart, Brain, Abdomen during Standard MRI Protocol

Standard		
Sequence	Approximate Imaging Time (min)	Outcome Measure
Cardiac		
2D Cine SSFP (short axis only)	10	LV global (EF) and regional wall motion abnormalities function LV mass index LV end-systolic volume index LV mass-to-volume ratio LA size and function RV volume and global function
Brain		
3D T1w MPRAGE	8	Brain Volume
2D Flair	3	Covert stroke and white matter lesion burden
Abdomen		
T1w TSE abdominal adipose tissue sequence	2	Visceral fat area
Liver 2D multi-echo gradient-echo sequence	1	Liver fat %
Cerebrovascular		
3D T1w MPRAGE	6	Plaque volume and intraplaque hemorrhage detection
TOF	6	Plaque volume and intraplaque hemorrhage detection
Additional time for positioning		
Coil Positioning	6	
Total time	42 ^a	

^aNote this varies depending on: Scanner make and model, hardware and software used for scanning, need for switching MR coils, participants heart rate, and MRI technologist experience

Table 4 Extended MRI Scan Protocol

Extended		
Sequence	Approximate Imaging Time (min)	Outcome Measure
Cardiac		
Cine SSFP (3 long axis views and 10–15 short axis views)	12	LV global (EF) and regional wall motion abnormalities function LV mass index LV end-systolic volume index LV mass-to-volume ratio LA size and function Circumferential strain RV volume and global function
Phase-contrast cine	4	Aortic elasticity
LGE	12	Myocardial fibrosis
T1 Mapping	10	Diffuse fibrosis
T2 star-weighted sensitive sequence	10	Microvascular function
Brain		
3D T1w MPRAGE	8	Brain Volume
PD/T2	4	Covert stroke and white matter lesion burden
T2 star-weighted gradient echo sequence	4	Presence of microbleeds
2D resting state fMRI	4	Functional connectivity
3D arterial spin labeling (ASL)	7	Cerebral blood flow
2D diffusion tensor imaging (DTI)	5	White matter connectivity
Abdomen		
T1w TSE abdominal adipose tissue sequence	2	Visceral fat area
Liver 2D multi-echo gradient-echo sequence	1	Liver fat %
Cerebrovascular		
3D T1w MPRAGE	8	Plaque volume and intraplaque hemorrhage detection
TOF	6	Plaque volume and intraplaque hemorrhage detection
3D T1w MPRAGE + contrast	5	Lipid core, calcification inflammation/angiogenesis
Additional time for positioning		
Coil Positioning	6	
Biobreak	10	
Total time	118	

morphology, function and tissue characteristics. Quantitative data are measured or calculated wherever possible. Aside from established parameters, novel markers are included, with most of them being acquired by additional images as part of an extended protocol, performed with the MR contrast agent gadobutrol.

Cardiac dysfunction

Cardiac MR (CMR) will provide data on global and regional left ventricular and right ventricular function. This rationale is based on data from the MESA cohort with its multi-ethnic population-based sample of 4510 individuals (mean age 61y), where a 25.6 % prevalence of regional wall motion abnormalities (RWMA), with a 2.6 % heart failure rate (vs. 1.0 % in individuals without RWMA) was observed [31]. With its obvious potential as a predictor for heart failure, the correlation of RWMA with other risk markers and especially environmental factors becomes an important target for preclinical research. Its standardized acquisition [32, 33], high prevalence in the general population and strong predictive value for subsequent heart failure render CMR-derived RWMA an excellent early marker and primary endpoint in CAHHM. Other markers include myocardial scarring [34, 35], and coronary vascular function [36–38]. Furthermore, this is an unprecedented opportunity to acquire multi-ethnic normal values for numerous quantitative cardiac markers. Because of its outstanding safety profile, standardized approaches, accuracy, reproducibility and comprehensive multi-parametric protocols, we considered CMR the most useful tool for detecting subtle, early and local changes which may precede cardiac, vascular and cognitive dysfunction.

