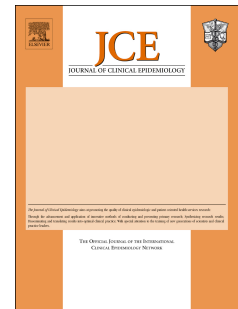


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Participant Diversity and Inclusive Trial Design: A Meta-Epidemiologic Study of Canadian Randomized Clinical Trials

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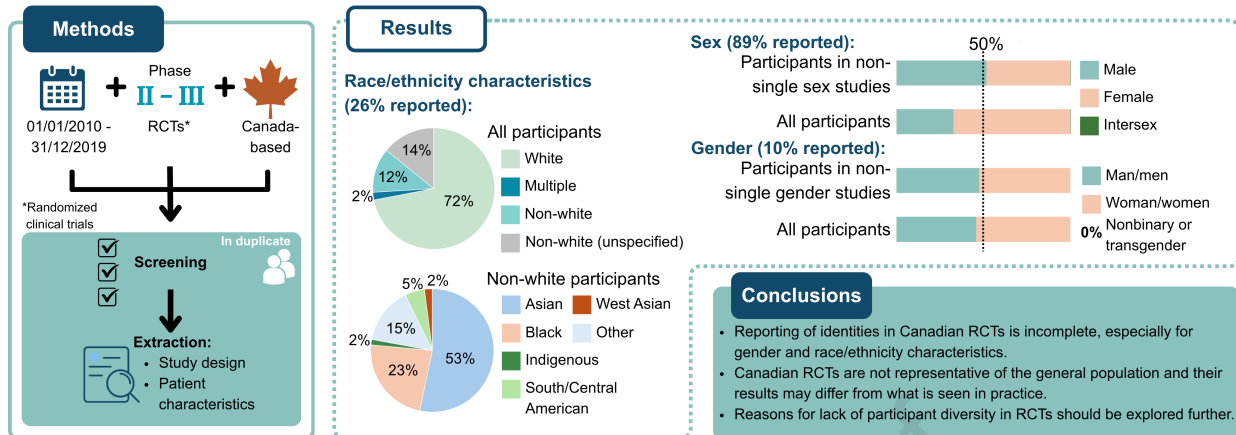
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Abstract

Objective: To describe the demographic and social identities of participants in contemporary Canadian randomized clinical trials (RCTs).

Study Design and Setting: A meta-epidemiologic study included published reports of phase 2 and 3 RCTs that exclusively recruited adults living in Canada and were registered on ClinicalTrials.gov between January 1, 2010, and December 31, 2019. Study design and participant demographics were abstracted from eligible articles in duplicate using frameworks for understanding participant diversity such as PROGRESS-PLUS.

Results: We identified 118 RCTs with 17,387 participants. Most reported participant sex (n=105, 89.0%), few reported gender (n=12, 10.2%), and none reported both. Among articles reporting sex, there were 11,066 female (63.6%), 5,402 male (32.8%), and one intersex (<0.1%) participants. There were 477 women (54.1%) and 404 men (45.9%) participants. No studies reported gender diverse participants. When excluding studies that only recruited one sex and/or gender, 51.8% of participants were male (n=4,774/9,219) and 47.5% were men (n=446/850). Race and/or ethnicity was reported for 4,124 participants (23.7%) in 31/118 (26.3%) of RCTs; of these, 72.0% were white (n=2,969), 2.7% were Black (n=113), and 0.2% were Indigenous (n=7). Eligibility criteria related to specific PROGRESS-PLUS factors was rare except for cognition (n=42, 35.6%), substance use (n=25, 21.7%), pregnancy (n=29, 24.5%), breastfeeding (n=16, 13.6%), and older age (n=26, 22.0%).

Conclusion: The data are encouraging regarding representation of female and women participants in Canadian trials. Due to underreporting of other identities, we cannot identify additional groups who may be underrepresented. Work to improve reporting of race and/or ethnicity, among other identities, is needed.

Plain Language Summary:

Clinical trials tell us what drugs and procedures are helpful for patients. In certain specialties, like cancer and heart disease, clinical trials are made up mostly of men, white people, and younger people. This means that the results of these trials may be different for other groups of people, especially older people, women, and racialized people, who are more likely to have these diseases. We looked at the demographic identities of all participants in 118 Canadian clinical trials that were done between 2010 and 2019. Of the 17,387 participants, there were 11,066 female, 5,402 male, 477 women, 404 men, and one intersex participant. We could find the race and/or ethnicity for only 4,124 participants in 31 of the trials. Most participants (72.0%) were white, and only 2.7% were Black and 0.2% were Indigenous. These results tell us that reporting of identities in Canadian clinical trials is incomplete. Canadian clinical trialists should do a better job telling us who is in their trials. These results suggest that Canadian clinical trials are not representative of the general population, and that we need to explore the reasons that people are not participating in clinical trials.

