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Physical Activity Trails in an Urban Setting and Cardiovascular Disease Morbidity and Mortality: A Study Protocol for a Natural Experiment

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Abstract

Introduction: Aspects of the built environment that support physical activity are associated with better population health outcomes. Few experimental data exist to support these observations. This protocol describes the study of the creation of urban trials on cardiovascular disease (CVD)-related morbidity and mortality in a large urban centre.

Methods and Analysis: Between 2008 and 2010, the city of Winnipeg Canada, built four, paved, multi-use (eg. cycling, walking, running), two-lane trails, that are 5-8km long and span ~60 neighbourhoods. Linking a population-based health data with census and environmental data, we will perform an interrupted time series analysis to assess the impact of this natural experiment on CVD-related morbidity and mortality among individuals 30-65 years of age residing within 400m-1200m of the trail. The primary outcome of interest is a composite measure of incident major adverse CVD events (i.e. CVD-related mortality, ischemic heart disease, stroke, congestive heart failure). The secondary outcome of interest is a composite measure of incident CVD-related risk factors (i.e. diabetes, hypertension, dyslipidemia). Outcomes will be assessed quarterly in the 10 years before the intervention and five years following the intervention, with a four year interruption. We will adjust analyses for differences in age, sex, ethnicity, immigration status, income, gentrification and other aspects of the built environment (i.e. greenspace, fitness/recreation centres, walkability). We will also assess trail use and trail user profiles using field data collection methods (Trial Registration: NCT04057417).

Ethics and Dissemination: Ethical approvals for the study have been granted by the Health Research Ethics Board at the University of Manitoba and the Health Information Privacy Committee within the Winnipeg Regional Health Authority. We have adopted an integrated knowledge translation approach. Information will be disseminated with public and government partners.

Strengths and Limitations:

- We are relying on natural experiment consisting of the expansion of trails within an urban environment to test our research hypothesis.
- We have access to data for the entire urban population over a 20-year time frame, capturing all health-related end-points
- We are triangulating health outcome data with robust field data on trail use to describe the population impact of the trail expansion
- We cannot determine individual-level physical activity levels in persons living within intervention neighbourhoods
- We will not be able to capture individual-level trail use and therefore do no know what percentage of the population within each neighbourhood are using the trails

Rationale

The built environment is at the interface of public and health policy[1,2]. Social scientists have explored the association between the environment and health for decades[3], and a growing body of evidence show some aspects of the built environment are associated with cardiovascular disease (CVD)[3] and its preceding risk factors[4-8]. The favourable associations between aspects of the built environment and CVD-related health have been observed primarily through the promotion of physical activity.

Various elements of the built environment are associated with increased physical activity, particularly access to walkable neighbourhoods and green space, and the proximity of recreation facilities[2,4]. Importantly, individuals living in built environments that facilitate physical activity (e.g. greater access to walkable neighbourhoods and green space) display more favourable cardiovascular health profiles[2,9,10]. For example, individuals are 10-20% more likely to meet daily recommendations for physical activity and 5% less likely to have obesity for every incremental increase in access to recreational facilities, green space, and walkable neighbourhoods[2,11]. Conversely, individuals living in environments with more fast food outlets and fewer healthy food options are more likely to eat unhealthy food, and live with obesity or diabetes[12,13]. Based on these associations, changes to the built environment are projected to be a cost-effective population health intervention to promote physical activity and prevent CVD[14,15]. Unfortunately, there are limited studies of the built environment and CVD-related morbidity and mortality. Additionally, current evidence in this field largely draws on underpowered cross-sectional studies[4,16]. While associations between the built environment and health behaviours

seem robust, it remains unclear if changes to the built environment are associated with improved health outcomes. Accordingly, experimental data are needed to determine if, and the extent to which, changes to the built environment are associated with reduced CVD-related morbidity and mortality[17-19].

Elements of the built environment that support physical activity include neighbourhood walkability, access to greenspace and proximity to fitness/recreation centres[2]. Urban multi-use trails are an additional, but poorly studied, aspect of the built environment that could support greater population-level daily physical activity[20]. Urban trails are multi-use protected areas for cycling alone or a combination of cycling, walking and running. They can be used to facilitate active transportation or a combination of active transport and recreational physical activity. Despite widespread growth of trail networks in urban areas, they are not included in calculations of walkability within a neighbourhood[21], and little information exists for their association with health outcomes.

As randomized controlled trials are virtually impossible in this field, natural experiments provide the only feasible opportunity to generate experimental evidence to examine a potential causal link between the built environment and health outcomes. The most recent systematic review and meta-analysis investigating the influence of the built environment on health outcomes, found no experimental studies and none of the studies included disease-specific CVD or CVD-related outcome measures (i.e. mortality, myocardial infarction, and/or co-morbid conditions)[9]. Consistent with the results of observational studies examining associations between the built environment and health, the majority of natural experiments revealed improvements in more proximal measures of CVD, for example physical activity; however, there is no experimental evidence examining whether changes in the built environment lead to changes in CVD-related morbidity or mortality[9].

The current study describes the methods and protocol for a natural experimental study evaluating the impact of a large expansion of an urban trail network on CVD-related morbidity and mortality in a large urban centre in Canada.

Methods and Analysis

Study Aims and Hypotheses

The primary objective of this natural experimental study is to capitalize on major changes to the built environment that occurred in Winnipeg, Canada between 2010 and 2014 to determine if a significant expansion of an urban trail network is associated with reduced CVD-related morbidity and mortality. The secondary aim of the study is to determine the cost-benefit ratio of this intervention compared to forecasted costs associated without the expansion of the urban trail network. The last aim of the study is to describe patterns of trail use and trail users during the intervention time period. Our primary study hypothesis is that an expansion of an urban trail network will reduce population-level CVD-related mortality and morbidity in neighbourhoods within 400-1200m of the new trail compared to neighbourhoods lying outside these boundaries.

Study Design

The most robust approach to test this research hypothesis is a quasi-experimental interrupted time series analysis with a comparison condition. The proposed interrupted time series analysis is strengthened by the use of a social and health data repository that provides an opportunity to link census, social and health data for the entire population of the City of Winnipeg beginning in 1995[22-27]. Interrupted time series designs are considered the most valid quasi-experimental designs when a randomized controlled trial is not possible[28,29]. They are the preferred design for population health interventions or pragmatic experiments as they strengthen pre-post designs, particularly if an appropriate comparison condition is available[28-30]. This approach is considered the gold standard for a natural experiment, as it captures real-world changes in population-level health outcomes following large policy or practice changes[31-34] that can eventually inform changes in health systems.

Using population-level outcome data over a 20-year period (2000 – 2019), we will construct an interrupted time series with a comparison condition. We selected a 20-year time frame as it will provide ~60 data points (~40 before and ~20 after the intervention) to test for changes in the slopes of CVD-related morbidity and mortality between groups before and after the expansion of urban trails. This design will allow us to better control for biases that

accompany non-randomized study designs [35-37] such as (1) secular trends, which in this case may be changes in CVD rates that could be interpreted as intervention effects if comparison neighbourhoods were not available; (2) seasonal effects, as rates of CVD tend to be higher during winter months[38]; (3) duration of the intervention where trails may only be used in the first few months or years following construction and data collected in the year or two following the expansion would not have identified this effect; (4) random short-term fluctuations in CVD rates that may occur which do not reflect overall trends and can lead to biased intervention effect estimates if only a short time window is studied, and (5) autocorrelation where rates of CVD are likely to be associated between time points and between neighbourhoods. In addition to employing an interrupted time series design to minimize biases, we will employ a series of complimentary statistical features that include segmented time series regression techniques[28,37] and autoregressive integrated moving average models[30,39]. To improve comparability of treatment and comparison neighbourhoods, we will create balanced treatment and comparison groups using propensity score matching[40].

Study population

This study will be conducted within the metropolitan area of Winnipeg, Manitoba, Canada's seventh largest urban centre. It is considered a slow growth city, relative to other major urban centres in Canada[41]. Winnipeg includes ~700,000 residents, representing >50% of the population of the province of Manitoba. Data from administrative health care databases within the Manitoba Centre for Health Policy (MCHP) will be used to derive population-level estimates of CVD and CVD-related co-morbid conditions as previously done[42-44]. Health information for local residents will be linked to dissemination-level data using individual postal codes. We will restrict the analyses to the adult population aged 30 to 65 years as previously done[21], as CVD end-points are <1/10,000 among persons under 30 years in Manitoba[42].