Covert stroke and cognitive dysfunction

Recent population-based studies have shown that the prevalence of unrecognized “covert” brain infarcts is as high as 30–40 % in the elderly/geriatric population, and current evidence is sufficient to document that covert strokes and ischemic white matter damage in the elderly are associated with cognitive impairments despite the lack of association with specific symptoms, and are highly predictive of future stroke and dementia. However, important gaps in knowledge include the prevalence of brain infarcts prior to age 60 (as previous studies have focused on the elderly), the predictive power of covert stroke and ischemic white matter damage as a marker of important CV events in addition to future stroke (such as myocardial infarction), and the relationship between covert stroke and subclinical manifestations of CVD in other organs. Additionally, both covert stroke and ischemic white matter damage are partly heritable but the genetic basis of this risk has not been well defined yet.

Emerging evidence suggests that alterations in brain structure and function accrue years before clinical symptoms of stroke or cognitive dysfunction. In Alzheimer’s

disease, regional brain atrophy and altered glucose metabolism can be detected on neuroimaging 15 years before the onset of symptoms [39]. By contrast, the changes in brain structure and function associated with CV and cerebrovascular disease are largely unknown, because previous population-based studies used last-generation MRI technology without high resolution imaging. We expect that changes in brain structure (eg as measured by volumetric brain MRI) and brain functional and structural connectivity (eg as measured by resting state functional MRI and diffusion tensor imaging of white matter tracts) can be detected in association with CVD such as hypertension and diabetes, both in the presence and absence of MRI-visible signs of irreversible ischemic damage (that is, covert stroke and ischemic white matter damage). This hypothesis will be addressed in the Alliance for Healthy Hearts and Minds, in which high-resolution brain MRI imaging and a comprehensive assessment of CV risk are collected.

Carotid atherosclerosis

Subclinical atherosclerosis detected through imaging of the carotid arteries can provide insights into the type and burden of atherosclerotic disease. Prior studies have shown that the carotid vascular bed also acts as a good representative of vascular disease throughout the body providing a ‘vascular phenotype’ for the individual [40]. A variety of imaging techniques are available for carotid artery imaging, for instance Ultrasound generated intimal medial thickness (IMT) and 3D ultrasound. These two sequences will provide quantitative data regarding luminal narrowing and vessel wall volume to detect carotid plaque. In addition, the vessel wall imaging is able to characterize plaques as high or low risk by detecting the presence or absence of plaque hemorrhage [41]. Among the subset of participants undergoing the extended scan in which intravenous gadolinium is administered plaques can be further characterized for the presence of lipid within the plaques.

Measuring ectopic fat deposition in CAHHM

Although several imaging studies have documented significant associations between measures of ectopic fat accumulation (including visceral adiposity), cardiometabolic risk markers and clinical outcomes, most of these large cohort studies (Framingham [42–48], Jackson Heart Study [49–51], MESA [52, 53], INSPIRE ME IAA [54], CARDIA [55, 56]) have used computed tomography to quantify abdominal subcutaneous and visceral adiposity as well as the accumulation of unwanted lipid deposition in normally lean tissues such as the heart, the liver, the pancreas and perivascular adipose tissue. Furthermore,

among studies using MRI such as the Dallas Heart Study, the Chengdu Study and the NEO Study, most of them have been limited in scope and do not cover the comprehensive spectrum of outcomes considered in CAHHM. The present study will therefore be one of the most comprehensive cardiometabolic MRI studies ever conducted and will provide a unique opportunity to decipher the respective contributions of specific ectopic fat depots to a plethora of clinical conditions, going way beyond various cardiovascular outcomes including particular attention to several indices of brain function and health. Furthermore, the substantial subgroup of First Nations people will generate very much needed data for that population for whom we do not currently have adequate imaging data to properly describe to what extent they are susceptible or not to ectopic fat deposition.

Contextual factors measured at the individual and community level

Data describing contextual factors that characterize the nutrition, physical and tobacco environments of communities from which participants are recruited as well as individual behaviors in these domains are collected using the modified EPOCH-1 and modified EPOCH-2 questionnaires modified from the PURE study [57, 58]. EPOCH-1 is a standardized community audit developed and validated in the PURE study [57] and EPOCH-2 captures individual's perceptions of their food, activity, and tobacco environment also developed in the PURE study [58] with added questions on social ties, alcohol use, and workplace activity and food choices and behaviors.