Keywords: Randomized trial diversity; Clinical trials; equity, diversity, inclusion, and accessibility; trial design; trial recruitment

Running title: Participant Diversity and Inclusive Trial Design: A Meta-Epidemiologic Study of Canadian Randomized Clinical Trials

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1. Introduction

Addressing the lack of diversity among participants in medical research is a global priority.¹⁻⁴ Participants in randomized clinical trials (RCTs) should reflect real-world populations to ensure representativeness and generalizability of research.² Patients should have equitable access to RCTs to promote fairness, foster trust and improve efficiency. Internationally, researchers have found that RCT participants are often not representative with regards to age,⁵ sex,⁵ gender,⁶ race,^{5,7} ethnicity,³ and disability⁸ in a variety of disease and therapeutic areas.^{9,10,11,12,13} In many RCTs, sociodemographic identities are not reported.^{7,14,15} This limits the visibility of marginalized groups in clinical trials⁶ which may impact their relationship with research as well as the interpretation of trial results.

The diversity of RCT participants in Canada has only been assessed for select disciplines¹⁶ and identities.^{17,18} The Accelerating Clinical Trials - Accélérer les Essais Cliniques (ACT-AEC) Consortium¹⁹ mandate is to improve the ecosystem for conducting trials in Canada. As a part of this work, the ACT-AEC inclusivity, diversity, equity and accessibility (IDEA) subcommittee undertook an assessment of the sociodemographic characteristics of Canadians who participated in RCTs to better understand potential gaps and inform future strategies.

2. Methods

2.1 Study Search and Selection

The objectives of this meta-epidemiologic study were to describe the diversity of adult Canadian RCT participants and summarize the reporting of participant sociodemographic identities. This manuscript is reported in accordance with an adaptation of the Preferred

Reporting Items for Systematic reviews and Meta-Analysis for meta-epidemiologic studies (Appendix 1).²⁰

Eligible trials were identified through a search of registered trials at ClinicalTrials.gov (D.C., June 30, 2023; Appendix 2). We included phase 2 or 3 randomized clinical trials as defined in ClinicalTrials.gov, as the intended study population for trials in these phases are anticipated to be the most representative of the general population, that were registered between January 1, 2010, and December 31, 2019, to account for a potential change in registrations due to the COVID-19 pandemic and lag between publication of results relative to registration of the trial, and published in a peer-reviewed journal. Trials in any field, regardless of disease, intervention, or comparator, were included. To be included, trials had to recruit adult participants in Canada, as the sociodemographics of participants recruited from other countries may not be comparable to Canadian participants. Non-randomized intervention trials and secondary analyses were excluded.

Identified trial registration records were downloaded to Excel (Microsoft Corporation) for data management and all sections of the ClinicalTrial.gov record was independently screened for inclusion by two study team members (S.M.R., K.C.L., A.S., M.L., S.H., and D.C.). Disagreements were resolved by a third study team member (S.M.R. or D.C.). The primary published article for eligible trials was retrieved using the National Clinical Trial (NCT) registration number in a literature search using Google Scholar and/or the “Results Posted” section of the ClinicalTrials.gov record (Appendix 2). If not identified, the contact person from the trial registration was emailed up to two times to obtain the full text article. Full text manuscripts, including supplementary materials, for each included trial were independently

assessed for inclusion in duplicate (S.M.R., K.C.L., C.S., S.T., D.O., and D.C.), with disagreements resolved by a third study team member (S.M.R. or D.C.).

2.2 Data Extraction

Data extraction was based on the full text of the published manuscript, including supplementary materials, and occurred in duplicate (S.M.R., K.C.L., C.S., S.T., D.O., A.S., and D.C.; Appendix 3) using an extraction form developed using previous protocols²¹ with input from the ACT-AEC IDEA subcommittee. All team members underwent training to standardize their approach to record screening and data extraction from S.M.R. Extracted data was reconciled, and disagreements were resolved by a third reviewer (S.M.R. or D.C.). Extracted data included trial information, including disease area, population, intervention, comparator and outcomes, design, eligibility criteria, and participant diversity.

Study discipline was categorized according to Canadian medical disciplines,²² with additional categories (e.g., dentistry) created when needed. To describe participant diversity, we extracted whether investigators reported participant demographics according to PROGRESS-PLUS²³ recommendations. PROGRESS-PLUS is a framework²⁴ endorsed by the Cochrane Collaboration in 2013 to guide investigators in considering which participant demographics may be relevant to report in their studies.²⁵ The elements are (1) Place of residence; (2) Race, ethnicity, culture, language; (3) Occupation; (4) Gender and sex; (5) Religion; (6) Education; (7) Socioeconomic status; (8) Social capital and (9) Personal characteristics that may be associated with potential discrimination such as age and disability. Inclusion of all PROGRESS-PLUS factors in all studies is not mandatory; rather, investigators should consider each PROGRESS-PLUS factor within the context of their trial and decide whether it is relevant to trial design, conduct, analysis, or reporting.²³

PROGRESS-PLUS does not name Indigenous status as a distinct identity but rather includes Indigeneity within “Race, ethnicity, language, and culture”. Indigenous identity is an important demographic to measure and report in Canadian health care settings due to colonization and ongoing structural and interpersonal anti-Indigenous discrimination in the healthcare system. The Truth and Reconciliation Commission Calls to Action require healthcare providers to “identify and close gaps in health outcomes between Aboriginal and non-Aboriginal communities”.²⁶ For these reasons, we report data about Indigenous participation separately from the “Race, ethnicity, language, and culture” category.