Intervention group: Winnipeg urban trail network expansion

In the Canadian context, an urban trail is a multi-use public path which creates an attractive transportation and leisure activity corridor through a built environment, used largely during the summer months[45]. Urban trails are an ideal component of the built environment to study with a quasi-experimental design and aggregated data. In contrast to more commonly

studied aspects of the built environment that promote physical activity (e.g. neighbourhood walkability, green space), trails are substantially easier to manipulate, as they require minimal space within the urban landscape and can affect a much larger segment of the urban population as they cross multiple neighbourhoods.

Between 2008 and 2010, the City of Winnipeg and Province of Manitoba invested $25 million to expand the infrastructure for leisure and transportation-based physical activity. Several mixed socio-economic neighbourhoods within Winnipeg were exposed to one of four new urban trails between 2008 and 2010, affecting roughly 250,000 residents within ~350 dissemination areas. Details of the greenways are provided in Table 1 and their location within the city are provided in Figure 1. The four multi-use urban trails are over five kilometers in length, paved, two lane paths that are cleared and maintained by the City of Winnipeg Department of Transportation 12 months of the year. They provide efficient and desirable trails for both active transportation and leisure physical activity. The majority of the population of Winnipeg do not live in dissemination areas that are within a reasonable distance to access the urban trails and therefore will be treated as the control condition. (Figure 1 – Map).

Outcome measures

The primary outcome measure will be a composite endpoint of incident CVD-related events including new hospital admissions for cardiac-related events (CVD-mortality, ischemic heart disease and stroke) and CVD-related co-morbidities (Table 2). ICD-9-CM codes will be used up to 1 April 2004 and ICD-10-CA codes afterwards for disease diagnosis (appendix, Table 1). These end-points were selected as they represent the largest burden of CVD-related morbidity in Canada, are the most relevant to policy makers and most likely to be modified by increased physical activity levels. These outcomes are derived from validated algorithms, providing an extremely accurate and sensitive capture of end-points[43,46]. Heart failure and peripheral artery disease will not be included in the composite outcome as algorithms have yet to be validated in the repository. The secondary outcome measure will be CVD-related co-morbidities, including hypertension, diabetes and dyslipidemia, as they are more proximal outcomes associated with changes in physical activity levels[1,2,21] and therefore more likely to change within neighbourhoods during the relatively short time frame of this intervention (Table 2).

Exploratory and Confounding Variables

Trail Usage

Eco-Counter Dual Inductive Loop Zelts are automated cyclist counters that will be used to measure trail usage as an exploratory variable, between 2014 and 2019[47]. Zelts have been discussed as an acceptable and reliable research tool to capture trail use[48]. Zelts are comprised of a main unit and sensory wiring. The main unit includes a battery, Global System for Mobile (GSM) transmission device and counting unit buried in manholes on the outer edge of a trail. Zelt counters will be placed at ten locations across the five trail developments and will collect cyclist data for 24 hours/day, seven days per week. Data collected from Zelts are time stamped and automatically uploaded to Eco-Visio online software via cellular networks at 3:00 a.m. everyday.

Field data collection to survey trail users

To determine trail user demographics, we will conduct two waves of intercept surveys among a convenience sample of ~1000 trail users, one wave in 2018 and one in 2019. Users will be asked to complete a brief survey to provide demographic information, self-reported trail usage and the perceived impact of usage on both their physical and mental health. These surveys will be designed to be completed in three to five minutes, to minimize participant burden and facilitate the collection of responses from the highest possible number of users. Demographic data will include self-identified gender and ethnicity, age group, residential postal code, newcomer status and annual household income. Analyses of these data will determine which, if any, specific groups experience disproportionate access to the trails. Usage data will outline typical weekly trail use (in terms of frequency, duration and types of activities), commute time to reach trail paths, and reasons for using the trail system. Survey collection will occur year-round when weather permits as either paper or technological survey instruments may not perform optimally in extreme winter conditions.

Survey participants will be asked to provide the first three digits of their postal code. This data will be used to geo-map the neighbourhoods of visiting users for each trail through dot density mapping techniques. Geo-maps will reflect the population distribution and demographic variation represented at each trail. Postal code data and produced geo-maps will also be

combined with City of Winnipeg Census data (2016) to provide insight into represented residential neighbourhood distributions for ethnicity and household income.

Confounding Variables

A detailed list of confounding variables and their source are provided in Table 3.

Socioeconomic status: Household income will be determined by census data, which are publically available every five years. We will rely on data from the 2006 and 2016 surveys to assess household income. We will also rely on a validated continuous index of material and social deprivation (socio-economic factor index, SEFI), that is calculated for each dissemination area in the province of Manitoba and reflects neighbourhood-level socio-economic well being[49].

Gentrification

Gentrification describes demographic changes that may occur in a community over time as individuals with a higher socioeconomic status move into lower socioeconomic areas[50]. Since socioeconomic status can have large implications for outcomes related to CVD[51-53], diabetes[51,54] and mortality[52,55], it will be important to account for gentrification within neighbourhoods. First, changes in property taxation between 2008 and 2018 assessed by the City of Winnipeg will be examined for each included neighbourhood to approximate increases or decreases in household value. Additionally, 2001 Canadian Census data and the 2016 National Household Survey data will be used to determine shifts in relevant indicators including poverty, education, unemployment rates, language barriers, average household income and ethnicity. Finally, data characterizing retail indicators will be obtained from DMTI Spatial Inc (2006 to 2016) to compare the number and ratio of specialty coffee houses versus coffee and doughnut shops per capita within neighbourhoods[21]. This will act as a surrogate variable representing demographic shifts in retail demands.

Built Environment Determinants of Physical Activity

The Canadian Urban Environmental Health Research Consortium (CANUE) is a multi-disciplinary collaboration of specialists focused on environmental exposures and population health.[56] CANUE integrates several population health databases and environmental exposure datasets into an openly available resource. From the CANUE dataset we will integrate examine

several estimates of greenspace, including accessibility of green space, type of vegetation, tree canopy cover in control for access to greenspaces in the treatment and comparison and intervention neighbourhoods across Winnipeg via the 2016 ArcGIS survey. All these data will be treated as confounding and adjusted for in the final analyses. We will also assess neighbourhood walkability using CAN-ALE scores calculated from a GIS-based composite of population density, mixed land use, access to public transportation and street connectivity. Finally, we will estimate the number of fitness and recreation centres within three kilometres of each household.

Patient and Public involvement: Members of the public will be involved at several stages of the study. Members of the public were involved in developing the study design, in response to priorities established by a local organization (Winnipeg Trails Association) dedicated to supporting urban trails for physical activity. Members of the public will help with recruitment of trail users during field data collection and collect survey responses. This organization will also develop public and policy maker-friendly tools to disseminate results of the study via their social media platforms and at local meetings. The organization, represented by its executive director (AS), acted as a co-applicant on the grant and a collaborator throughout the project.

Power calculation and sample size

We have the advantage of leveraging a health data repository that includes the majority of residents in Winnipeg and captures all endpoints that occurred within each time point for residents in that neighbourhood. During the pre-intervention period (2006/07 and 2011/12), overall mortality, annual incident rates of ischemic heart, hypertension, and diabetes were nearly identical between treatment and comparison neighbourhoods[42]. The stability of outcome measures will facilitate the detection of small, but meaningful, changes in trends or absolute events within treatment neighbourhoods. Segmented regression with propensity score matching will be used to compare changes in event rates between treatment and comparison neighbourhoods. The goal of the propensity score matching will be to pair the approximately 60 treated units (i.e. neighbourhoods) with approximately 60 randomly selected comparison units balanced on key covariates known to influence physical activity levels and CVD-related mortality and morbidity, (socioeconomic status [SES], age, ethnicity and walkability) permitting

analysis of data as if it arose from a randomized design[57]. Power analysis is based on a comparison of incidence rates in matched treated and comparison units.

Sample size calculations for clustered count data, where treatment assignment is at the neighbourhood level and the outcome is an incidence rate (e.g. Poisson count), were used to estimate the minimal detectable effect size[18]. We applied the Hayes-Donner method to estimate the number of neighbourhoods required to discern a given effect size, expressed as the difference between group-specific incidence rates under the assumption of a shared coefficient of variation across groups. These are conservative estimates, since they do not account for the paired nature of the data[58]. Using pre-intervention neighbourhood incidence rates[42], we created a power plot of the minimal detectable effect based on number of neighbourhoods affected by trail expansion. Outcome-specific incidence rates were calculated from MCHP-led Health Atlases[42,59] for 26 well-defined Winnipeg neighbourhoods between 2002-2007 (pre-intervention, crude rates per 100 person-years). Assuming an alpha = 0.05, beta = 0.2, and an average neighbourhood incidence rate for the composite outcome ≈ 4.95 ± 0.45 per 100 person years in treatment and comparison tracts[42], we are powered to detect a 10% difference in the primary outcome with 50 treatment neighbourhoods and 9% with 60 neighbourhoods[58]. This effect size is relevant to stakeholders as it translates into 350 fewer CVD-related events annually within the city. The effect is conservative, as previous population interventions like smoking bans (17% reduction in CVD events[60]), new public transportation (80% difference in odds of obesity[61]) or more walkable neighbourhoods (19% reduced incidence of type 2 diabetes[21]) have yielded larger effects.