Community audits

To study community level contextual factors as related to individual risk factors and clinical events we retrospectively defined "community" as participants are already recruited. After review of the communities from which participants in the 5 CPTP cohorts and the 2 partner cohorts originate, the forward sortation areas (FSA) was deemed to be the optimal community unit. (Table 5) We have chosen the FSA as our definition of community because: 1) there was low representation of cohort participants from census tracts in rural areas and eastern provinces of Canada, 2) the FSA are those reported by census respondents for their place of residence and this information collected from the census is available in aggregate for each FSA. This census information includes age, sex, marital status, families and household information, housing costs, mobility and migration, immigration and citizenship, income and earnings, and ethnic groups. This is balanced by some limitations of this approach include: for certain highly populated urban areas the FSA is too large to well represent the

Table 5 Number of FSAs represented by the 7 Cohorts making up the CAHHM

Province	FSA total	FSA to be assessed in CAHHM (Postal Codes)*	# in reliability assessment (%)	Number of postal codes within FSAs being assessed (sum)
BC	190	190 (+50)		112904
AB	153	153 (+46)	40 (21.1 %)	76924
SK	49	49 (+8)		21541
MN	66	66 (+12)		23943
ON	526	526 (+208)		282123
QC	419	419 (+108)	55 (10.4 %)	215565
Atlantic	230	230 (+72)		92809
NS	77	77 (+26)		28171
NB	111	111 (+30)		59530
PEI	7	7 (+2)		3995
N/L	35	35 (+14)		1113

*For FSA with income discrepancies across postal codes within the FSA, 2 audits were done to reflect the 25th percentile an

community—in this scenario, we surveyed multiple postal codes within the FSA to capture the diversity. The community level information will be used together with self-reported perception of community environment as well as behavior patterns, ie shopping, activity, and workplace. These will be used together with objective measures of the built environment from publically available databases (ie streetsmart walk-score at www.walkscore.com), which provides information by postal code on neighborhood walkability, land use mix, transportation availability and location of food retail outlets [59].

Social capital and social ties

A series of validated questions were used to measure social support from the family and the wider social environment and included questions such as participation in community organizations, civic engagement, perceived social standing, and intensity of social relationships with close confidants, and type of contact with confidants (ie in-person, telephone, email, Facebook, text messages).

Culture and immigration

Among immigrants to Canada we will probe the reasons for immigration (economic, family, refugee) and the socio-cultural connections they have made since immigration using the Immigration Questionnaire [60] and the Vancouver Inventory of Acculturation [61]. This information will be used along with measures of socioeconomic status (education, household income, employment and marriage) which has already been collected in each of the participating cohorts.

Access to and quality of health care services

A health services questionnaire was developed to collect information at the individual level and will be supplemented by record linkage to administrative, laboratory and clinical databases available in various Canadian provinces. With these data sources we plan to analyze existing population-based databases to create unique community-level profiles of access and quality of health care services including the rates of selected CV related diagnostic tests and treatments. This will be a unique component of this initiative because health care services have not been a focus of most traditional cohort studies to date and yet, it is increasingly recognized that quality of health care provided to individuals can play a major role in determining their likelihood of suffering and surviving clinical events [62]. Furthermore, how Canadians with CV risk factors are managed likely varies across the country due to factors such as physician and allied health care personnel availability, type and nature of primary care services, patient education, and socioeconomic status.

Inclusion criteria

1. Participants between ages 35 and 69 y (inclusively) at time of screening
2. Provision of Informed Consent
3. The participant is willing to undergo an MRI scan

Exclusion criteria

1. Participant is claustrophobic and/or is known to suffer from moderate to severe anxiety during MRI scans or similar procedures
2. Participant is obese and/or exceeds equipment weight limit and/or circumference of the MRI portal at time of screening
3. Participant has a metallic implant or another foreign body which is not compatible with Magnetic Resonance Imaging (MRI) (eg pacemakers, defibrillator, vascular clips, drug pumps, implant(s), or any other foreign bodies, extensive tattoo covering a large part of their chest or head)
4. Female participants that are or may be pregnant (confirmed or uncertain)
5. Received an MRI contrast agent within 72 h prior to the MRI scan.