The total number of participants and participant sex and gender were abstracted according to definitions provided by Clayton and Tannenbaum.²⁷ In this classification, we used participant sex if authors used the terms “male(s)” and/or “female(s)” and gender if authors used the terms “man/men” and/or “woman/women”, even when authors used these terms differently (e.g., “female gender”) to avoid adjudicating whether the study team consistently or correctly applied the terms sex and gender.²⁷ If only one sex and/or gender was reported in the manuscript, we assumed that the study authors were implying a binary sex/gender framework and estimated the number of participants from the second sex/gender by subtracting the number of participants from the reported sex/gender from the total number of participants without any intersex or gender diverse participants. Race and/or ethnicity data was abstracted as described by the authors, and categories were grouped by similar geographical regions by the study team using Statistics Canada race and/or ethnicity categories.²⁸ Additional participant demographics were abstracted and categorized based on the PROGRESS-PLUS definitions.²⁵

Eligibility criteria were extracted and categorized using the PROGRESS-PLUS categories when applicable. Eligibility criteria may have explicitly restricted participation by

identity (e.g., studies that recruited pregnant participants were categorized as sex-related eligibility) or implicitly limited participants (e.g., studies that required participants to have daily access to a computer were categorized as socioeconomic status-related eligibility). Exclusion criteria related to ability, chronic illness, mental health, and cognition (represented by the “PLUS” categories in PROGRESS-PLUS) were further classified using the framework outlined by DeCormier Plosky et al., which describes eligibility criteria that may disproportionately exclude participants with disabilities from clinical trials (e.g., “any disorder which in the investigator’s opinion might jeopardize subject’s safety or compliance with the protocol,”).²⁹ We did not adjudicate whether eligibility criteria were ‘appropriate’ for each study. First, we do not have the subject-matter expertise or knowledge of the ethical or regulatory context for each study to make retrospective judgements for the broad range of disciplines included in this review. Second, exclusion of people with marginalized identities from clinical trials due to eligibility criteria is important to describe regardless of whether these eligibility criteria are appropriate. Determination of whether eligibility criteria are unnecessarily exclusive may be subjective and may change across cultural contexts; for example, some argue that pregnant people should be able to provide informed consent to participate in drug trials for life-threatening illnesses like COVID-19.³⁰

2.3 Analysis and Reporting

Descriptive statistics are reported, including frequencies and percentages, means (standard deviation) and medians (interquartile range, [IQR]) for normally distributed and non-normally distributed variables, respectively.

3. Results

The search strategy identified 2,749 trial records (Figure 1) and 203 trial records were selected for full text retrieval. There were fifty-five trials that were not published (27.1%) and 30 trials were excluded after full text review. Altogether, 118 articles representing unique RCTs published between 2011 and 2023 (after the 2010-2019 registration period) were included. Four studies recruited groups (e.g., pharmacies [n=1] or clinics [n=3]). The remaining 114 studies recruited 17,387 individual participants (median 59.5 participants per study, IQR 30-111, range 10-5,498).

3.1 Study Characteristics and Design

Study characteristics are described in Tables 1 and 2. Most studies were single center (n=61, 51.7%) and performed at academic centers (n=81, 68.6%). At least one study was conducted in each Canadian province, and no studies were conducted in the territories (Northwest Territories, Nunavut, or Yukon). Fourteen studies recruited participants in municipalities with less than 100,000 residents (11.9%). The most common intervention was pharmacologic (n=44, 37.3%) and most comparators were active or usual care (n=83, 70.3%). Recruitment methods were not described for 43 studies (n=36.4%). The median study duration was 11 weeks (IQR 1 day to 26 weeks, range 1 day to 3.8 years) and follow-up visits were most often in-person (n=87, 73.7%). Virtual visits (n=8, 6.8%), telephone visits (n=5, 4.2%), and e-mail (n=5, 4.2%) were less common. Twelve studies had no long-term follow-up (e.g., occurred on one visit, 10.2%). 10.2% of studies reported compensation for participants' time (n=12) and 3.4% reimbursed participants for out-of-pocket expenses (n=4). The most common discipline of trials was anesthesiology and pain medicine (n=11, 9.4%) followed by combined internal medicine specialties (n=10, 8.5%); however, the range of disciplines of RCTs was broad and most disciplines included fewer than 4 studies per topic (eTable 1).

3.2 Inclusivity and Eligibility Criteria

Eligibility criteria related to the PROGRESS-PLUS identities are reported in Table 3 with additional subcategories and examples in eTable 2.

3.2.1 Place of Residency, Occupation, Socioeconomic Status, and Social Capital

Participants required housing for inclusion in 11 studies, including studies that used home visits (n=4) or required a drug to be refrigerated (n=1). Housing was implicitly required in studies that recruited “community dwelling” participants (n=4) or required participants to avoid “excessive sun exposure” (n=1). Four studies recruited participants with specific occupations (e.g., resident physicians). Socioeconomic status examples include requirements for participants to have access to the Internet and/or a computer (n=5), good oral health (n=2), or no risk factors for MRSA (n=1). Social capital (e.g., need for a family member or caregiver) was an eligibility criterion in 5 studies; of these, 3 specifically recruited heterosexual couples.