Proposed analyses

To test the primary study hypothesis, that an expansion of an urban trail network will reduce population-level CVD-related mortality and morbidity in neighbourhoods within 400m-1200m of a new trail (intervention group), to a greater extent than neighbourhoods outside those boundaries, outcome data will initially be aggregated by neighbourhood and trends analyzed for the entire study period. The two primary outcome measures, composite end-points of incident major adverse CVD-related events and CVD-related risk factors will be treated as binary outcomes collected ~36 during the pre-intervention period and at 36 time points after the intervention (i.e. trail expansion), following Cochrane recommendations[35]. There will be a

two-year[35] lag incorporated into the time series reflecting the time during which the trails were being constructed. These time points reflect extensive literature showing that CVD-related behaviours[62,63] and endpoints vary seasonally[64,65] and that the impact of natural experiments requires several years to be detected at the population level[28,35,37].

Time Series Analyses

We will use two different time series methods to estimate the effect of the intervention on CVD-related end-point incident rates in treatment neighbourhoods relative to trends among the comparison neighbourhoods. First, a multi-group segmented regression of interrupted time series data will be used to assess the effect of the intervention on CVD-related incidence, both immediately (change in level) and over time (change in trend) by creating indicator variables as described elsewhere[37,40]. The level will be the base rate of CVD-related end-points at the beginning of the pre-intervention period (2000) and the value immediately following each change point at which successive segments join until 2010. The trend is the rate of change of CVD-related end-points (in other words, the slope) during a segment. Autoregressive errors will be modeled to account for correlated outcomes.

Autoregressive integrated moving average

An autoregressive integrated moving average (ARIMA) model will be fitted for the CVD incidence time series by using the standard approach for identification, estimation, and checking[66]. Trend and periodic seasonal terms will be applied to the entire study period (January 2000 to July 2019). A separate ARIMA model will also be built for the pre-intervention period to forecast CVD evolution of the treated neighbourhoods. The number of CVD end-points prevented by the intervention will be estimated by calculating the difference between the predicted number and the observed number of cases. Should we encounter difficulty fitting an ARIMA model to a relatively small dataset, we will rely on exponential smoothing models or the Holt Winters Algorithm[66]. Although they require larger sample sizes, these methods are ideal for this project as (1) they permit a variety of different types of intervention effects to be modeled explicitly, and (2) they are well suited to forecasting future trends.

Cost-Benefit analysis

The cost-benefit analysis will focus on describing the "value for money" of the intervention. The objective of the economic analysis is to compare the cost and effect of the treatment group relative to the comparison group data collected in the study[67]. To align with the effectiveness analysis, the primary outcome variable in the economic analysis will be a composite endpoint of incident composite CVD-related end-points, similar to previous studies by one of the team members[67-69]. Costs for each participant will include those associated with the intervention (e.g., trail construction and maintenance costs) and health service utilization obtained from administrative data. From the perspective of the public payers (provincial and federal governments), we will conduct the economic analysis using the net benefit regression framework[70,71] which enables an adjustment for potential confounders. The main output of the economic analysis is the incremental net benefit of the treatment relative to the comparison group. In addition, we will estimate incremental cost-effectiveness ratios which will represent an incremental cost per one incident CVD end-point prevented or one CVD-related co-morbidity prevented. Furthermore, as there are more than one public payer for this intervention (e.g., Government of Winnipeg, Government of Manitoba), we will conduct separate analyses for each relevant perspective to assess the "value for money" specifically to each payer. We will characterize the uncertainty of our findings using a cost-effectiveness acceptability curve and 95% confidence interval. In addition, we will explore the possibility of building a decision analytic model which will examine the potential long-term economic impact of the intervention after the study period[72]. This economic model will use various data sources to estimate costs including the study[73,74], published literature[67-69], and expert opinion.

Ethical Approval: All aspects of the study design have been approved by the Biomedical Research Ethics Board at the University of Manitoba (Approval ID: REB_HS20928 (H2017232)) and the Health Information Privacy Committee within the Province of Manitoba (Approval ID: HIPC - 2019/2020-05)

Discussion

The proposed natural experimental study will fill a large gap in our understanding of the impacts of changes to the built environment on CVD-related outcomes. Specifically, we will provide critical experimental evidence for the impact of changes to urban spaces for recreational physical activity and active transportation on CVD-related morbidity and mortality. Additionally, to support evidence for future policies relating to urban activity corridors, we will also provide an estimate for the cost-effectiveness of large urban trail networks within cities.

DECLARATIONS

Ethics approval and consent to participate: This study was approved by the Biomedical Research Ethics Board at the University of Manitoba (H2017:232) and the Health Information Privacy Committee at the Winnipeg Regional Health Authority (HIPC - 2019/2020-05).

Competing Interests: The authors declare that they have no competing interests.

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Tables and Figures

Figure 1. Map of Trail Locations within Winnipeg, Manitoba Canada.

Table 1. Details of the intervention: New Urban Trails

Table 2: Outcome Measures

Table 3: Potential sources of confounding between intervention and control arms that are available within linked databases.

Table 1. Details of the intervention: New Urban Trail Greenways

Variable	Northeast Pioneers	Yellow Ribbon	Bishop Grandin	Transcona Trail
Original Land Use	Converted rail line	Paved grassland	Paved grassland	Paved grassland / industrial re-appropriation
Const. Start Date	Summer '07	Summer '09	Summer '08	Summer '10
Completion date	~Autumn '12	~Autumn '11	~Autumn '10	~Autumn '10
Const. Start Date	Summer '07	Summer '09	Summer '08	Summer '10
Completion date	~Autumn '12	~Autumn '11	~Autumn '10	~Autumn '10
Distance of Trail	6.5km	5km	8km	6.7 km
Dissemination areas within 800m access	103	48	243	45
Estimated pop. within 800m	53 308	20 376	153 015	21 915
Immediate adjacent environment	Trail located between two major roadways	Greenspace, neighbourhood, airport	Major roadway and neighbourhoods/ business parks	Neighbourhood, grassland, business park
Mixed land use	High (homes, schools, shopping, recreation, parks)	Medium (homes, schools, parks)	High (homes, schools, shopping, parks)	Medium (homes, shopping, parks)

Table 2. Outcome Measures in the natural experiment of urban trail expansion

Category	Variable	Outcome	Definition	Source
Primary	Major adverse cardiovascular events (MACE) - Composite	CVD-related mortality	Death in vital statistics mortality data with most responsible cause of death coded as CHF, IHD or stroke.	Vital statistics mortality
		Ischemic heart disease	-1+ Inpatient Hospitalizations -2+ Physician visits in 5 years -1 Physician Visit & 2+ Rx in 5 years	Hospital abstracts, Medical claims, DPIN prescription dispensations
		Congestive heart failure	-1+ inpatient visits or 2+ physician visits	Hospital abstracts, Medical claims
		Cerebrovascular event	- 1+ Inpatient Hospitalizations - death in hospital	Hospital abstracts
Secondary	CVD-related risk factors - Composite	Hypertension	-1+ Inpatient Hospitalizations -2+ Physician visits in 2 years	Hospital abstracts, Medical claims
		Diabetes	-1+ Inpatient Hospitalizations -2+ Physician visits in 3 years -2+ Rx for glucose lowering agents in 3 years,	Hospital abstracts, Medical claims, Prescription dispensations
		Dyslipidemia	-1+ Hospitalization -2+ Physician visits in 3 years -2+ Rx for statins in 3 years	Hospital abstracts, Medical claims, Prescription dispensations
Secondary	Trail use	Bicycle counts		Eco-Counter Magnetic Zelts

				located beneath greenways
Exploratory	Income	Household	Self-reported	Intercept surveys
	Ethnicity		Self-reported	
	Gender	Male, female, other	Self-reported	
	Residence	Postal code	Self-reported	
	Weekly use	Visits/week	Self-reported	
	Time on trail	Minutes/use	Self-reported	