Record linkage with health administrative databases

Data collected of participants from the CAHHM will be linked with health care administrative databases, available in various provinces, for ascertainment of cardiovascular-related health care services before and after enrollment in the study as well as long-term CVD outcomes. (Table 6) The International Classification of Diseases (ICD) codes that will be used to

Table 6 Health system quality indicators

Health system quality indicators measurable from the CPTP CVD Survey	
Participants with a family doctor	
Difficulties accessing primary or specialist care	
Weight assessment by a health professional	
Screening for hypertension, diabetes, hyperlipidemia	
Diabetics who have had eyes examined by an ophthalmologist, feet examined, urine protein tested	
Smokers who have been offered smoking cessation counseling and/or stop smoking aids	
Hypertensives who have their blood pressure treated and controlled	
Participants with hyperlipidemia who have been treated with medication to control their blood cholesterol levels	
Participants with atrial fibrillation who have been treated with blood thinners	
Health system indicators measurable from administrative data	
A. Structural variables	
# of family doctors/specialists per capita	
#, costs and types of ambulatory care visits	
#, costs and types of hospitalizations	
B. Processes of Care	
CV and non-CV medications (statins, ACE inhibitors, diuretics, Beta-blockers)	
Laboratory screening rates (lipids, diabetes)	
Lab results (lipids, diabetes)	
ECG, Stress Test, Echo, CT scans, MRI scans	
Cardiac Catheterization	
PCI	
Cardiac Surgery	
C. Outcomes	
Myocardial Infarction (STEMI/NSTEMI, unstable angina)	
Congestive Heart Failure	
Stroke (Ischemic/Hemorrhagic/TIA)	
Death (including cause of death)	
Atrial Fibrillation	
Diabetes and Hypertension	

measure various outcomes have been validated and described in detail elsewhere [63]. Most provincial health care administrative databases in Canada contain a patient health card number as a unique identifier that enables efficient deterministic data linkage of various data sets, in this instance cohort data sets with province- or region-specific administrative databases. To protect patient privacy, the health card number (HCN) in each database is typically scrambled creating another unique anonymized identifier before the actual data linkage. All participants were asked on the informed consent if they were willing to provide HCN as part of their parent cohort participation or as a

new request (and thus far out of the first 1000 participants 99.2 % have consented to provide their HCN). Due to the federated nature of the health care system in Canada, there is no single repository of administrative databases. As a result, data linkage activities will involve working with multiple data custodians and governments across the country, and will require understanding of and compliance with each province's health information privacy legislation. The Alliance is planning to work with key data custodians such as the Canadian Institute for Health Information (CIHI), which collects hospital discharge abstracts for the entire country except for Quebec, Statistics Canada which houses the Canadian Mortality Database and the Canadian Cancer Registry and various provincial health services research units located across Canada including the Institute for Clinical Evaluative Sciences (ICES) in Ontario, Population Data BC, the Population Health Research Unit, Dalhousie University, Régie de l'assurance maladie Québec (RAMQ), etc. - each of which hold administrative databases for their region/province.

Study outcomes

Primary outcomes

The primary outcomes include MI, Stroke, angioplasty, percutaneous coronary interventions, coronary artery bypass graft surgery, and other important chronic disease outcomes and death. Associations between contextual factors, CV risk factors and MRI markers will be evaluated with these outcomes individually and as a composite measure of CV events.

Secondary outcomes

Secondary outcomes for this project include:

- Congestive Heart Failure requiring hospitalization

New onset established risk factors using validated algorithms [63, 64]

- Incident diagnosis of diabetes by physician
- Incident diagnosis of hypertension by physician
- Incident diagnosis of significant cognitive dysfunction (ie dementia) by physician.

Risk markers acquired through imaging and blood samples

- Acquired parameters that are linked to the present health status
- Candidate parameters for predicting cardiovascular events which affect cardiac and cognitive dysfunction. For further details, please refer to the outcomes in the questionnaires and the MRI protocol described in the Design and Methods section above.

Statistical considerations

Power

Risk factor proportions

The proportion of risk factors will be examined across cohorts and overall. It is anticipated given the roughly representative subcohorts that recruitment of the target sample of 7000 will provide high power to compare the relative frequency of risk factors comparing men and women, participants across age strata and between non-First Nations and First Nations' Participants.

Risk factors to MRI findings

The prevalence of traditional CV risk factors will enable determination of the relative risk of the risk factors on subclinical MRI findings of RWMA, covert stroke and liver adipose tissue. For example, if among 7000 CAHBM participants the frequency of hypertension is 25 % and the frequency of covert stroke is 6.6 %, we will have a high power to detect a relative risk of hypertension on silent stroke of brain of 1.5 (95 % CI: 1.36 to 1.65).