3.2.2 Sex- and Gender-Based Eligibility Criteria

Sex-based eligibility criteria were explicit in studies that recruited only males (n=3), females (n=1), fathers (n=1), mothers (n=2), and participants with diseases of sex-based anatomy (n=5 and n=4, respectively). Sex was an implicit criterion when the eligibility criteria included diagnostic tests with ranges that differed for male and female participants in 7 studies; for example, studies that used anemia, waist circumference, or substance use as an eligibility criterion and defined these differently for male and female participants. One study that examined the effect of polydextrose supplements on colonic transit time excluded participants who had used misoprostol (n=1).³¹ Similarly, there were studies with gender-based eligibility criteria that explicitly recruited women (n=5) or women living with a man (n=1). Criteria that may have implicitly excluded based on participant sex and/or gender were excluding participants on

androgen deprivation therapy or participants on hormone replacement therapy (n=1 each).

Exclusive sex and gender language may have also led to exclusion or non-participation of sex and gender minority participants in studies that recruited “males and females” (n=5) or “men and women” (n=3).

Twenty-nine studies excluded pregnant participants, 16 excluded participants who were breastfeeding, 4 required female participants to provide a negative pregnancy test, and 11 excluded participants who could become pregnant or required female participants to use contraception. One study had eligibility criteria related to fertility and pregnancy that referenced male participants. Seven studies recruited pregnant (n=3), post-partum (n=2), or breastfeeding (n=2) participants.

3.2.3 *‘PLUS’ Eligibility Criteria*

Of the 41 studies that restricted participation based on age, 16 had an age restriction of 65 years or younger (39.0%) and an additional 10 studies had an upper age limit between 65 to 85 years (24.4%). Thirteen studies recruited participants who were between 40-55 years and older (31.7%).

Ability was the most common PROGRESS-PLUS identity referenced in study eligibility criteria (n=69, 58.5%) and was most often used as an exclusion criterion (eTable 3). Cognition was the most common subcategory of ability (n=42 studies) and was referenced as being “able to follow study instructions” or “able to provide informed, written consent” though many exclusion criteria were vague (e.g., exclusion for “cognitive illness”). Chronic medical condition exclusion criteria were often specific (e.g., precise creatinine clearance values) but vague criteria (e.g. “any significant medical abnormality that could affect study participation”) were noted in 50 studies.

There were 25 studies that excluded participants with substance use (21.2%), which was variably defined across studies.

3.3. Reporting and Diversity of Study Participants

The diversity of participants is reported in Table 4. Occupation and education level were each reported by 19 studies (16.1%). No study reported the religion of participants.

3.3.1 Sex and Gender of Study Participants

Most studies reported the sex of participants (n=105, 89.0%) and a minority reported gender (n=12, 10.2%). No study reported both the sex and gender of participants. Of the studies that reported sex of participants, 67.2% were female (n=11,066) and 5,498 of these female participants were recruited for a single study of mammogram screening reminders.³² After excluding studies that recruited a single sex, there were 9,219 participants, of which 48.2% were female (n=4,444). When excluding studies that recruited a single gender, gender was reported 850 participants and 53.5% were women (n=446). The median proportion of females per study was 51.0% (IQR 37-72%, range 0-100%) (eTable 4), which was similar when studies that included a single sex and/or gender were excluded from the analysis (eTable 4).

Only one study, examining training for generalized anxiety disorder,³³ reported the number of intersex participants: one participant who was described as “other” sex. Of the studies that reported participant gender, 404 were men (45.9%) and 477 were women (54.1%). No study reported the number of transgender, non-binary, or gender diverse participants.

3.3.2 Race and/or Ethnicity of Study Participants

Race and/or ethnicity were reported by 31 studies (26.3%) that included 4,124 participants (23.7%). The race and/or ethnicity categories reported across studies were heterogeneous (Table 5). No study reported how race and/or ethnicity of participants was

determined. All studies that reported race and/or ethnicity included a category for white participants, who comprised 72.0% of participants (n=2,969/4,124). The second most common category was Asian (n=18 studies and n=260/4,124 [6.3%] participants), though the definition of “Asian” varied across these studies. Twelve studies (38.7% of all studies) reported the number of Black participants (n=113/4,124 [2.7%] participants).

3.3.3 Indigenous Participants

Three trials included a category for Indigenous participants, of which there were a total of 7 participants (0.2%). None of the 3 trials distinguished between First Nations, Inuit, and Métis participants.

4. Discussion

This meta-epidemiologic study of RCTs describes the reported diversity of adult trial participants recruited in Canada over a 10-year period from 2010-2019. Overall, we found equitable representation of female and male participants but underreporting and potential underrepresentation of intersex, non-binary, and transgender (collectively, sex and gender minority) participants. Similar to other reviews of trial diversity,^{7, 13, 34} we found that many aspects of participant identity, in particular race and/or ethnicity, were not reported. Due to low reporting of certain demographic identities, we cannot differentiate between low recruitment or inclusion versus lack of reporting of these demographic identities. The reason for low reporting of PROGRESS-PLUS identities in Canadian RCTs is not known; the PROGRESS-PLUS identities may have been determined to not be relevant by the study team, may have been measured and not reported, or may have been unconsidered by the study team. Lastly, we identified that eligibility criteria might explicitly or implicitly limit the participation of

underrepresented groups (whether justifiably or not), particularly for potential participants with disabilities or impairments, sex and gender minorities, and females with childbearing potential.