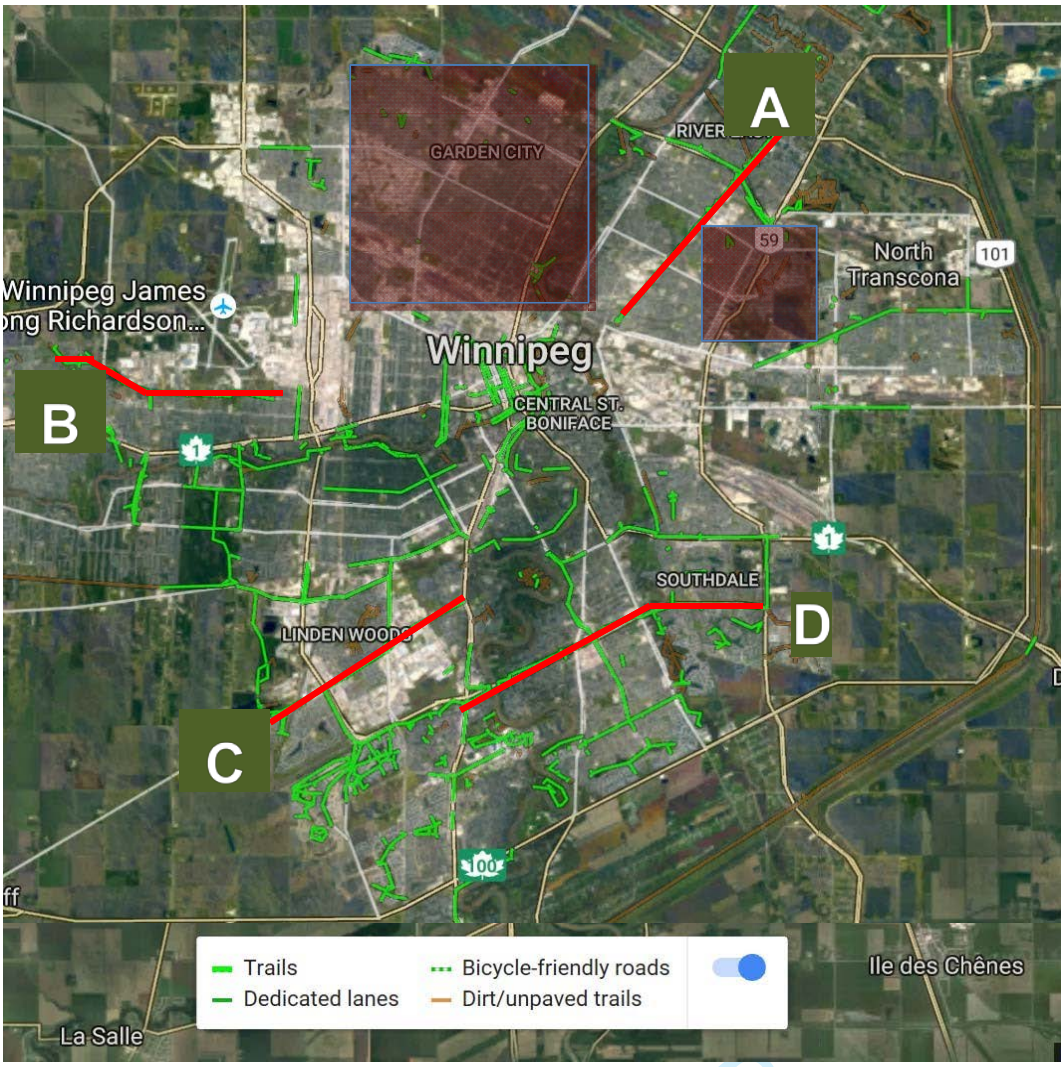
CHF = congestive heart failure; CVD = cardiovascular disease; ICD = international classification code; IHD = ischemic heart disease, Rx = prescription

Table 3. Potential sources of confounding between intervention and control groups that are available within linked databases

Category	Variable	Definition	Source	Years available
Socio-economic status	Income	Household income	Census	2006 and 2016
	SEFI	Material and social deprivation	MCHP repository	Annual
Demographics	Age		Census	2006 and 2016
	Sex		Census	2006 and 2016
	Ethnicity		Census	2006 and 2016
	Immigration status		Census	2006 and 2016
Gentrification	Change in mean age neighbourhood	Taxation valuation of value of property	City of Winnipeg	2008 to 2018
	Property value			
Built environmental factors that support physical activity	Greenspace	Distance to park (kms)	DMTI/CANUE	2006 and 2016
	Walkability	Population density, mixed land use, connectivity	CAN-ALE (CANUE)	2006 and 2016
	Fitness/Recreation Centres	Distance to centre	CANUE	2006 and 2016

SEFI = socioeconomic factor index; DMTI = Digital Mapping company name; MCHP = Manitoba Centre for Health Policy; kms = kilometers

Figure 1. Trails included in the natural experiment as of 2016



Complete trail map includes old and new trails, comprising ~400km of total trails. Large red trails are "high dose" multi-use trails that extend across multiple neighbourhoods and accessible 12 months of the year

(A= Northeast pioneers greenway; B= Yellow ribbon greenway; C= Harte Trail & D= Bishop Grandin green way).Other green lines represent medium or low impact bike trails or gravel trails not used in winter or only for active commuting. Note large red areas that have not received trails.

Appendix sTable 1. Diseases or risk factors classification and corresponding International Classification of Disease (ICD) codes, in alphabetical order.

INDICATION	ICD TITLE	ICD 10 CODE	ICD 9 CODE
Diagnoses indicative of a cardiovascular disease endpoint – Primary outcome			
Ischemic heart disease	Angina pectoris	I20	413
	Acute myocardial infarction	I21	410, 434.91
	Subsequent myocardial infarction	I22	412
	Other acute ischaemic heart diseases	I24	411
	Chronic ischaemic heart disease	I25	414
Cardiac arrest	Cardiac arrest	I46	427.5
Heart failure	Heart failure	I50	428
Cerebral infarction	Cerebral infarction	I63	433, 434, 435
	Stroke	I64	437.0, 437.1, 437.3
Diagnoses indicative of a cardiovascular disease risk factor – Secondary Outcome			
Diabetes	Diabetes	E11	250
Hyperlipidemia	Dyslipidemia	E78	272.3, 272.5, 272.6
Hyperlipidemia	Pure hypercholesterolaemia	E78.0	272.0
	Pure hyperglyceridaemia	E78.1	272.1
	Mixed hyperlipidaemia	E78.2	272.2
	Hyperlipidaemia, unspecified	E78.5	272.4
Hypertension	Essential (primary) hypertension	I10	401, 459.3
	Hypertensive heart disease	I11	402

	Hypertensive renal disease	I12	403
	Hypertensive heart and renal disease	I13	404
Diagnoses leading to exclusion from the cohort			
Cardiomyopathy	Endocardial fibroelastosis	I42.4	425.3
	Endomyocardial disease	I42.3	425.0
	Congenital cardiomyopathy	I42.8	Not applicable
	Familial cardiomyopathy	I42.9	425.9
Congenital malformation of circulatory system	Congenital malformations of the circulatory system	Q20 to Q28	745, 746, 747, 759.9
Cystic fibrosis	Cystic fibrosis	E84	277.0
Ineligible diagnoses (not considered as outcome, but did not warrant exclusion of the participant)			
Other cardiovascular problems (eg cause is viral, genetic, alcoholic, etc.)	Other cardiovascular problems	E78.7, E78.8	424.9, 425.2, 425.5, 425.7, 425.8, 425.9
Arrhythmia*	Cardiac dysrhythmias	I49	427 excluding 427.5 (see Cardiac arrest)
	Abnormalities of heart beat	R00 to 03	785.3

*Arrhythmias were ineligible because their definition in administrative databases has not yet been validated and a local pediatric cardiologist informed us that most dysrhythmia diagnoses or referrals would not be considered cardiovascular disease or risk.

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Physical Activity Trails in an Urban Setting and Cardiovascular Disease Morbidity and Mortality in Winnipeg, Manitoba, Canada: A Study Protocol for a Natural Experiment

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Abstract

Introduction: Aspects of the built environment that support physical activity are associated with better population health outcomes. Few experimental data exist to support these observations. This protocol describes the study of the creation of urban trials on cardiovascular disease (CVD)-related morbidity and mortality in a large urban centre.