MRI to clinical events

Several MRI markers have been tested for their predictive value versus CV events in several populations. Given the planned 7000 subjects and a predicted incident CV 5 year event rate of 5.98 % [1], we have high power (ie >90 %) to detect a hazard ratio (HR) of 2.6 among those with RWMA by MRI, high power to detect a HR of 2.85 for stroke among those with silent stroke by MRI. Further we will have approximately 80 % power to detect a 1.6-fold increase in new diabetes in those with liver fat as estimated by MRI assuming an incidence of new diabetes of approximately 10 %. Estimations of power for sample sizes lower than this (ranging from 5000 to the anticipated 7000 subjects) are also shown in Table 7. Given the limited information regarding the predictive relationship between liver fat and CVD, we identified only one published study conducted in diabetics which suggested that liver fat was associated with a 1.9-fold increase in CV incidence [65], on the other hand a study by Lazo et al. [66] reported that NAFLD by ultrasound was not associated with excess in all-cause or cardiovascular mortality in the NHANES III study – general population. While our power is too low to detect a HR of 1.9 between liver fat and CVD, our multiethnic sample which includes 2 high risk groups for visceral fat and especially liver fat and in whom we are using a superior measure of liver fat (which has greater precision as compared to ultrasound) [67] provides an opportunity for us to test the association between liver fat and CVD events in otherwise understudied populations.

Table 7 Power of given sample size between 6400 and 7400 participants recruited to detect expected hazard ratios

Exposure	Assumed prevalence of exposure	Outcome	Assumed incidence of Outcome	Expected hazard ratio	7000/ (5920) ¹	6000 / (5120) ¹	5000/(4320)
Regional Wall Motion Abnormality	0.253	CVD	0.0598	2.60	>0.99/>0.99	>0.99/0.99	>0.99/>0.99
Silent Stroke	0.069	CVD	0.0598	2.85	>0.99	>0.99	>0.99
Liver Fat ^a	0.063	T2DM	0.0974–0.1275	1.60	0.82	0.76	0.68

¹ Assuming 20 % of the participants will have existing CVD the Number of Participants free of CVD and Cancer are shown in parenthesis; ^a (assuming a higher proportion of First Nations participants are retained, relative to other groups)

Analysis

To investigate the association between risk factors and subclinical MRI findings linear (visceral fat) and logistic (RWMA, covert stroke, liver fat %) regression models must be built separately for each MRI outcome used as the dependent variable. Exposures such as age, sex, ethnicity, history of hypertension, diabetes, waist circumference, apolipoprotein B/A ratio, current smoking, physical activity, selected dietary (ie prudent diet score, or ratio polyunsaturated fat/saturated fat), and measures of cognitive function (ie when covert stroke is the outcome) will first be tested univariately, and exposures with a $P < 0.10$ will be taken forward and tested in multivariate regression models. If ethnicity is found to be an independent predictor of an MRI outcome, it will be tested with a composite CV risk score for an interaction with the outcome.

After 5 years, when enough CVD events have been accrued and ascertained through record linkage, the MRI subclinical exposure of covert stroke, global or regional ventricular function abnormalities, liver fat and visceral fat will be tested versus CVD and death to determine their predictive value of clinical events using the area under the curve (C statistics), and net reclassification improvement methods [68].

Contextual factors

Comparisons between urban and rural communities will be conducted by linear mixed models for continuous variables (ie BMI) and generalized linear mixed model (GLMM) for categorical variables (ie CVD events), in each case treating community as the random effect. Using a similar model, unadjusted correlations will be estimated between the perceived (EPOCH-2) and objective environmental measures (EPOCH-1) with the continuous or categorical outcomes. Multilevel modeling will be used to evaluate the relation between exposures at the community (FSA-level) and individual level with outcomes for each individual. All models will examine both perceived and objective environmental measures as covariates adjusted for individual and community socio-demographics. Interaction terms between urban and rural and the perceived and objective environmental measures will be investigated to determine if the contextual factors differ based on the type of community ie

urban or rural. The contribution of variance in outcomes explained by community risk factors as opposed to the individual risk factors will be quantified using the variance partition coefficient from each model. For the continuous outcomes, linear multi-level modeling will be used. For categorical outcomes (ie CVD), similar generalized linear multi-level models will be fit. Models will be adjusted a priori for individual (age, sex, ethnicity, and household income) and community variables.