In contrast to discipline-specific studies in other settings,^{10, 16, 35} we found that the overall median proportion of female and male trial participants in all included trials was representative of the general Canadian population.³⁶ While this finding is reassuring, there was a wide range across trials in the proportion of male and female participants, in part due to the trial topic. For example, there were eleven trials that recruited only female participants, including a single study examining mammogram reminders³² that recruited nearly half of all the female Canadian RCT participants identified in our study. To be confident about adequate representation of sexes/genders, a comparison of participant sex/gender to the disease-specific sex/gender prevalent ratios³⁷ would be helpful, though was not within the scope of our present study due to the degree of heterogeneity with regards to trial populations and diseases. Similar to other investigators,¹⁸ we found that no study reported both the sex and gender of participants, as recommended by the Institute of Medicine since 2011.³⁸ Of 17,387 participants, there was only 1 intersex participant and no study reported transgender or non-binary participants. This is out-of-keeping with estimates of the prevalence of sex and gender minorities in Canada, which represent 1-3% of the population.³⁹⁻⁴¹ The lack of inclusion of sex and gender minorities is potentially harmful and may contribute to an ongoing lack of trust and engagement in research with this segment of the population. We recommend that study teams use a two-step question to describe sex and gender of participants, as is used in the Canadian census since 2021.⁴¹

Not reporting race and/or ethnicity in clinical trials is common⁴² and is a focus of many Canadian⁴³ and international groups to ensure representativeness. However, we note that mandating subgroup analyses by race and/or ethnicity may be harmful due to the potential for

false positives so this needs to be carefully considered based on rationale with pre-specification.⁴⁴ Previous systematic reviews of medical research estimate that about 37%⁴⁵ to 52%¹⁴ of studies reported race and/or ethnicity compared to 26% of studies in our review. Considering that race and/or ethnicity was missing for 75% of studies, we report that Black participants were underrepresented relative to their proportion in the general Canadian population; 4.3% of the Canadian population self-identifies as Black⁴⁶ compared to 2.7% of trial participants. Similarly, 6.1% of Canadians identify as Indigenous compared to 0.2% of trial participants.⁴⁶ A previous study reported that there were no Indigenous participants among 804 trial participants enrolled in Canada.¹⁷ Indigenous issues in clinical trials require separate and distinct considerations from IDEA principals given the unique historical context of Indigenous populations in Canada and truth and reconciliation. While equitable inclusion of Indigenous people in ongoing Canadian trials is an important goal, principles of self-determination and autonomy also require Canadian research systems to support studies led by Indigenous scholars based on community-defined priorities and goals.⁴⁷ Key informants involved in clinical trials in Canada that focus on Indigenous populations must acknowledge and respect Indigenous data governance and sharing agreements including ownership, control, access, and possession (OCAP®)⁴⁸, methodologies for First Nations, Metis and Inuit identifiers, the impact colonialism on study design and conduct (e.g., mistrust leading to non-participation, unacceptability of randomization as a study procedure, disinterest in providing samples for genetic testing or biobanking for future research) and how Indigenous policies and procedures interact with Good Clinical Practices and Health Canada regulations. When relevant, research teams should partner with Indigenous nations and healthcare organizations so that traditional knowledge and cultural

practices are honoured to enhance Indigenous participation in clinical trials with respect for self-determination.

Despite development and endorsement of tools²⁵ to improve equity reporting in clinical trials such as the 2017 CONSORT-Equity statement,⁴⁹ reporting of PROGRESS-PLUS characteristics in our setting was much lower for all categories compared to findings from a scoping review of international health-equity studies published in 2021.³⁴ Altogether, these results define the current state of participant diversity in Canadian clinical trials and can be used guide improvements to individual study design and reporting. However, we are not suggesting that collecting and reporting every participant identity is appropriate in all trials, but rather that data collection and reporting should be tailored to each trial's research question, hypotheses, population and analyses with consideration of IDEA principles.

Our findings highlight the potential for eligibility criteria to influence participant diversity.^{50, 51} Researchers in other settings have identified how eligibility criteria can indirectly reduce participant diversity; for example, in one study of alcohol treatment programs, eligibility criteria based on substance use and housing led to greater exclusion of Black and other racialized participants compared to white participants.⁵² In our results, 6 studies had explicit housing requirements, an additional 14 had criteria related to in-person follow-up, and 5 required access to a computer or telephone, which may exclude participants with unstable housing. Criteria based on psychiatric illness and housing led to greater exclusion of women than men in a study of alcohol treatment programs⁵² and we identified 39 studies that restricted eligibility based on mental health conditions. Restrictions on participant body mass index (BMI), found in 15 Canadian RCTs, may lead to disproportionate exclusion of participants from racial or ethnic

identities that fall outside of the ‘normal’ BMI range defined through study of white participants.⁵³

Further, we found that vague exclusion criteria that allowed trial teams to subjectively judge whether a participant may be “uncompliant”³¹ or had a “cognitive disorder that may affect trial participation”^{54, 55} were common.²⁹ A review of exclusion criteria relevant to people with disabilities found that nearly 20% of studies excluded participants with “inability to grant informed consent”,⁸ which was similar to the proportion of Canadian trials with this criterion in our work. Ethics review boards may have a central role in ensuring that eligibility criteria do not needlessly exclude specific groups unless justified as threat to scientific validity. Research teams should also be aware that decision-making capacity and compliance may vary over time and may be specific to settings and interactions, but ultimately qualified investigators have the responsibility for deciding what is best for potential participants and the overall study.