Methods and Analysis: Between 2008 and 2010, the city of Winnipeg Canada, built four, paved, multi-use (eg. cycling, walking, running), two-lane trails, that are 5-8km long and span ~60 neighbourhoods. Linking a population-based health data with census and environmental data, we will perform an interrupted time series analysis to assess the impact of this natural experiment on CVD-related morbidity and mortality among individuals 30-65 years of age residing within 400m-1200m of the trail. The primary outcome of interest is a composite measure of incident major adverse CVD events (i.e. CVD-related mortality, ischemic heart disease, stroke, congestive heart failure). The secondary outcome of interest is a composite measure of incident CVD-related risk factors (i.e. diabetes, hypertension, dyslipidemia). Outcomes will be assessed quarterly in the 10 years before the intervention and five years following the intervention, with a four year interruption. We will adjust analyses for differences in age, sex, ethnicity, immigration status, income, gentrification and other aspects of the built environment (i.e. greenspace, fitness/recreation centres, walkability). We will also assess trail use and trail user profiles using field data collection methods (Trial Registration: NCT04057417).

Ethics and Dissemination: Ethical approvals for the study have been granted by the Health Research Ethics Board at the University of Manitoba and the Health Information Privacy Committee within the Winnipeg Regional Health Authority. We have adopted an integrated knowledge translation approach. Information will be disseminated with public and government partners.

Strengths and Limitations:

- We are relying on natural experiment consisting of the expansion of trails within an urban environment to test our research hypothesis.
- We have access to data for the entire urban population over a 20-year time frame, capturing all health-related end-points
- We are triangulating health outcome data with robust field data on trail use to describe the population impact of the trail expansion
- We cannot determine individual-level physical activity levels in persons living within intervention neighbourhoods
- We will not be able to capture individual-level trail use and therefore do no know what percentage of the population within each neighbourhood are using the trails

Rationale

The built environment is at the interface of public and health policy[1,2]. Social scientists have explored the association between the environment and health for decades[3], and a growing body of evidence show some aspects of the built environment are associated with cardiovascular disease (CVD)[3] and its preceding risk factors[4-8]. The favourable associations between aspects of the built environment and CVD-related health have been observed primarily through the promotion of physical activity.

Various elements of the built environment are associated with increased physical activity, particularly access to walkable neighbourhoods and green space, and the proximity of recreation facilities[2,4]. Importantly, individuals living in built environments that facilitate physical activity (e.g. greater access to walkable neighbourhoods and green space) display more favourable cardiovascular health profiles[2,9,10]. For example, individuals are 10-20% more likely to meet daily recommendations for physical activity and 5% less likely to have obesity for every incremental increase in access to recreational facilities, green space, and walkable neighbourhoods[2,11]. Conversely, individuals living in environments with more fast food outlets and fewer healthy food options are more likely to eat unhealthy food, and live with obesity or diabetes[12,13]. Based on these associations, changes to the built environment are projected to be a cost-effective population health intervention to promote physical activity and prevent CVD[14,15]. Unfortunately, there are limited studies of the built environment and CVD-related morbidity and mortality. Additionally, current evidence in this field largely draws on underpowered cross-sectional studies[4,16]. While associations between the built environment and health behaviours

seem robust, it remains unclear if changes to the built environment are associated with improved health outcomes. Accordingly, experimental data are needed to determine if, and the extent to which, changes to the built environment are associated with reduced CVD-related morbidity and mortality[17-19].

Elements of the built environment that support physical activity include neighbourhood walkability, access to greenspace and proximity to fitness/recreation centres[2]. Urban multi-use trails are an additional, but poorly studied, aspect of the built environment that could support greater population-level daily physical activity[20]. Urban trails are multi-use protected areas for cycling alone or a combination of cycling, walking and running. They can be used to facilitate active transportation or a combination of active transport and recreational physical activity. Despite widespread growth of trail networks in urban areas, they are not included in calculations of walkability within a neighbourhood[21], and little information exists for their association with health outcomes.

As randomized controlled trials are virtually impossible in this field, natural experiments provide the only feasible opportunity to generate experimental evidence to examine a potential causal link between the built environment and health outcomes. The most recent systematic review and meta-analysis investigating the influence of the built environment on health outcomes, found no experimental studies and none of the studies included disease-specific CVD or CVD-related outcome measures (i.e. mortality, myocardial infarction, and/or co-morbid conditions)[9]. Consistent with the results of observational studies examining associations between the built environment and health, the majority of natural experiments revealed improvements in more proximal measures of CVD, for example physical activity; however, there is no experimental evidence examining whether changes in the built environment lead to changes in CVD-related morbidity or mortality[9].

The current study describes the methods and protocol for a natural experimental study evaluating the impact of a large expansion of an urban trail network on CVD-related morbidity and mortality in a large urban centre in Canada.

Methods and Analysis

Study Aims and Hypotheses

The primary objective of this natural experimental study is to capitalize on major changes to the built environment that occurred in Winnipeg, Canada between 2010 and 2014 to determine if a significant expansion of an urban trail network is associated with reduced CVD-related morbidity and mortality. The secondary aim of the study is to determine the cost-benefit ratio of this intervention compared to forecasted costs associated without the expansion of the urban trail network. The last aim of the study is to describe patterns of trail use and trail users during the intervention time period. Our primary study hypothesis is that an expansion of an urban trail network will reduce population-level CVD-related mortality and morbidity in neighbourhoods within 400-1200m of the new trail compared to neighbourhoods lying outside these boundaries.

Study Design

The most robust approach to test this research hypothesis is a quasi-experimental interrupted time series analysis with a comparison condition. The proposed interrupted time series analysis is strengthened by the use of a social and health data repository that provides an opportunity to link census, social and health data for the entire population of the City of Winnipeg beginning in 1995[22-27]. Interrupted time series designs are considered the most valid quasi-experimental designs when a randomized controlled trial is not possible[28,29]. They are the preferred design for population health interventions or pragmatic experiments as they strengthen pre-post designs, particularly if an appropriate comparison condition is available[28-30]. This approach is considered the gold standard for a natural experiment, as it captures real-world changes in population-level health outcomes following large policy or practice changes[31-34] that can eventually inform changes in health systems.

Using population-level outcome data over a 20-year period (2000 – 2019), we will construct an interrupted time series with a comparison condition. We selected a 20-year time frame as it will provide ~60 data points (~40 before and ~20 after the intervention) to test for changes in the slopes of CVD-related morbidity and mortality between groups before and after the expansion of urban trails. This design will allow us to better control for biases that

accompany non-randomized study designs [35-37] such as (1) secular trends, which in this case may be changes in CVD rates that could be interpreted as intervention effects if comparison neighbourhoods were not available; (2) seasonal effects, as rates of CVD tend to be higher during winter months[38]; (3) duration of the intervention where trails may only be used in the first few months or years following construction and data collected in the year or two following the expansion would not have identified this effect; (4) random short-term fluctuations in CVD rates that may occur which do not reflect overall trends and can lead to biased intervention effect estimates if only a short time window is studied, and (5) autocorrelation where rates of CVD are likely to be associated between time points and between neighbourhoods. In addition to employing an interrupted time series design to minimize biases, we will employ a series of complimentary statistical features that include segmented time series regression techniques[28,37] and autoregressive integrated moving average models[30,39]. To improve comparability of treatment and comparison neighbourhoods, we will create balanced treatment and comparison groups using propensity score matching[40].

Study population

This study will be conducted within the metropolitan area of Winnipeg, Manitoba, Canada's seventh largest urban centre. It is considered a slow growth city, relative to other major urban centres in Canada[41]. Winnipeg includes ~700,000 residents, representing >50% of the population of the province of Manitoba. Data from administrative health care databases within the Manitoba Centre for Health Policy (MCHP) will be used to derive population-level estimates of CVD and CVD-related co-morbid conditions as previously done[42-44]. Health information for local residents will be linked to dissemination-level data using individual postal codes. We will restrict the analyses to the adult population aged 30 to 65 years as previously done[21], as CVD end-points are <1/10,000 among persons under 30 years in Manitoba[42].

Intervention group: Winnipeg urban trail network expansion

In the Canadian context, an urban trail is a multi-use public path which creates an attractive transportation and leisure activity corridor through a built environment, used largely during the summer months[45]. Urban trails are an ideal component of the built environment to study with a quasi-experimental design and aggregated data. In contrast to more commonly

studied aspects of the built environment that promote physical activity (e.g. neighbourhood walkability, green space), trails are substantially easier to manipulate, as they require minimal space within the urban landscape and can affect a much larger segment of the urban population as they cross multiple neighbourhoods.

Between 2008 and 2010, the City of Winnipeg and Province of Manitoba invested $25 million to expand the infrastructure for leisure and transportation-based physical activity. Several mixed socio-economic neighbourhoods within Winnipeg were exposed to one of four new urban trails between 2008 and 2010, affecting roughly 250,000 residents within ~350 dissemination areas. Details of the greenways are provided in Table 1 and their location within the city are provided in Figure 1. The four multi-use urban trails are over five kilometers in length, paved, two lane paths that are cleared and maintained by the City of Winnipeg Department of Transportation 12 months of the year. They provide efficient and desirable trails for both active transportation and leisure physical activity. The majority of the population of Winnipeg do not live in dissemination areas that are within a reasonable distance to access the urban trails and therefore will be treated as the control condition. (Figure 1 – Map).

Outcome measures

The primary outcome measure will be a composite endpoint of incident CVD-related events including new hospital admissions for cardiac-related events (CVD-mortality, ischemic heart disease and stroke) and CVD-related co-morbidities (Table 2). ICD-9-CM codes will be used up to 1 April 2004 and ICD-10-CA codes afterwards for disease diagnosis (appendix, Table 1). These end-points were selected as they represent the largest burden of CVD-related morbidity in Canada, are the most relevant to policy makers and most likely to be modified by increased physical activity levels. These outcomes are derived from validated algorithms, providing an extremely accurate and sensitive capture of end-points[43,46]. Heart failure and peripheral artery disease will not be included in the composite outcome as algorithms have yet to be validated in the repository. The secondary outcome measure will be CVD-related co-morbidities, including hypertension, diabetes and dyslipidemia, as they are more proximal outcomes associated with changes in physical activity levels[1,2,21] and therefore more likely to change within neighbourhoods during the relatively short time frame of this intervention (Table 2).

Exploratory and Confounding Variables

Trail Usage

Eco-Counter Dual Inductive Loop Zelts are automated cyclist counters that will be used to measure trail usage as an exploratory variable, between 2014 and 2019[47]. Zelts have been discussed as an acceptable and reliable research tool to capture trail use[48]. Zelts are comprised of a main unit and sensory wiring. The main unit includes a battery, Global System for Mobile (GSM) transmission device and counting unit buried in manholes on the outer edge of a trail. Zelt counters will be placed at ten locations across the five trail developments and will collect cyclist data for 24 hours/day, seven days per week. Data collected from Zelts are time stamped and automatically uploaded to Eco-Visio online software via cellular networks at 3:00 a.m. everyday.

Field data collection to survey trail users

To determine trail user demographics, we will conduct two waves of intercept surveys among a convenience sample of ~1000 trail users, one wave in 2018 and one in 2019. Users will be asked to complete a brief survey to provide demographic information, self-reported trail usage and the perceived impact of usage on both their physical and mental health. These surveys will be designed to be completed in three to five minutes, to minimize participant burden and facilitate the collection of responses from the highest possible number of users. Demographic data will include self-identified gender and ethnicity, age group, residential postal code, newcomer status and annual household income. Analyses of these data will determine which, if any, specific groups experience disproportionate access to the trails. Usage data will outline typical weekly trail use (in terms of frequency, duration and types of activities), commute time to reach trail paths, and reasons for using the trail system. Survey collection will occur year-round when weather permits as either paper or technological survey instruments may not perform optimally in extreme winter conditions.

Survey participants will be asked to provide the first three digits of their postal code. This data will be used to geo-map the neighbourhoods of visiting users for each trail through dot density mapping techniques. Geo-maps will reflect the population distribution and demographic variation represented at each trail. Postal code data and produced geo-maps will also be

combined with City of Winnipeg Census data (2016) to provide insight into represented residential neighbourhood distributions for ethnicity and household income.

Confounding Variables

A detailed list of confounding variables and their source are provided in Table 3.

Socioeconomic status: Household income will be determined by census data, which are publically available every five years. We will rely on data from the 2006 and 2016 surveys to assess household income. We will also rely on a validated continuous index of material and social deprivation (socio-economic factor index, SEFI), that is calculated for each dissemination area in the province of Manitoba and reflects neighbourhood-level socio-economic well being[49].

Gentrification

Gentrification describes demographic changes that may occur in a community over time as individuals with a higher socioeconomic status move into lower socioeconomic areas[50]. Since socioeconomic status can have large implications for outcomes related to CVD[51-53], diabetes[51,54] and mortality[52,55], it will be important to account for gentrification within neighbourhoods. First, changes in property taxation between 2008 and 2018 assessed by the City of Winnipeg will be examined for each included neighbourhood to approximate increases or decreases in household value. Additionally, 2001 Canadian Census data and the 2016 National Household Survey data will be used to determine shifts in relevant indicators including poverty, education, unemployment rates, language barriers, average household income and ethnicity. Finally, data characterizing retail indicators will be obtained from DMTI Spatial Inc (2006 to 2016) to compare the number and ratio of specialty coffee houses versus coffee and doughnut shops per capita within neighbourhoods[21]. This will act as a surrogate variable representing demographic shifts in retail demands.

Built Environment Determinants of Physical Activity

The Canadian Urban Environmental Health Research Consortium (CANUE) is a multi-disciplinary collaboration of specialists focused on environmental exposures and population health.[56] CANUE integrates several population health databases and environmental exposure datasets into an openly available resource. From the CANUE dataset we will integrate examine

several estimates of greenspace, including accessibility of green space, type of vegetation, tree canopy cover in control for access to greenspaces in the treatment and comparison and intervention neighbourhoods across Winnipeg via the 2016 ArcGIS survey. All these data will be treated as confounding and adjusted for in the final analyses. We will also assess neighbourhood walkability using CAN-ALE scores calculated from a GIS-based composite of population density, mixed land use, access to public transportation and street connectivity. Finally, we will estimate the number of fitness and recreation centres within three kilometres of each household.

Patient and Public involvement: Members of the public will be involved at several stages of the study. Members of the public were involved in developing the study design, in response to priorities established by a local organization (Winnipeg Trails Association) dedicated to supporting urban trails for physical activity. Members of the public will help with recruitment of trail users during field data collection and collect survey responses. This organization will also develop public and policy maker-friendly tools to disseminate results of the study via their social media platforms and at local meetings. The organization, represented by its executive director (AS), acted as a co-applicant on the grant and a collaborator throughout the project.

Power calculation and sample size

We have the advantage of leveraging a health data repository that includes the majority of residents in Winnipeg and captures all endpoints that occurred within each time point for residents in that neighbourhood. During the pre-intervention period (2006/07 and 2011/12), overall mortality, annual incident rates of ischemic heart, hypertension, and diabetes were nearly identical between treatment and comparison neighbourhoods[42]. The stability of outcome measures will facilitate the detection of small, but meaningful, changes in trends or absolute events within treatment neighbourhoods. Segmented regression with propensity score matching will be used to compare changes in event rates between treatment and comparison neighbourhoods. The goal of the propensity score matching will be to pair the approximately 60 treated units (i.e. neighbourhoods) with approximately 60 randomly selected comparison units balanced on key covariates known to influence physical activity levels and CVD-related mortality and morbidity, (socioeconomic status [SES], age, ethnicity and walkability) permitting

analysis of data as if it arose from a randomized design[57]. Power analysis is based on a comparison of incidence rates in matched treated and comparison units.

Sample size calculations for clustered count data, where treatment assignment is at the neighbourhood level and the outcome is an incidence rate (e.g. Poisson count), were used to estimate the minimal detectable effect size[18]. We applied the Hayes-Donner method to estimate the number of neighbourhoods required to discern a given effect size, expressed as the difference between group-specific incidence rates under the assumption of a shared coefficient of variation across groups. These are conservative estimates, since they do not account for the paired nature of the data[58]. Using pre-intervention neighbourhood incidence rates[42], we created a power plot of the minimal detectable effect based on number of neighbourhoods affected by trail expansion. Outcome-specific incidence rates were calculated from MCHP-led Health Atlases[42,59] for 26 well-defined Winnipeg neighbourhoods between 2002-2007 (pre-intervention, crude rates per 100 person-years). Assuming an alpha = 0.05, beta = 0.2, and an average neighbourhood incidence rate for the composite outcome ≈ 4.95 ± 0.45 per 100 person years in treatment and comparison tracts[42], we are powered to detect a 10% difference in the primary outcome with 50 treatment neighbourhoods and 9% with 60 neighbourhoods[58]. This effect size is relevant to stakeholders as it translates into 350 fewer CVD-related events annually within the city. The effect is conservative, as previous population interventions like smoking bans (17% reduction in CVD events[60]), new public transportation (80% difference in odds of obesity[61]) or more walkable neighbourhoods (19% reduced incidence of type 2 diabetes[21]) have yielded larger effects.