Data management and data access

Participants provide information through self-reporting (eg Health Services Research - HSR, Food Frequency Questionnaire - FFQ) and interviewer administered tests (eg cognitive function testing). Participants are invited by email/mail and then directed to provide a brief informed consent and complete 2 questionnaires on-line (HSR, FFQ), once booked for an MRI visit and screened for contraindication to MRI, they complete the remainder of the assessment at the MRI site prior to or immediately after their MRI. Physical measurements are taken by clinic staff following a standardized protocol. Participants are given a card or self-record their physical measurements, highlighting any abnormal results. Data is then entered at the clinical site or faxed in using Datafax. Quality control notes are sent by the coordinating centre to the sites to correct any missing or abnormal values.

Results reporting

CV risk score

All participants receive a CV risk score report after their baseline assessment. The majority of participants receive the non-lab INTERHEART risk score which includes age, sex, family history, diabetes, hypertension, diet, activity, smoking, second hand smoke and psychosocial factors as previously described [69], and the First Nations participants receive the lab-based risk score which include apolipoproteins A and B and HbA1c..

Incidental findings (CIF)

Four core labs separately assess the Brain (Calgary or Sunnybrook), Cardiac (Montreal Heart Institute), Carotid (Sunnybrook) and Abdomen (IUCPQ). The readers follow a standardized reading protocol. Results are sent to the central project office, where they are linked with

the clinical data. These severe structural abnormalities are reported back to participants and their primary care physicians if they consented to this on their informed consent. (Fig. 1) The severe structural abnormalities are shown in the Table 8. The letter emphasizes that this is a research scan which should be followed up with a targeted clinical scan organized by the primary care physician.

Discussion

The Canadian Alliance for Healthy Hearts and Minds seeks to understand the individual and contextual origins of CVD risk and will aid in the design of effective policy and health interventions aimed at reducing population levels of risk factors in Canada. CAHHM is a unique cohort study which brings together participants’ enrolled in diverse cohorts from chronic disease focused cohort studies, in addition to creation of a new First Nations cohort.

First, CAHHM is unique as MRI is being used to identify subclinical disease, and is only one of two studies we are aware of interrogating the brain, heart, carotid arteries, and abdominal adiposity [70]. MRI represents an advantage over other imaging modalities as it is sensitive

to detect early, subclinical stages of disease on a systematic (blood) or regional (tissue) level. Availability of such validated predictors may allow the development of more effective early treatment and personalized primary prevention strategies.

Second, we developed a detailed health services questionnaire which collects information on primary care visits, counseling for health behaviors, screening for risk factors, access to pharmacists, and visits to specialist physicians. To our knowledge such a detailed collection of cardiovascular-related health services information has not been collected on such a large cross section of Canadians and will provide valuable information to enable creation of a Health Services “Report Card” for Canadians in urban and rural/remote regions.

Third, our contextual assessment of communities across Canada together with data from individuals included in our partner cohorts will enable an investigation of the “causes of the causes”, specifically the influence of contextual factors on CV risk factors. Two contextual factor assessments are being undertaken. The modified EPOCH-1 is a standardized audit completed by research personnel at the FSA level in all provinces of Canada and First Nations reserves. This will provide information on the tobacco