The design and conduct of clinical trials are challenging. Trialists must balance recruitment, inclusion, and diversity with the funding and budgetary resources needed for data collection and risks of participant identifiability when deciding which participant factors are relevant to their trials. Existing toolkits,^{1, 56, 57} resources,^{43, 50, 58} and guidelines^{25, 49, 59} may be helpful to inform data collection and reporting. Investigators should consider which identities may be most relevant based on context, intervention, disease and feasibility. At a minimum, international consensus-building processes involving researchers and patients report that investigators should accurately report sex and gender identities, place of resident, race and/or ethnicity, education level, financial position, and work status, when relevant to their study.^{58, 60} Centralized efforts to create standardized race and/or ethnicity categories for Canadian clinical trialists^{44, 56} could facilitate better understanding of representativeness. Further studies to

understand barriers to inclusive trial recruitment from the perspectives of potential participants and research teams may be helpful. There remain clear scientific and ethical reasons for justifiably excluding participants such as enriching for trial populations with disease mechanisms that are responsive to interventions, selecting for participants with outcomes of interest and not for competing risks, safety, and removing other threats to internal validity and to improve the certainty of treatment effects.

The strength of this study includes its search strategy, duplicate screening/abstraction and detailed data abstraction. However, our search strategy used ClinicalTrials.gov and may have missed eligible trials registered elsewhere. We only extracted data from the primary manuscript for each trial; it is possible that additional articles may have included relevant information not included in the primary publication or investigators may have collected additional demographic data that was not reported in the manuscript. We excluded international trials with Canadian recruitment as we anticipated that there would not be separate reporting of Canadian participants. Information on how investigators collected sex and/or gender was not reported in any study, and we do not know if these data were reported correctly. This study protocol was not registered in advance and our dataset is not publicly available. Lastly, we did not assess the appropriateness of eligibility criteria, but we acknowledge these may be justified from ethical and regulatory perspectives and the degree to which this impacted trial participant diversity is unclear.

The data from this meta-epidemiologic study is encouraging regarding the representation of select groups in RCTs conducted solely in Canada. However, there still may be groups that are underrepresented although this may not be completely accurate due to potential underreporting. Research understanding if and why this occurs and solutions to improve trial participation are needed.

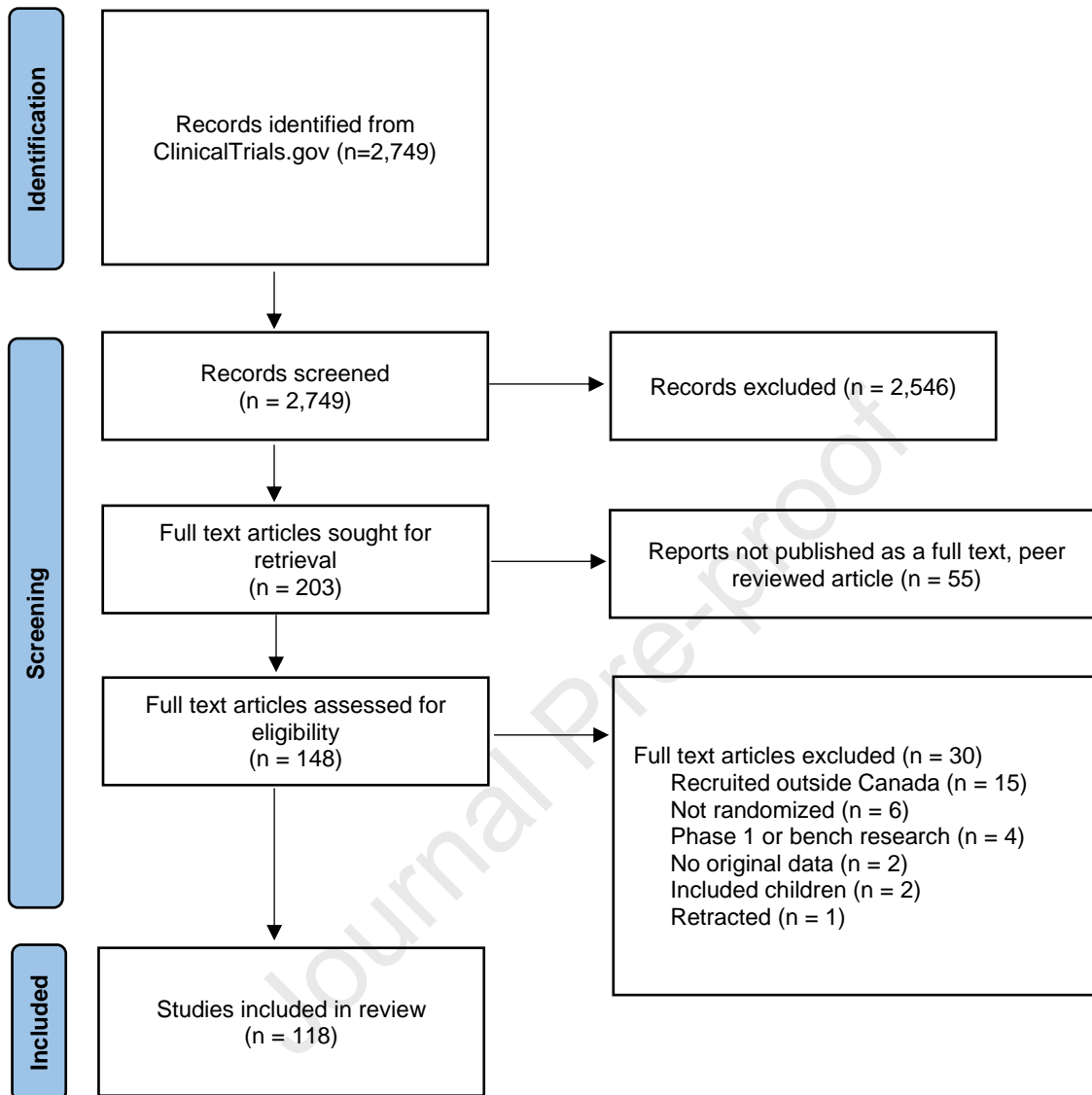
Figure 1. PRISMA diagram describing study identification, screening, and inclusion.