Proposed analyses

To test the primary study hypothesis, that an expansion of an urban trail network will reduce population-level CVD-related mortality and morbidity in neighbourhoods within 400m-1200m of a new trail (intervention group), to a greater extent than neighbourhoods outside those boundaries, outcome data will initially be aggregated by neighbourhood and trends analyzed for the entire study period. The two primary outcome measures, composite end-points of incident major adverse CVD-related events and CVD-related risk factors will be treated as binary outcomes collected ~36 during the pre-intervention period and at 36 time points after the intervention (i.e. trail expansion), following Cochrane recommendations[35]. There will be a

two-year[35] lag incorporated into the time series reflecting the time during which the trails were being constructed. These time points reflect extensive literature showing that CVD-related behaviours[62,63] and endpoints vary seasonally[64,65] and that the impact of natural experiments requires several years to be detected at the population level[28,35,37].

Time Series Analyses

We will use two different time series methods to estimate the effect of the intervention on CVD-related end-point incident rates in treatment neighbourhoods relative to trends among the comparison neighbourhoods. First, a multi-group segmented regression of interrupted time series data will be used to assess the effect of the intervention on CVD-related incidence, both immediately (change in level) and over time (change in trend) by creating indicator variables as described elsewhere[37,40]. The level will be the base rate of CVD-related end-points at the beginning of the pre-intervention period (2000) and the value immediately following each change point at which successive segments join until 2010. The trend is the rate of change of CVD-related end-points (in other words, the slope) during a segment. Autoregressive errors will be modeled to account for correlated outcomes.

Autoregressive integrated moving average

An autoregressive integrated moving average (ARIMA) model will be fitted for the CVD incidence time series by using the standard approach for identification, estimation, and checking[66]. Trend and periodic seasonal terms will be applied to the entire study period (January 2000 to July 2019). A separate ARIMA model will also be built for the pre-intervention period to forecast CVD evolution of the treated neighbourhoods. The number of CVD end-points prevented by the intervention will be estimated by calculating the difference between the predicted number and the observed number of cases. Should we encounter difficulty fitting an ARIMA model to a relatively small dataset, we will rely on exponential smoothing models or the Holt Winters Algorithm[66]. Although they require larger sample sizes, these methods are ideal for this project as (1) they permit a variety of different types of intervention effects to be modeled explicitly, and (2) they are well suited to forecasting future trends.

Cost-Benefit analysis

The cost-benefit analysis will focus on describing the "value for money" of the intervention. The objective of the economic analysis is to compare the cost and effect of the treatment group relative to the comparison group data collected in the study[67]. To align with the effectiveness analysis, the primary outcome variable in the economic analysis will be a composite endpoint of incident composite CVD-related end-points, similar to previous studies by one of the team members[67-69]. Costs for each participant will include those associated with the intervention (e.g., trail construction and maintenance costs) and health service utilization obtained from administrative data. From the perspective of the public payers (provincial and federal governments), we will conduct the economic analysis using the net benefit regression framework[70,71] which enables an adjustment for potential confounders. The main output of the economic analysis is the incremental net benefit of the treatment relative to the comparison group. In addition, we will estimate incremental cost-effectiveness ratios which will represent an incremental cost per one incident CVD end-point prevented or one CVD-related co-morbidity prevented. Furthermore, as there are more than one public payer for this intervention (e.g., Government of Winnipeg, Government of Manitoba), we will conduct separate analyses for each relevant perspective to assess the "value for money" specifically to each payer. We will characterize the uncertainty of our findings using a cost-effectiveness acceptability curve and 95% confidence interval. In addition, we will explore the possibility of building a decision analytic model which will examine the potential long-term economic impact of the intervention after the study period[72]. This economic model will use various data sources to estimate costs including the study[73,74], published literature[67-69], and expert opinion.

Ethical Approval: All aspects of the study design have been approved by the Biomedical Research Ethics Board at the University of Manitoba (Approval ID: REB_HS20928 (H2017232)) and the Health Information Privacy Committee within the Province of Manitoba (Approval ID: HIPC - 2019/2020-05)

Discussion

The proposed natural experimental study will fill a large gap in our understanding of the impacts of changes to the built environment on CVD-related outcomes. Specifically, we will provide critical experimental evidence for the impact of changes to urban spaces for recreational physical activity and active transportation on CVD-related morbidity and mortality. Additionally, to support evidence for future policies relating to urban activity corridors, we will also provide an estimate for the cost-effectiveness of large urban trail networks within cities.

DECLARATIONS

Ethics approval and consent to participate: This study was approved by the Biomedical Research Ethics Board at the University of Manitoba (H2017:232) and the Health Information Privacy Committee at the Winnipeg Regional Health Authority (HIPC - 2019/2020-05).

Competing Interests: The authors declare that they have no competing interests.

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Author Contributions: All authors contributed to the study and manuscript in alignment with current ICMJE guidelines. The study was conceived by JM, AS and EH. JM and EH are the principal investigators on the original funded grant. EH, AS, GB, KR, LR, BS, WI and JM participated in designing the study and submitting the original grant. JM and SW were involved in recruiting the City of Winnipeg to share data. EH, AS, KR and JM designed the field data collection processes. EM is leading the geomapping of trail users and interpretation of gentrification data. WI is leading the cost effectiveness analyses of the study and SW is providing data for these analyses. AS, NB and JM are involved in data cleaning and verification. EH, NB and JM drafted the original manuscript. All authors contributed to critically revising the manuscript for important intellectual content, gave their final approval and agreed to be accountable for all aspects of the work, and they will participate in future interpretation of the data and drafting of further manuscripts arising from this work.

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Tables and Figures

Figure 1. Map of Trail Locations within Winnipeg, Manitoba Canada as of 2016

Table 1. Details of the intervention: New Urban Trails

Table 2: Outcome Measures

Table 3: Potential sources of confounding between intervention and control arms that are available within linked databases.

Table 1. Details of the intervention: New Urban Trail Greenways

Variable	Northeast Pioneers	Yellow Ribbon	Bishop Grandin	Transcona Trail
Original Land Use	Converted rail line	Paved grassland	Paved grassland	Paved grassland / industrial re-appropriation
Const. Start Date	Summer '07	Summer '09	Summer '08	Summer '10
Completion date	~Autumn '12	~Autumn '11	~Autumn '10	~Autumn '10
Const. Start Date	Summer '07	Summer '09	Summer '08	Summer '10
Completion date	~Autumn '12	~Autumn '11	~Autumn '10	~Autumn '10
Distance of Trail	6.5km	5km	8km	6.7 km
Dissemination areas within 800m access	103	48	243	45
Estimated pop. within 800m	53 308	20 376	153 015	21 915
Immediate adjacent environment	Trail located between two major roadways	Greenspace, neighbourhood, airport	Major roadway and neighbourhoods/ business parks	Neighbourhood, grassland, business park
Mixed land use	High (homes, schools, shopping, recreation, parks)	Medium (homes, schools, parks)	High (homes, schools, shopping, parks)	Medium (homes, shopping, parks)

Table 2. Outcome Measures in the natural experiment of urban trail expansion

Category	Variable	Outcome	Definition	Source
Primary	Major adverse cardiovascular events (MACE) - Composite	CVD-related mortality	Death in vital statistics mortality data with most responsible cause of death coded as CHF, IHD or stroke.	Vital statistics mortality
		Ischemic heart disease	-1+ Inpatient Hospitalizations -2+ Physician visits in 5 years -1 Physician Visit & 2+ Rx in 5 years	Hospital abstracts, Medical claims, DPIN prescription dispensations
		Congestive heart failure	-1+ inpatient visits or 2+ physician visits	Hospital abstracts, Medical claims
		Cerebrovascular event	- 1+ Inpatient Hospitalizations - death in hospital	Hospital abstracts
Secondary	CVD-related risk factors - Composite	Hypertension	-1+ Inpatient Hospitalizations -2+ Physician visits in 2 years	Hospital abstracts, Medical claims
		Diabetes	-1+ Inpatient Hospitalizations -2+ Physician visits in 3 years -2+ Rx for glucose lowering agents in 3 years,	Hospital abstracts, Medical claims, Prescription dispensations
		Dyslipidemia	-1+ Hospitalization -2+ Physician visits in 3 years -2+ Rx for statins in 3 years	Hospital abstracts, Medical claims, Prescription dispensations
Secondary	Trail use	Bicycle counts		Eco-Counter Magnetic Zelts

				located beneath greenways
Exploratory	Income	Household	Self-reported	Intercept surveys
	Ethnicity		Self-reported	
	Gender	Male, female, other	Self-reported	
	Residence	Postal code	Self-reported	
	Weekly use	Visits/week	Self-reported	
	Time on trail	Minutes/use	Self-reported	

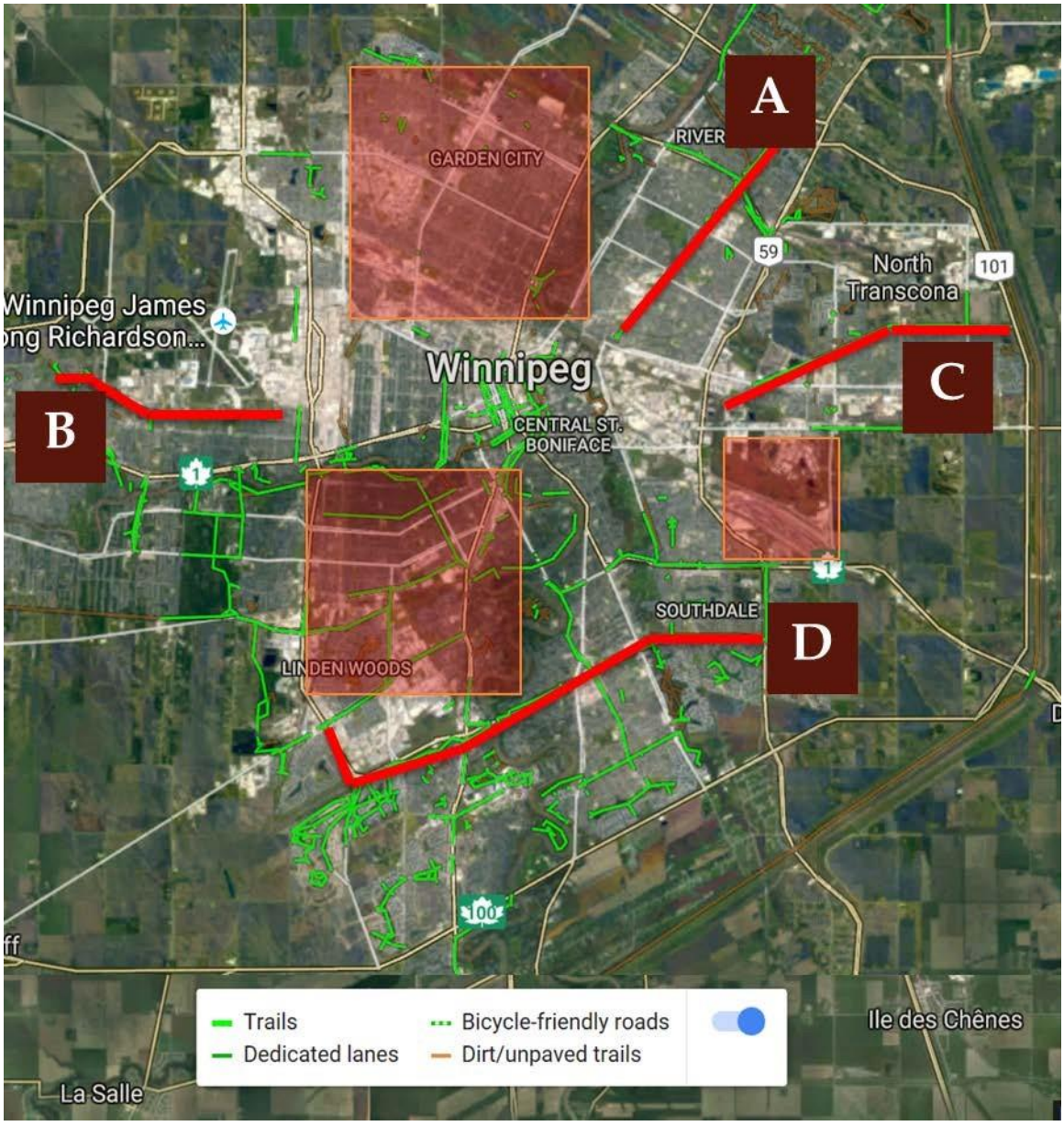
CHF = congestive heart failure; CVD = cardiovascular disease; ICD = international classification code; IHD = ischemic heart disease, Rx = prescription

Table 3. Potential sources of confounding between intervention and control groups that are available within linked databases

Category	Variable	Definition	Source	Years available
Socio-economic status	Income	Household income	Census	2006 and 2016
	SEFI	Material and social deprivation	MCHP repository	Annual
Demographics	Age		Census	2006 and 2016
	Sex		Census	2006 and 2016
	Ethnicity		Census	2006 and 2016
	Immigration status		Census	2006 and 2016
Gentrification	Change in mean age neighbourhood	Taxation valuation of value of property	City of Winnipeg	2008 to 2018
	Property value			
Built environmental factors that support physical activity	Greenspace	Distance to park (kms)	DMTI/CANUE	2006 and 2016
	Walkability	Population density, mixed land use, connectivity	CAN-ALE (CANUE)	2006 and 2016
	Fitness/Recreation Centres	Distance to centre	CANUE	2006 and 2016

SEFI = socioeconomic factor index; DMTI = Digital Mapping company name; MCHP = Manitoba Centre for Health Policy; kms = kilometers

Figure 1. Map of Trail Locations within Winnipeg, Manitoba Canada as of 2016



Complete trail map includes old (green lines) and new trails/greenways (red lines), comprising ~400km of total trails. Large red trails are “high dose” multi-use trails that extend across multiple neighbourhoods and accessible 12 months of the year (A= Northeast Pioneers Greenway; B= Yellow Ribbon Greenway; C= Transcona Trail & D= Bishop Grandin Greenway). Other green lines represent medium or low impact bike trails or gravel trails not used in winter or only for active commuting. Note large red areas that have not received trails.

Appendix sTable 1. Diseases or risk factors classification and corresponding International Classification of Disease (ICD) codes, in alphabetical order.

INDICATION	ICD TITLE	ICD 10 CODE	ICD 9 CODE
Diagnoses indicative of a cardiovascular disease endpoint – Primary outcome			
Ischemic heart disease	Angina pectoris	I20	413
	Acute myocardial infarction	I21	410, 434.91
	Subsequent myocardial infarction	I22	412
	Other acute ischaemic heart diseases	I24	411
	Chronic ischaemic heart disease	I25	414
Cardiac arrest	Cardiac arrest	I46	427.5
Heart failure	Heart failure	I50	428
Cerebral infarction	Cerebral infarction	I63	433, 434, 435
	Stroke	I64	437.0, 437.1, 437.3
Diagnoses indicative of a cardiovascular disease risk factor – Secondary Outcome			
Diabetes	Diabetes	E11	250
Hyperlipidemia	Dyslipidemia	E78	272.3, 272.5, 272.6
Hyperlipidemia	Pure hypercholesterolaemia	E78.0	272.0
	Pure hyperglyceridaemia	E78.1	272.1
	Mixed hyperlipidaemia	E78.2	272.2
	Hyperlipidaemia, unspecified	E78.5	272.4
Hypertension	Essential (primary) hypertension	I10	401, 459.3
	Hypertensive heart disease	I11	402

	Hypertensive renal disease	I12	403
	Hypertensive heart and renal disease	I13	404
Diagnoses leading to exclusion from the cohort			
Cardiomyopathy	Endocardial fibroelastosis	I42.4	425.3
	Endomyocardial disease	I42.3	425.0
	Congenital cardiomyopathy	I42.8	Not applicable
	Familial cardiomyopathy	I42.9	425.9
Congenital malformation of circulatory system	Congenital malformations of the circulatory system	Q20 to Q28	745, 746, 747, 759.9
Cystic fibrosis	Cystic fibrosis	E84	277.0
Ineligible diagnoses (not considered as outcome, but did not warrant exclusion of the participant)			
Other cardiovascular problems (eg cause is viral, genetic, alcoholic, etc.)	Other cardiovascular problems	E78.7, E78.8	424.9, 425.2, 425.5, 425.7, 425.8, 425.9
Arrhythmia*	Cardiac dysrhythmias	I49	427 excluding 427.5 (see Cardiac arrest)
	Abnormalities of heart beat	R00 to 03	785.3

*Arrhythmias were ineligible because their definition in administrative databases has not yet been validated and a local pediatric cardiologist informed us that most dysrhythmia diagnoses or referrals would not be considered cardiovascular disease or risk.