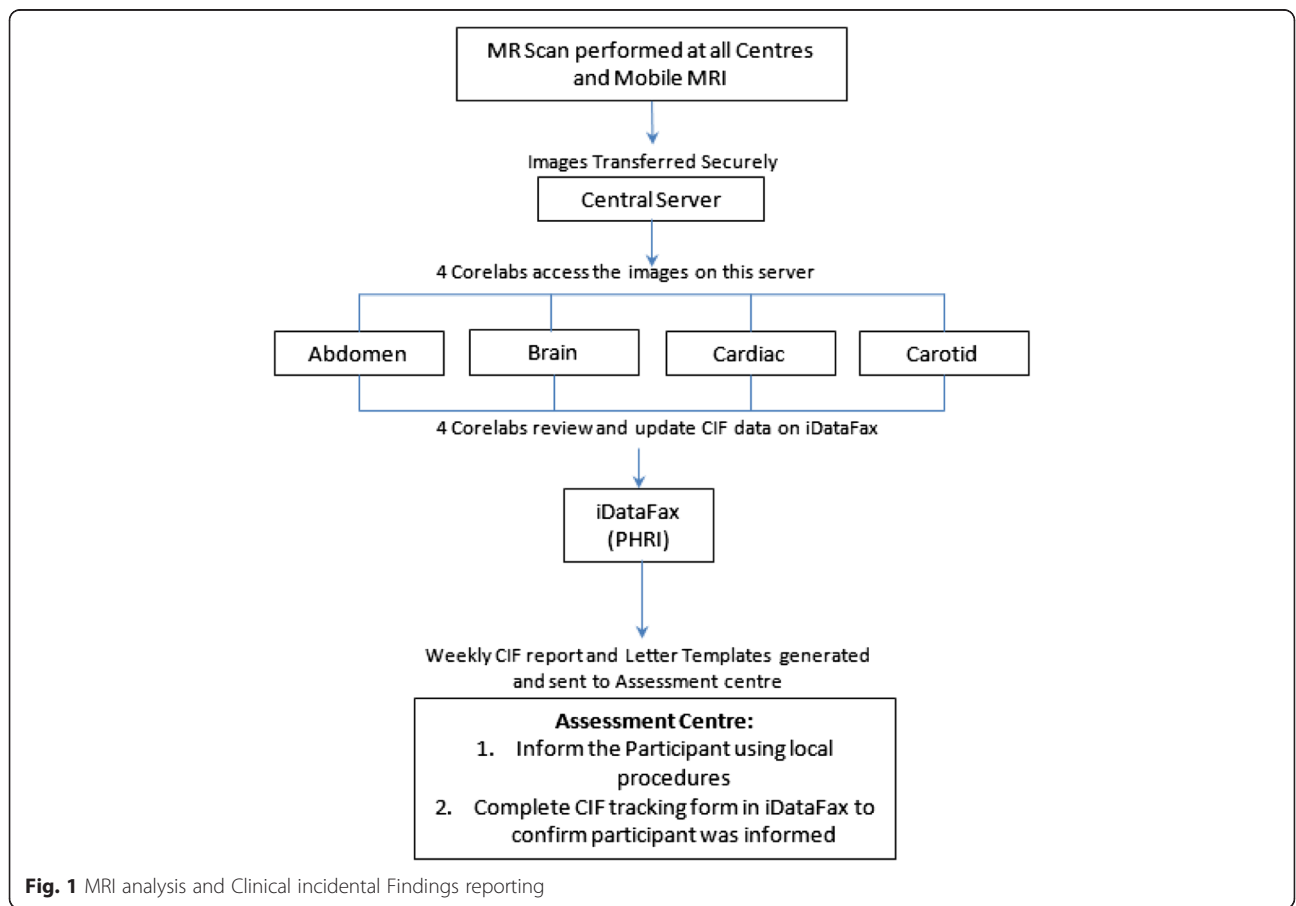


Fig. 1 MRI analysis and Clinical incidental Findings reporting

Table 8 Severe Structural Abnormalities

Abnormality	Criteria
Brain infarct	Diameter \geq 15 mm or cortical location
Myocardial infarction	High signal in LGE images from extended MRI scan or a segmental wall thickening of $<$ 10% (severe hypokinesis/akinesis) for at least 1 of the 16 standardized segments.
Aortic dilatation	Thoracic \geq 50 mm (men), \geq 45 mm (women) Abdominal \geq 45 mm (men), \geq 40 (women)
Valvular dysfunction	Moderate or severe, with LV dilatation or dysfunction
Mass	Positive criteria for malignancy or significant compression or infiltration of vital structures

environment, nutrition environment, activity environment, and social connectedness. Their precise characterization in communities across Canada will aid policy development and inform population health interventions aimed at reducing the risk for cardiac and cognitive dysfunction, and other chronic diseases.

Finally, we strive to establish a diverse cohort. Specific strategies we have adopted to enhance diverse ancestry recruitment include: i. establishment of a new First Nations cohort recruited from 10 communities across Canada, ii. prioritization by ethnicity ie South Asian, Chinese and African origin participants in the CPTP cohorts'; and iii. targeted ethnic recruitment for South Asians and Chinese origin people in Ontario.

Anticipated challenges

The CAHBM initiative is a massive undertaking to coordinate the recruitment of new and existing cohort participants from 7 existing cohorts and a new First Nations cohort, facilitating MRI scanning in urban, rural and remote regions, and conducting record linkage for clinical events using Health Card Number, across provinces, at multiple future time points. However, the study is robustly underway due to the strong commitment of interested participants, researchers, academic institutions, and funding agencies.

Conclusions

The Canadian Alliance for Healthy Hearts and Minds is a prospective cohort being established in Canada with unique features including recruitment of individuals from existing cohort studies, use of MRI of brain, heart, carotid artery and abdomen to detect subclinical abnormalities, detailed measurement of health services utilization, and measurement of individual and community level contextual factors. The information generated in CAHBM will be used to develop community and individual level CV prevention strategies for the people of Canada.

CAHBM coordination and working groups

Central coordination

Population Health Research Institute: Project Manager: Dipika Desai; Study Coordinator: Melissa Thomas; Research and Data Management Assistants: Sherry Zafar, Shaathaka Nandakumar, Sheila Bouseh, Natalie Campbell. Finance and Contracts: Beena Cracknell, Tanya Chow, Inosha Witharana, Colin Russell; Information and Communication Technology: Kevin Archibald, Kristen Avery; Statistics and Biometrics Programming: Karleen Schulze, Xiumei Yang, Cissy Tang

Advisory Committee: Pierre Boyle, Jean Rouleau, Eldon Smith, Caroline Wong.

Magnetic Resonance Imaging Coordination: Montreal Heart Institute: Felipe Henriques, François Marcotte, Julie Lebel, Matthias Friedrich.

Health Services/Record Linkage Coordination: Jack Tu, Natasa Tusevljak, Laura Maclagan.

CPTP National Coordinating Centre: Jacques Magnan, Celine Moore.

Imaging Working Group: Richard Frayne, Cheryl McCreary, Eric Smith, Sandra Black, Alan Moody, Christopher Scott, Jean-Pierre Despres, Eric Larose, General Leung, Tarik Hafyane.

Health Services Working Group: Finley McAlister, Nadia Khan, Jafna Cox, Dennis Ko, Douglas Lee, Louise Pilote, Jack Tu.

Contextual Working Group: Sonia Anand, Joseph Beyene, Gillian Booth, Daniel Corsi, Russell de Souza, Lise Gauvin, Scott Lear, Ayesha Rana, Fahad Razak, SV Subramanian, Jack Tu.

First Nations Working Group: Sonia Anand, Ellen Toth, Sharon Bruce, Stewart Harris, Christopher Lai, Paul Poirier, Sylvia Abonyi, Heather Castleden, James Irvine, Diana Lewis, Laura Arbour.

Ethnic Working Group: Maria Chiu, Gordon Moe, Jack Tu, Sonia Anand.

Data Harmonization and Ethics: Isabel Fortier, Bartha Knoppers, Ma'n Zawati.

Additional file

Additional file 1: CAHBM Local Site Investigators and MRI Coordination. CAHBM Participating Cohorts Pls. (DOCX 12 kb)

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Availability of data and material

Not applicable.

Authors' contributions

SSA, JVT, MGF, DD, RdS, PA, PR, JS, KKT, SL, LP, ES, EL, AM, SB contributed to the overall study design; all other authors contributed to the design and implementation of the study in their local centre SSA wrote the first draft of the manuscript; all other authors contributed to subsequent revisions. All authors read and approved the final manuscript.

Authors' information

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Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

Ethics approval and consent to participate

The project has been approved by Hamilton Integrated Research Ethics Board: Project# 13–255. All participants have signed consent forms prior to participating in the study.

Author details

¹McMaster University, Hamilton, Canada. ²University of Toronto, Toronto, Canada. ³University of Montreal, Montréal, Canada. ⁴Sunnybrook Research Institute, Toronto, Canada. ⁵CARTaGENE, Quebec, Canada. ⁶Quebec Heart and Lung Institute, Quebec, Canada. ⁷Hamilton Health Sciences, Hamilton, Canada. ⁸Population Health Research Institute, Hamilton, Canada. ⁹Laval University, Québec, Canada. ¹⁰Dalhousie University, Halifax, Canada. ¹¹McGill University, Montréal, Canada. ¹²Simon Fraser University, Burnaby, Canada. ¹³Alberta Health Sciences, Edmonton, Canada. ¹⁴University of Calgary, Calgary, Canada. ¹⁵Montreal Heart Institute, Montréal, Canada. ¹⁶Institute for Clinical Evaluative Sciences, Toronto, Canada. ¹⁷BC Cancer Agency and University of British Columbia, Vancouver, Canada.

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