Table 1. Characteristics of Canadian randomized clinical trials

Characteristic	Number of Studies	(%)
Total	118	100
Study Design		
Cluster	3	2.5
Crossover	19	16.1
Parallel	96	81.4
Number of Sites		
Single	61	51.7
Multiple	48	40.7
Unclear	9	7.6
Type of Centers Involved*		
Academic	81	68.6
Community	27	22.9
Not reported	23	19.5
Intervention Types*		
Behavioural	7	5.9
Device	18	15.3
Exercise	11	9.3
Multiple	5	4.2
Pharmacologic	44	37.3
Other	33	28.0
Comparison Types*		
Placebo	32	27.1
Sham	8	6.8
Usual Care/Active	83	70.3
Other	1	0.9
Funding*		
Investigator-Initiated	74	62.7
Industry	41	34.8
Other	6	5.1
Not reported	10	8.5

*Multiple responses allowed

Table 2. Study design elements of Canadian randomized clinical trials (N=118)

Study Design Element	N	N
Study size		
Total participants (range)	17,387	10 – 5,498
Median participants per study (IQR)	59.5	30 - 111
	N	%
Recruited in a municipality with less than 100,000 people	14	11.9
Provinces and Territories*		
Alberta	17	14.4
British Columbia	26	22.0
Manitoba	11	9.3
New Brunswick	4	3.4
Newfoundland & Labrador	4	3.4
Northwest Territories	0	0
Nova Scotia	8	6.8
Nunavut	0	0
Ontario	68	57.6
Prince Edward Island	1	0.9
Quebec	29	24.6
Saskatchewan	2	1.7
Yukon	0	0
Participant allocation by*		
Age	5	4.2
Sex	6	5.1
Gender	2	1.7
Race and/or ethnicity	0	0
Another PROGRESS-PLUS identity	6	5.1
Participant Recruitment*		
In-person	60	50.9
Telephone	5	4.2
Virtual	8	6.8
E-mail	5	4.2
Unclear	43	36.4
Other [‡]	20	17.0
Participants Compensated		
Yes	12	10.2
No/Unclear	108	89.8
Participants Reimbursed		
Yes	4	3.4
No/Unclear	114	96.6
Participant Follow-up*		
In person	87	73.7
Telephone	23	19.5
Virtual	1	0.9

Email	0	0
Other	2	1.7
None [§]	12	10.2
Unclear	10	8.5
Primary outcome statistically significant		
Yes	51	43.2
No	61	51.7
Unclear [¶]	6	5.1

*Multiple responses allowed.

†Examples: "Lower Extremity Functional Scale score to ensure similar physical function" (n=1), BMI (n=2), gambling addiction status (n=1), urban versus rural (n=1), mental health diagnosis (n=1).

‡"Advertisements", "chart review of medical records", "promotional sessions", "word of mouth", "newspapers"

§Referring to studies that occurred over a single encounter such as one surgery.

¶Examples: Pilot studies that did not have a primary outcome, studies that did not define a primary outcome.

Table 3. Trial eligibility (inclusion or exclusion) criteria relevant to PROGRESS-PLUS identities in Canadian randomized clinical trials (N=118).

PROGRESS-PLUS Eligibility Criteria	Subcategory	N	%
Place of residence	Address	15	12.7
	Geography*	13	11.0
Race, ethnicity, culture, or language	Race and/or Ethnicity	2	1.7
	Language	28	23.7
Occupation	-	4	2.4
Gender and Sex	Sex	33	28.0
	Gender	13	11.0
	Contraception	12	10.2
	Pregnancy	40	33.9
	Lactation	18	15.3
Religion [†]	-	1	0.9
Education	-	0	0
Socioeconomic status	-	8	6.8
Social capital	Need for a caregiver or family member	5	4.2
	In-person follow-up required	43	36.4
PLUS	Ability	69	58.5
	Age [‡]	42	35.6
	BMI	14	11.9
	Mental Health	38	32.2
	Other [§]	28	23.7

Detailed eligibility criteria can be found in the appendix (eTable 2).

*Examples: had to be “living within 100 km of the university”, excluded if “geographically inaccessible” to the study team, or “recruited from a community center”

[†]Participants had to be “willing to accept blood products” to be included.

[‡]To be included in this review, studies had to recruit only adults. Age was therefore only included as an additional eligibility criteria if there were further restrictions on the age of participants in the study.

[§]Examples: Excluded participants with “breast augmentation, reduction, or nipple piercing”, “oral or tongue piercings”, “same sex couples”, and history of “domestic violence”

Table 4. Demographic characteristics of participants as reported Canadian randomized clinical trials (N=118, 17,387 participants)

	N	%
Number of studies that reported sex and/or gender		
Studies that reported participant sex	105	89.0
Studies that reported participant gender	12	10.2
Studies that reported intersex or non-binary participants*	1	1.0
Studies that reported sex and gender of participants	0	0
Studies that reported neither sex or gender of participants	0	0
Number of studies that reported PROGRESS-PLUS demographics		
Place of residence [†]	15	12.7
Race/ethnicity	31	26.3
Languages	6	5.1
Occupation	19	16.1
Religion	0	0
Education Level	19	16.1
Socioeconomic Status	11	9.3
Social capital [‡]	5	4.2
Other [§]	4	3.4
Participant Sex		
Male	5,402	32.8
Female	11,066	67.2
Intersex	1	<0.1
Participant Gender		
Men	404	45.9
Women	477	54.1
Transgender participants	NR	NR
Non-binary participants	NR	NR
Participant Sex, excluding studies that only recruited a single sex		
Male	4,774	51.8
Female	4,444	48.2
Intersex	1	<0.1
Participant Gender, excluding studies that only recruited a single gender		
Men	404	47.5
Women	446	53.5
Transgender participants	NR	NR
Non-binary participants	NR	NR

*Described as "Other", presumed to be intersex based on the other categories being female and male

[†]Includes studies that report marital status of participants

[‡]"co-habiting with the infant's mother", recruited with a caregiver, recruited only couples

[§]"uses IV drugs", "men who had sex with men", tobacco users, "had anxiety/depression"

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Table 5. Description of the race and/or ethnicity categories reported in Canadian randomized clinical trials (N=31/118 = 26.3%)

Race / Ethnicity category	Euphemisms/Subcategories (n studies)	Studies reported of 31 studies that reported race and/or ethnicity (n, %)	Median Percentage of Participants per study that reported (IQR)	Total Number of Participants	Proportion of participants from trials that reported race/ethnicity (n=4,124)
Asian	South Asian (n=4) Chinese (n=1) East Asian (n=3) South East Asian, South/East Asian, Southeast Asian (n=4) Asian/Native Hawaiian/Other Pacific Islander (n=1)	18 (58.1)	14.0% (4.0-17.5%)	260	6.3%
Black	Africans (n=1) African American (n=4) African Canadian (n=4) Black Canadian (n=1) [†] Black Caribbean (n=1) [†]	12 (38.7)	8.0% (4.0-15.0%)	113	2.7%
Indigenous	North American Indian (n=1) Aboriginal (n=1) North American First Nations (n=1)	3 (9.7)	1.0% (1.0-2.5%)	7	0.2%
Multiple	Mixed (n=5) Multiple (n=1) Non-Caucasian (n=1) Non-white (n=2)	9 (29.0)	7.0% (6.0-12.0%)	84	2.0%
Other	N/A	12 (38.7)	4.0% (2.0-7.8%)	73	1.8%
South or Central American	Hispanic (n=2) Hispanic or Latino (n=3) Central American (n=1) South American (n=1)	6* (19.4)	2.0% (1.3-4.5%)	25*	0.6%
West Asian	Arab/West Indian (n=1) Middle Eastern (n=1)	3 (9.7)	3.0% (2.0-4.0%)	10	2.4%

	East Indian (n=1)				
White	Caucasian (n=9) European, European Canadian, Euro-Canadian, White/European, White European Origin, Western European White, Eastern European White (n=6), White – Arabic/North African (n=1) Born in Canada (n=1) None (n=14)	31 (100)	78.5% (61.4-86.0%)	2,969	72.0%

*One trial³¹ reported Hispanic and Non-Hispanic identities separately from South American and Central American identities while the other 4 trials reported Hispanic/Latino as a racial category without reporting the number of “non-Hispanic” participants. Each participant is counted only once.

†One trial⁶¹ reported “Black Caribbean” and “Black Canadian” as separate categories.

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Highlights:

- International bodies have prioritized diversity among clinical trial participants.
- Underreporting of participant sociodemographics limits assessment of diversity.
- Sex and gender minorities are underreported and likely to be underrepresented among participants.
- Standardized, thoughtful and inclusive race and/or ethnicity categories are needed.

SMR, KCL, and DC conceived of and designed the study, provided supervision, performed formal analysis, and wrote the first draft of the manuscript. SMR, KCL, DC, CS, ST, AS, ML, SH, MS, and DO contributed to data collection, data analysis, and visualization. WC, DAF, SRI, PL, SM, SGN, CLP, LP, AEQ, and SB contributed to study design, methodology, validation, and revised and edited the final manuscript.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: