Can nurse home visiting reduce prenatal substance use in a cohort coping with socioeconomic disadvantage? Randomized controlled trial findings in British Columbia

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Abstract (250/ 250 words)

Background: We are evaluating the Nurse-Family Partnership (NFP) program regarding its effectiveness in improving child and maternal outcomes, and report here on reducing prenatal substance use.

Methods: We are conducting this randomized controlled trial in British Columbia with 739 participants (14–24 years) who are experiencing socioeconomic disadvantage and parenting for the first time. Participants were randomly allocated (1:1) to intervention (n=368) or comparison (n=371) groups. Public-health nurses delivered NFP during frequent home visits starting before 28 weeks gestation and continuing until children reached age two years. The pre-specified prenatal outcome indicators were changes in nicotine/cigarette and alcohol use by late pregnancy. Exploratory cannabis and street drug use data were also analyzed.

Results: All 739 participants were included in intention-to-treat analyses. By late pregnancy, we observed decreased rates of prenatal cigarette (difference in changes [DIC] of proportions -3.2%, 95% confidence interval [CI] -7.3%~ 1.57%) and alcohol (DIC -0.5%, 95% CI -4.2%~ 3.2%) use for NFP participants but decreases were not significant. In smokers, however, we found a significant reduction in daily cigarette smoking (DIC [count] -1.78, 95% CI -3.0~ 0.32). NFP also significantly reduced rates of prenatal cannabis use (DIC -5.4%, 95% CI -10.9%~ -1.2%), but not rates of street drug use or "any" substance use.

Interpretation: We found no evidence that NFP was effective in reducing rates of prenatal cigarette and alcohol use in a cohort experiencing socioeconomic disadvantage. However, NFP reduced prenatal cigarette use for smokers, and reduced prenatal cannabis use, a growing public health problem in Canada.

Introduction

Prenatal exposure to substances such as nicotine/cigarettes (hereafter cigarettes), alcohol, cannabis, cocaine and opioids put children at risk for adverse outcomes including preterm birth, low birth weight, early motor abnormalities, mental health problems and cognitive impairments.[1–10] Canadian rates of prenatal substance use nevertheless remain concerning, particularly for cigarettes (11–23%), alcohol (10–15%) and cannabis (2–7%).[11–15] Cannabis use is also predicted to increase following recent legalization in Canada.[15,16] Accordingly, preventing prenatal substance use is strongly warranted[17,18] — particularly with those who are young, living on low income and coping with mental health concerns and therefore at higher risk of using substances prenatally.[12,19]

Aiming to improve child and maternal wellbeing, Nurse-Family Partnership (NFP) involves public-health nurses (PHNs) providing intensive home visits to girls and young women who are experiencing socioeconomic disadvantage and preparing to parent for the first time.[20] Randomized controlled trials (RCTs) in the United States (US) have shown that NFP improves child mental health and cognitive development and reduces child injuries by age two years, while also improving maternal wellbeing.[20] Yet evidence has been mixed on NFP's effectiveness in reducing prenatal substance use, particularly outside the US.[21,22] As well, it is not known how NFP's benefits may translate to Canada, given the greater availability of publicly-funded health and social services compared to the US.

To address this evidence gap, we launched the British Columbia Healthy Connections Project (BCHCP) RCT in 2013.[23,24] Here we report data from this RCT on NFP's impact on prenatal cigarette and alcohol use (pre-specified outcome indicators). We also report exploratory

data on program effects for prenatal cannabis and street drug use. The trial is still in progress. Future reports will provide data on additional child and maternal outcomes.

Methods

Design, setting and population

The BCHCP is a single-blind RCT being conducted across 26 urban-suburban local health areas (LHAs) in four BC regional health authorities (HAs). The trial was registered in 2012 with ClinicalTrials.gov (NCT01672060). The HAs obtained trial referrals from primary-care providers and community agencies and passed these to the study team, who contacted potential participants to introduce the RCT, confirm eligibility and schedule baseline interviews. (See Table 1).

[Insert Table 1]

Table 1. Inclusion and exclusion criteria at time of baseline interview

Inclusion criteria
1. Age 24 years or younger
2. Preparing to parent for the first time[a]
3. Less than 28 weeks gestation [b]
4. Competent to provide informed consent, including conversational in English[c]
5. Experiencing socioeconomic disadvantage • Age 19 years or younger • Age 20–24 years and meets 2 of 3 indicators: a) lone parent[d]; b) less than grade 12[e]; c) low income (one or more of the following): i. Receiving income assistance ii Finding it very difficult to live on total household income regarding food or rent iii. Homeless, defined as living on the streets, in an emergency or homeless shelter, staying in places not meant as residences, e.g., car or tent, or experiencing "hidden homelessness" such as "couch surfing"
Exclusion criteria
1. Planning to have the child adopted
2. Planning to leave the catchment area for 3 months or longer during the trial [f]

Notes: [a] Eligible if a previous pregnancy ended in termination, miscarriage or stillbirth or if previous parenting involved step-parenting only; [b] must receive first NFP visit by end of 28th week of gestation, according to Nurse-Family Partnership fidelity requirements; [c] must be able to participate without an interpreter; [d] not married or living with the same partner for one year or more consecutively; [e] did not complete secondary school or did not receive secondary school equivalency certificate; [f] catchment refers to designated BC Local Health Areas offering the BCHCP; table adapted from Catherine et al., 2016[23] and 2019[24].

Randomization procedures

Following completion of baseline interviews, participants were randomly assigned (1:1) to either intervention (NFP plus existing services) or comparison (existing services) groups. We used an unpredictable, randomized sequence protocol developed by an independent statistician. We applied a separate schedule using a blocked randomization scheme for each of the 26 LHAs using used two block sizes: when 18 or fewer participants were expected annually, and when 19 or more were expected. A senior study team member, uninvolved in data collection, performed computerized allocation and informed participants and NFP PHNs of treatment allocation (i.e., they were not masked). Field interviewers involved in data collection and data preparation were masked to group allocation; they also reminded participants prior to each interview not to reveal their group. The main analyses were conducted by trial statisticians/methodologists masked to group assignment.

Intervention

Following enrollment, NFP PHNs contacted participants allocated to the intervention group to schedule the first home visit before 28 weeks gestation. PHNs delivered NFP during regular 60–90-minute home visits throughout the pregnancy then through until children reached age two years, totalling as many as 60 or more visits of varying intensity over 2.5 years. Through skill development and motivational interviewing, PHNs assisted girls and young women in identifying individual goals and plans for behavioural change, such as reducing prenatal substance use. PHNs had access to NFP program materials focused on prenatal substance use to facilitate this process. PHNs also received intensive NFP education and were supervised to ensure fidelity to core program elements.[25]

Existing services

All participants (NFP and comparison) were entitled to receive existing health and social services within their HAs. Prenatally these could include: primary and/or specialist healthcare; hospital and/or emergency room services; public health services including outreach and prenatal classes; and social services and community programs.

Data sources

All eligible participants provided written informed consent before starting the study. An array of validated scales and items were then administered at baseline (before 28 weeks gestation; in person) and in late pregnancy (34−36 weeks gestation; by telephone). (Table 2 summarizes the prenatal measures used.) Following each interview, participants received gift cards ($50−75 CAD) for local stores. Field interviewers verbally administered questionnaire items to ensure accuracy. For items prone to response bias (including prenatal substance use), in-person interview questions were administered using private audio-recordings, with participants responding confidentially on paper; responses were then placed in sealed envelopes for processing by the study team. Participants could decline to answer questions. In-person interview settings were chosen by participants and usually involved their homes.

[Insert Table 2]

Table 2. Summary of measures in early and late pregnancy

Measurement Construct & Description	Scoring
Sociodemographic characteristics[1]	
• Age and cultural background (baseline only); marital status, education, and income, where income was defined as pre-tax annual income from all sources of employment including unreported income and excluding any money received from family, friends or income assistance.	Low income (living on a less than $20,000 per year); limited education (having less than high school); single (not married or common-law); dichotomous (yes/no) variable.
Unstable housing	
• Having to move 3 or more times or experiencing homelessness (past year).	Dichotomous (yes/no) variable.
Psychological distress[2]	
• Kessler Psychological Distress Scale; Likert scale with 10 items, e.g., "*About how often did you feel hopeless*?"	Moderate-to-severe anxiety or depression.
Maltreatment experiences	
• Child maltreatment; Childhood Trauma Questionnaire, Short Form;[3] Likert scale with 28 items, e.g., "*When I was growing up, I didn't have enough to eat*."	Moderate-to-severe levels of neglect, physical abuse, emotional abuse and/or sexual abuse.
• Intimate partner violence (past year); Composite Abuse Scale;[4] Likert scale with 30 items, e.g., "*My partner told me that I wasn't good enough*;" partner was defined as husband/wife, partner, or boy/girlfriend for longer than one month.	Any physical abuse, emotional abuse and harassment.
Prenatal substance use[5]	
• Tobacco (number of cigarettes smoked in past 2 days)	Count.
• Alcohol (frequency of drinking in past month)	Frequency; dichotomous (yes/no) variables.
• Cannabis (frequency of using all forms of cannabis, marijuana or hashish in past month);	
• Street drugs (frequency of using LSD, magic mushrooms, ecstasy, cocaine, speed, heroin and/or crystal methamphetamines in past month).	
• "Any" substance use was defined as any-or-all of tobacco, alcohol, cannabis and/or street drugs.	

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Ethics approval

The trial received research ethics approvals from: Simon Fraser University; University of BC; University of Victoria; McMaster University; Public Health Agency of Canada; and Fraser, Interior, Island and Vancouver Coastal Health Authorities. An independent Data and Safety Monitoring Committee has also tracked participant safety and protocol compliance.

Outcome indicators

The pre-specified main trial outcome indicators were: prenatal substance use (cigarettes and alcohol); child injuries (primary indicator) and cognitive development and behaviour by age two years; and maternal subsequent pregnancies by 24-months postpartum.[23] The prenatal indicators were defined as changes in cigarette and alcohol use between early and late pregnancy; exploratory data on other prenatal substances used were also collected.

Sample size calculation

The sample size was determined based on detecting clinically meaningful differences in reducing the primary outcome indicator, healthcare encounters for childhood injuries by age two years. We originally estimated that we needed a sample size of 1040 to detect a 30% relative risk reduction where alpha=.05 and beta=0.20 and presuming low attrition (<5%) due to accessing provincial administrative health data on child injuries.[23] However, re-estimations based on analysis of 10 years of provincial childhood injury data in a similar population (children born to pregnant girls and young women receiving income assistance and preparing to parent for the first time) indicated a lower expected incidence of childhood injuries, allowing a smaller sample (739) to suffice.

Statistical analysis

We conducted the intention-to-treat (ITT) analyses of NFP's effects: on pre-specified substance use outcomes, namely cigarette and alcohol use (n=739); subgroup analysis examining the number of cigarettes smoked daily for those who reported smoking in either early or late pregnancy or both (*n*=211 "smokers"); and exploratory ITT analyses on additional (non-pre-specified) substance use outcomes of interest, specifically cannabis and street drugs, that may be influenced by NFP. We analyzed the longitudinal measures of substance use at baseline (less than 28 weeks gestation) and late pregnancy (34–36 weeks gestation) using Generalized Linear Mixed-effect Models (GLMMs). GLMMs incorporated fixed effects for: 1) time period (baseline versus late pregnancy) for time effects; 2) NFP versus comparison at baseline; and 3) time period by NFP interaction for NFP intervention effect by late pregnancy. These models also included random effects for clusters (i.e., participants nested within LHAs within HAs). Model estimates (95% confidence intervals [CI]) and the associated two-side *p*-values were determined. We estimated proportions using the fitted models and calculated 95% CIs using 1,000 bootstrap samples. We also estimated GLMMs adjusting additionally for baseline covariates. (See Table 3.) We assessed the sensitivity of the results to missing-at-random assumptions via selection models.[26–29] All analyses were conducted using R 3.5.[30] (See Appendix 1 for details.)

Results

Participant recruitment and flow

Recruitment occurred from October 2013 through December 2016. Prenatal follow-up closed in March 2017. NFP delivery concluded in June 2019 when all children reached age two years. Research interviews will conclude in late 2019, while final provincial administrative health data on child injuries will be received in 2020. Overall, 739 participants were randomly allocated to either intevention (NFP plus existing services, n=368) or comparison (existing services, n=371) groups; 667 (90%) completed the follow-up interview in late pregnancy. (See Figure 1.) All 739 participants were included in the ITT analyses. Baseline characteristics were well balanced across the two trial groups (See Table 3.) No protocol deviations or unanticipated problems, including unanticipated serious adverse events, have been identified/reported since the trial commenced in 2013. (See Appendix 2 for definitions.)

[Insert Figure 1 and Table 3; Figure 1 submitted separately]

Table 3. Participant characteristics at baseline*

	Comparison *n* = 371	NFP *n* = 368
Sociodemographic characteristics	n/N (%)	n/N (%)
• Age (19 years or younger)	175/371 (47.2)	186/368 (50.5)
• Single (not married or common-law)	337/369 (91.3)	333/367 (90.7)
• Cultural background*		
– White	217/371 (58.5)	201/368 (54.6)
– Indigenous including First Nations, Métis and Inuit	44/371 (11.9)	35/368 (9.5)
– Indigenous including First Nations, Métis and Inuit and Other	56/371 (15.1)	65/368 (17.7)
– Mixed heritage ≥ 2	23/371 (6.2)	32/368 (8.7)
– Asian (Chinese, South Asian or Other)	16/371 (4.3)	16/368 (4.3)
– Other (including Latin-American, Black)	15/371 (4)	19/368 (5.2)
• Highest educational qualification		
– Less than high school	193/371 (52)	191/367 (52)
– High school diploma or equivalent	139/371 (37.5)	131/367 (35.7)
– College or other non-university or university degree	39/371 (10.5)	45/367 (12.3)
• Income from employment (CAD)		
– Less than $5,000	146/362 (40.3)	162/364 (44.5)
– $5,000 – 9,999	64/362 (17.7)	54/364 (14.8)
– $10,000 – 19,999	87/362 (24)	93/364 (25.5)
– $20,000 – 29,999	38/362 (10.5)	37/364 (10.2)
– $30,000 or more	27/362 (7.5)	18/364 (4.9)
Unstable housing		
• Homeless ever (including currently)	157/356 (44.1)	176/360 (48.9)
• Currently homeless	11/359 (3.1)	11/362 (3)
• Moved 3 or more times or homeless (past year)	187/366 (51.1)	198/365 (54.2)
Mental health		
• Moderate/severe psychological distress (past month)	122/370 (33)	112/364 (30.8)
Maltreatment experiences		
• Child maltreatment at age 16 years or younger	206/367 (56.1)	204/361 (56.5)
• Exposure to intimate partner violence (past year)	187/369 (50.7)	176/365 (48.2)

* Categories according to Statistics Canada; participants could give more than one answer.

Outcomes and effect estimation

Cigarette smoking

In early pregnancy, 26.6% of participants reported smoking cigarettes (in the past two days). By late pregnancy, the proportion decreased in both groups (by 5.8% for NFP versus 2.4% for comparison; see Table 4). The estimated differences in the before-after changes of log odds and proportions of cigarette use were: -1.72 ([95% CI=-3.86 to 0.42], p=0.116; see Table 5), and -3.2 (95% CI=-7.3 to 0.8) percentage units (see Table 6), respectively.

[Insert Tables 4–6; Table 5 submitted separately]

Table 4. Substance use in early and late pregnancy*

	Baseline (<28 Weeks)		Weeks 34–36	
	Early Pregnancy		Late Pregnancy	
	Comparison	NFP	Comparison	NFP
N	371	368	371	368
Cigarette				
Cigarette (%)	103/370 (27.8)	93/366 (25.4)	85/335 (25.4)	64/326 (19.6)
Cigarette count, smokers,** mean (SD)/N	6.83 (6.07)/115	8.37(6.81)/96	5.86 (5.85)/106	6.06 (7.03)/79
Alcohol (%)	19/369 (5.1)	23/367 (6.3)	11/335 (3.3)	12/326 (3.7)
Cannabis (%)	96/371 (25.9)	93/367 (25.3)	71/335 (21.2)	55/326 (16.9)
Street drug (%)	4/369 (1.1)	9/366 (2.5)	2/335 (0.6)	0/326 (0)
Any substance use (%)	158/367 (43.1)	159/363 (43.8)	127/335 (37.9)	106/326 (32.5)

* Data are n/N (%) or mean (SD)/N.

** "Smokers" defined those using cigarettes in either early or late pregnancy or both.

Table 6. Estimated difference in before-after change in proportions of substance use

	Difference in Before-After Change in Proportions	
	Crude	**Estimated (95% CI)**
Cigarette (%)	-3.31	-3.2 (-7.3, 0.8)
Cigarette – All (Count)	-0.57	-0.36 (-0.82, 0.16)
Cigarette – Smokers only (Count)	**-1.74**	**-1.78 (-3.0, -0.32)**
Alcohol (%)	-0.72	-0.5 (-4.2, 3.2)
Cannabis (%)	**-3.79**	**-5.4 (-10.9, -1.2)**
Street drugs (%)	-1.97	-2.0 (-4.3, 0.2)
Any substance use (%)	-6.14	-6.4 (-14.5, 1.8)

Note: 95% confidence intervals (CI) were estimated using 1,000 bootstrap sampling; bolding indicates statistical significance.

Subgroup analysis – smokers

We explored cigarette use in participants who reported smoking in either early or late pregnancy or both (n=211; 28.9%). By late pregnancy, the average number of cigarettes smoked decreased in both groups — by 1.2 per day in the NFP group versus 0.5 per day in the comparison group. (See Table 4.) The estimated differences in the before-after changes of log rate and mean number of cigarette counts were: -0.2 ([95% CI=-0.36 to -0.05], p=0.011; see Table 5), and -1.78 (95% CI=-3.0 to -0.32) counts (see Table 6), respectively.

Alcohol use

In early pregnancy, 5.7% of participants reported consuming alcohol (in the past month). By late pregnancy, the proportion decreased in both groups — by 2.6% in the NFP group versus 1.8% in the comparison group. (See Table 4.) The estimated difference in the before-after changes of percentage of alcohol use was -0.5 ([95% CI=-4.2 to 3.2], p=0.791) percentage units (see Table 4).

Exploratory analyses

Cannabis use

In early pregnancy, 25.6% of participants reported using cannabis (in the past month). By late pregnancy, the proportion decreased in both groups — by 8.4% in the NFP group versus 4.7% in the comparison group (see Table 4). The estimated differences in before-after changes of log odds and percentage of cannabis use were: -3.39 ([95% CI=-5.35 to -1.42], p<0.001; see Table 5), and -5.4 (95% CI=-10.9 to -1.2) percentage units (see Table 6), respectively.

Street drug use

In early pregnancy, 1.8% of participants reported using street drugs (in the past month). By late pregnancy, the proportion decreased in both groups — by 2.5% in the NFP group versus 0.5% in the comparison group (see Table 4). The estimated difference in the before-after changes of percentages of street drug use was -2.0 ([95% CI=-4.3 to 0.2], p=0.074) percentage units (see Table 6).

Any substance use

In early pregnancy, 43.4% of participants reported using any substance (cigarettes, alcohol, cannabis and/or street drugs). By late pregnancy, the proportion decreased in both groups — by 11.3% in the NFP group versus 5.2% in the comparison group (see Table 4). The estimated differences in before-after change of log odds and percentages of any substance use were: -0.61 ([95% CI=-1.31 to 0.09], p=0.085; Table 5), and -6.4 (95% CI=-14.5 to 1.8) percentage units (see Table 6), respectively.

Sensitivity analysis

We found negligible impacts of non-random missingness on the ITT estimates (see Table 7; Appendix).[31] GLMM analyses including additional baseline covariates showed that the intervention effect estimates remained similar (see Table 5; last two columns).

Interpretation

All 739 participants were included in the ITT analyses. By late pregnancy, we observed decreased rates of prenatal cigarette and alcohol use for NFP participants but decreases were not significant. In smokers, however, we found a significant reduction in daily cigarette smoking (p=0.01). NFP also significantly reduced prenatal rates of cannabis use (p<0.001), but not rates of "any" substance use or street drug use.

For cigarette use, we found high smoking rates (26.6%) in early pregnancy but no evidence of benefit from NFP by late pregnancy. However, among smokers, daily cigarette counts were significantly reduced in the NFP group (by 1.2 for NFP versus 0.5 for controls; p=.01). Similarly, previous NFP trials in the US[20] and the Netherlands[21] have shown small but significant prenatal smoking reductions, although a trial in England did not.[22] Between-study differences may be attributable to divergences in populations, NFP implementation and baseline health and social services. Yet while the prenatal smoking decreases among smokers in our study were modest, even minimal reductions are associated with benefits for the developing fetus.[5] NFP therefore shows promise for populations like our cohort, particularly given the high smoking rates we found —building on other harm reduction efforts.[32–34]

For prenatal alcohol use, we found relatively low alcohol use rates (5.7%) in early pregnancy but no evidence of benefit from NFP by late pregnancy. Similarly, previous US NFP trials have not shown significant reductions in prenatal alcohol use.[20] As there is no safe level of prenatal alcohol consumption, ongoing harm reduction efforts remain crucial.[6,35] Even so, our findings suggest that prenatal alcohol use — despite its clinical and public health importance — may be too infrequent to be a useful focus for an intervention such as NFP in a cohort like ours.

While prenatal cannabis was not a pre-specified outcome indicator, we identified high rates of use (25.6%) — and found that NFP significantly reduced these rates by late pregnancy (p<0.001). Prenatal cannabis use is rising in Canada, particularly in young, at-risk populations.[16] Possible explanations include greater access to cannabis compared with alcohol for these populations.[36] Yet the rates are concerning given adverse consequences for the developing fetus,[1,2,7] increasing potency of cannabis,[37] and public perceptions of cannabis as relatively harmless or even beneficial in pregnancy.[38] Prenatal cannabis harm reduction efforts should

therefore be intensified. Based on our findings, NFP shows considerable promise as part of these efforts, particularly for disadvantaged populations.

At the same time, we found no evidence of benefit from NFP regarding "any" substance use or street drug use, two other exploratory outcomes of interest. Similarly for street drugs, previous NFP trials in the US, the Netherlands and England have not shown significant reductions in prenatal use.[20–22] The lack of effect in our case may also be due to the low rate of baseline use (1.8%).

Our study also has limitations. We relied on maternal self-report data on prenatal substance use. For cigarettes in particular, self-reports may underestimate smoking by up to 25% compared to serum cotinine.[39] Yet previous US trials have shown that NFP participants who were smokers, compared to control-group counterparts, became more accurate reporters by the end of pregnancy.[40] This suggests that our findings for smokers may indeed reflect program effects. We also collected only limited/preliminary data on prenatal e-cigarette use. The use of this mode of nicotine delivery has increased considerably since we commenced the trial, particularly with youth.[41] Future trials should examine prenatal e-cigarette use. Similarly, we did not collect specific data on opioid use, although opioids were included with general questions on street drugs. Opioids have become of high clinical and public health salience since we commenced the trial.[42] Future trials of a similar nature should therefore examine opioid use. Finally, our findings are specific to a high-risk Canadian cohort of pregnant girls and young women who were preparing to parent for the first time and so, may not be generalizable to other populations.

In conclusion, we found no evidence that NFP was effective in reducing rates of prenatal cigarette and alcohol use in a young Canadian cohort experiencing socioeconomic disadvantage.

However, for prenatal smokers, the program was effective in reducing the daily number of cigarettes consumed. As well, NFP reduced prenatal cannabis use — a growing public health problem in Canada.

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Data sharing: Following completion of this trial and following publication of all major findings papers, anonymized participant data and associated documents including the study protocol and statistical analysis plan may be shared. Protocols for accessing study data and information will be governed by a data-sharing agreement. For more information, please contact the corresponding author.

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Figure 1: Participant Flow Diagram

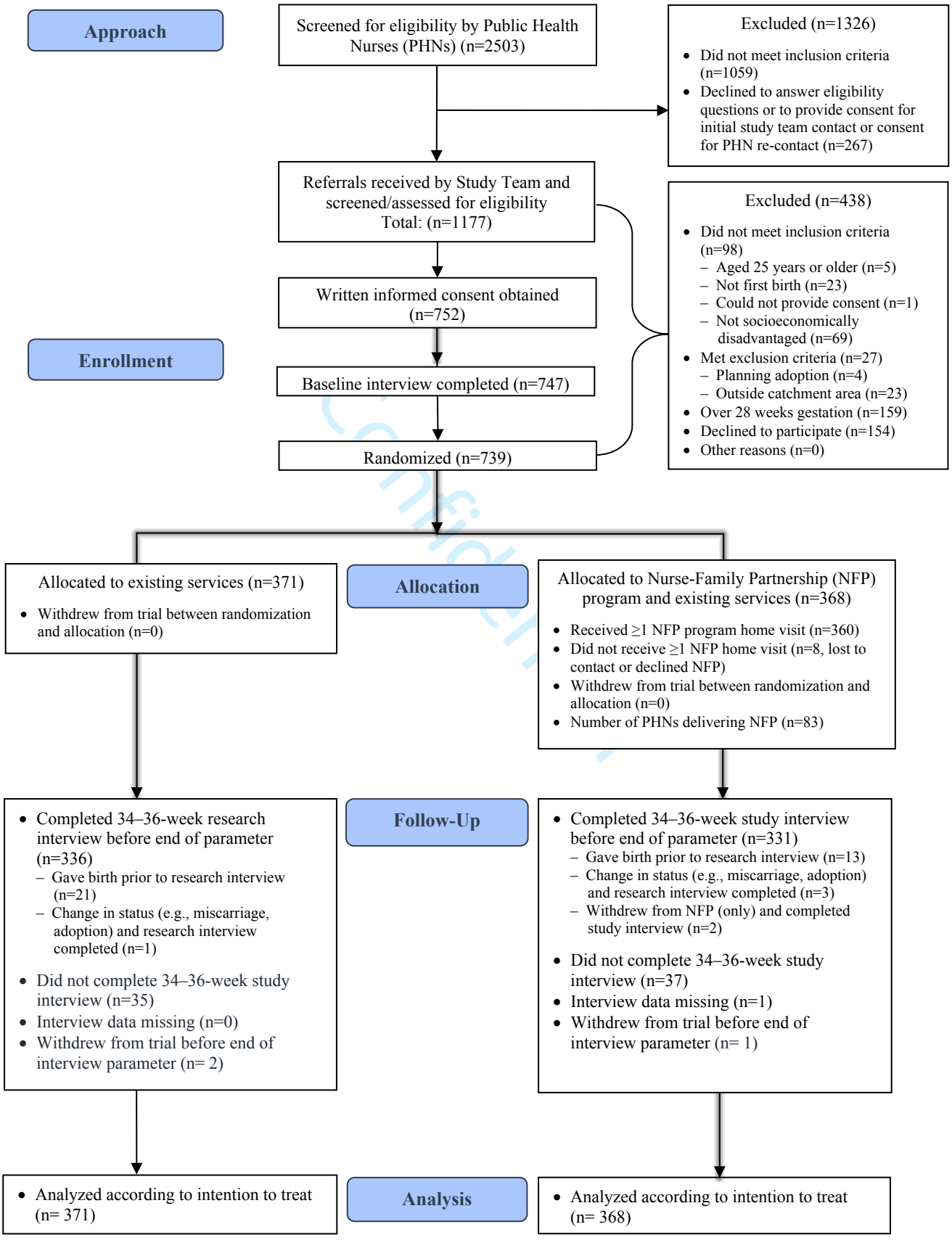

Figure 1: Participant Flow Diagram

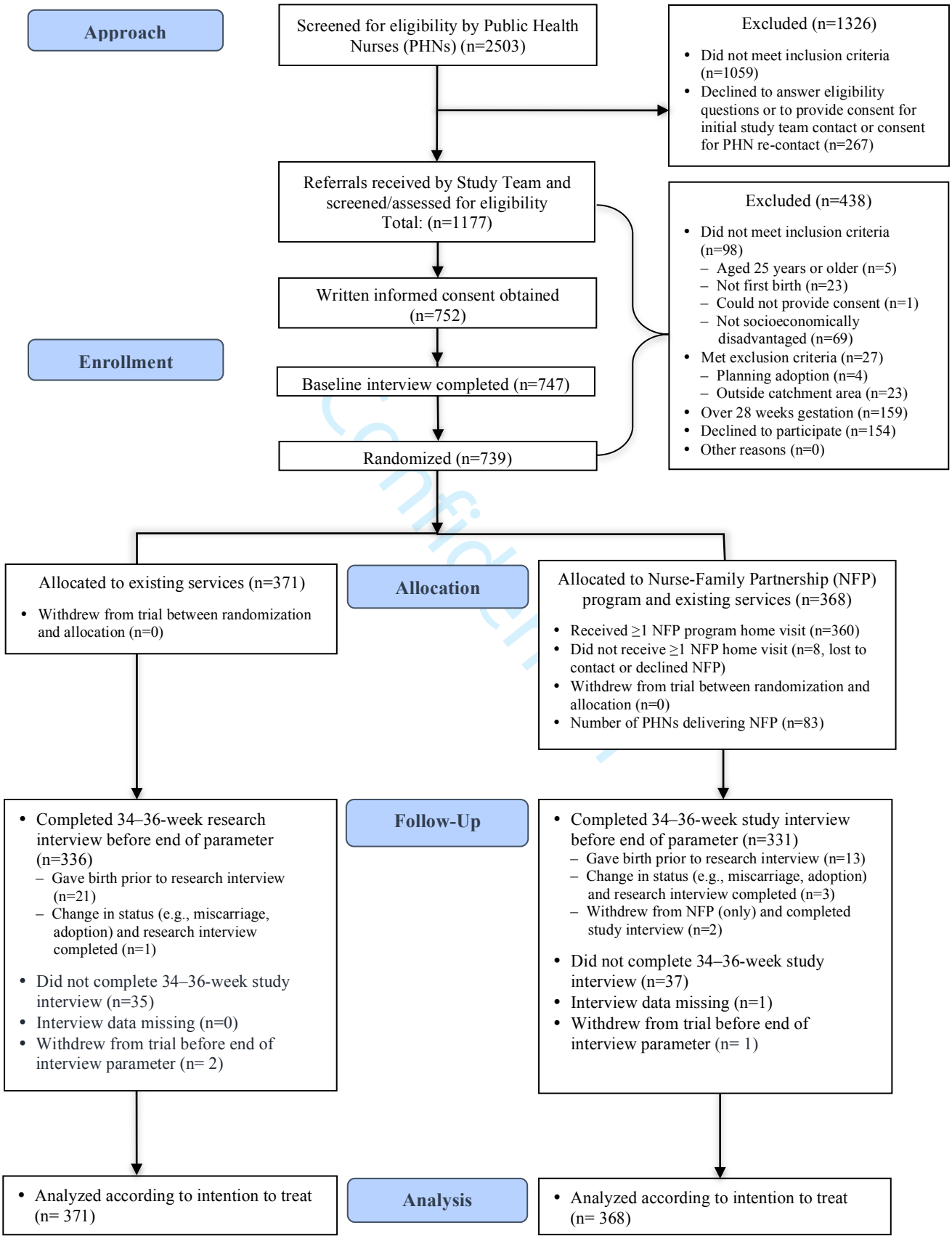

Table 5. Coefficients from two-level mixed effect models: Primary and robustness analysis*

	Primary Analysis						Robustness Analysis	
	Week 34−36		NFP		Treatment Effect		Treatment Effect	
	Estimate	*p*-value	Estimate	*p*-value	Estimate	*p*-value	Estimate	*p*-value
Cigarette (Yes/No)†	-1.28 (-2.35, -0.21)	0.019	-0.01 (-1.29, 1.28)	0.99	-1.72 (-3.86, 0.42)	0.116	-1.91 (-4.08, 0.26)	0.085
Cigarette – Smokers (Count)‡	-0.12 (-0.23, -0.02)	0.02	0.23 (-0.03, 0.48)	0.082	**-0.2 (-0.36, -0.05)**	**0.011**	-0.2 (-0.36, -0.04)	0.012
Alcohol (Yes/No)§	-0.02 (-0.046, 0.005)	0.122	0.011 (-0.019, 0.042)	0.47	-0.005 (-0.04, 0.032)	0.787	-0.005 (-0.042, 0.032)	0.791
Cannabis (Yes/No)†	-1.8 (-2.8, -0.8)	<0.001	0.07 (-1.07, 1.21)	0.906	**-3.39 (-5.35, -1.42)**	**<0.001**	-3.82 (-5.86, -1.79)	<0.001
Street drugs (Yes/No)§	-0.005 (-0.02, 0.01)	0.53	0.014 (-0.001, 0.029)	0.07	-0.02 (-0.04, 0.002)	0.074	-0.021 (-0.043, 0.002)	0.074
Any substance (Yes/No)†	-0.53 (-1.02, -0.05)	0.031	0.03 (-0.73, 0.8)	0.934	-0.61 (-1.31, 0.09)	0.085	-1.06 (-1.94, -0.19)	0.017

†: Binary outcomes, logistic mixed effect model. The coefficient for treatment effect represents the estimated group difference in before-after change of log odds of substance use.
‡: Count outcomes, Poisson mixed effect model. The coefficient for treatment effect represents the estimated group difference in before-after change of log rate of substance use.
§: Binary outcomes, linear mixed effect model. The coefficient for treatment effect represents the estimated group difference in before-after change of proportion of substance use.
* Bolding indicates statistical significance.

Table 5. Coefficients from two-level mixed effect models: Primary and robustness analysis*

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§: Binary outcomes, linear mixed effect model. The coefficient for treatment effect represents the estimated group difference in before-after change of proportion of substance use.
* Bolding indicates statistical significance.

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4
	2b	Specific objectives or hypotheses	4
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	5
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	NA
Participants	4a	Eligibility criteria for participants	6
	4b	Settings and locations where the data were collected	8
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	7
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	10
	6b	Any changes to trial outcomes after the trial commenced, with reasons	NA
Sample size	7a	How sample size was determined	10
	7b	When applicable, explanation of any interim analyses and stopping guidelines	NA
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	7
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	7
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	7
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	7
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	7

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	NA
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	11
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	17
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	Figure 1
	13b	For each group, losses and exclusions after randomisation, together with reasons	Figure 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	12
	14b	Why the trial ended or was stopped	NA
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	13
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Tables 4-6
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Tables 4-6
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	Tables 4-6
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	17
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	12
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	20
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	20
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	18
Other information			
Registration	23	Registration number and name of trial registry	5
Protocol	24	Where the full trial protocol can be accessed, if available	22
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	2

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

Appendices

1. Statistical analysis

We analyzed the longitudinal data of repeated measures of substance use at baseline (<28 weeks gestation) and at late pregnancy (34–36 weeks gestation) using Generalized Linear Mixed-effect Models (GLMMs). The longitudinal data analytical approach was capable of including all subjects in the intention-to-treat (ITT) analysis even when some subjects may have missing outcome values at either baseline or at late pregnancy, and the GLMMs can account for outcome data missing at random without the need to perform explicit imputations of the missing values.[1] The GLMMs include normal mixed-effect models for continuous outcomes, logistic mixed-effect models for binary outcomes, and Poisson mixed-effect models for count outcomes as special cases. The GLMMs are the most efficient and recommend statistical methods for analyzing longitudinal and clustered clinical trial data[2], and have been widely used for conducting the ITT analysis of such trials with missing data.[3] We analyzed binary outcomes (cigarette smoking, alcohol, cannabis, street drug, and any substance use) using logistic mixed effect models and the count outcome (number of cigarettes smoked among smokers) using Poisson mixed effect models. For alcohol and street drugs, the logistic mixed effect models did not converge. Thus we fitted the binary outcomes using linear mixed effect models. This approach is acceptable for binary outcomes when there are sufficient degrees of freedom.[3,4]

These GLMMs incorporated the following predictor variables as fixed effects: 1) Time period (baseline versus late pregnancy) for time effects, 2) NFP intervention versus comparison for baseline group difference, and 3) Time period by NFP interaction. The effect of the intervention on the outcome variables at late pregnancy was taken as the Time period by NFP

interaction term. Thus, the longitudinal modeling approach has the advantage of examining treatment effects via the difference-in-difference approach, which can account for group differences in the outcomes at baseline.[5] Additionally, these models included random effects for clusters (26 participating Local Health Areas [LHAs] within four health authorities [HAs] and for 739 participants nested within these higher-level clusters) to account for random variations among higher-level clusters and among participants within the same higher-level clusters. The analysis showed that the clustering effects at the higher-level of LHA and HA were small with variance components being statistically insignificant from zero. The Akaike information criterion (AIC) statistic also supported the simpler models with random effects for participant only for best fit. Thus, we reported results using the simpler two-level model with clustering at the participant level. Model estimates (including the Time period by NFP interaction term for treatment effect estimates), 95% confidence intervals (CIs) and the associated two-side p-values were reported.

To present treatment effects in terms of absolute risk (i.e., proportion), we estimated proportions using estimated parameters from the fitted models. We calculated 95% confidence intervals (CI) using the bootstrap method with 1,000 re-samples. These treatment effect estimates at the scale of absolute risks were reported and compared with the crude difference-in-differences, which was the difference in the crude (unadjusted) proportion of women who reported substance use from baseline to late pregnancy.[5]

We conducted sensitivity analysis via selection models and computed the Index of Local Sensitivity to Nonignorable missingness (ISNI) using the R package isni to assess the robustness

of the results to the violation of missing at random assumptions.[6] We also conducted sensitivity analyses based on the above mixed effect models adjusting for baseline covariates (see Table 3).

To select relevant baseline covariates in the multivariable model for each outcome, we first run univariate analysis that relates each outcome to each baseline covariate in Table 3. Then we include all the baseline covariates with $p<0.10$ in the final multivariable model for each outcome with results reported in the last two columns of Table 5. All analyses were conducted using R 3.5.[7]

Sensitivity analysis on missing data assumptions

Missing outcome data occurred mostly at the late pregnancy with 11.4% missing outcome values in NFP group and 9.7% in the comparison group (see Figure 1). Prior research has shown that the estimation results are robust to the violation of missing at random assumption, when missing data proportion is small (<= 10%).[8] Thus with the small amount of missing data that are comparable in both groups in our trial, we anticipate that the ITT analyses conducted above should be insensitive to the assumption of data missing at random (MAR). To formally quantify the robustness of our ITT analyses to alternative missing data assumptions, we conducted the following analyses. Selection models were used that permit nonrandom missingness where the missingness probability depends on the unobserved outcome values after conditioning on the observed data and then we computed an Index of local Sensitivity to Nonignorable Missingness (ISNI).[9,10,11] ISNI estimates the change in ITT intervention effect estimates listed in the column "Treatment Effect" of Table 5 for a moderate size of nonrandom missingness where a participant with the binary outcome = Yes has an increase of e^1=2.7-fold in the odds of being missing relative to a participant with the outcome = No, given that both participants have the same values

of observed predictors for missingness. As reported in Table 7, the ISNI values were very small relative to the ITT estimates assuming MAR for all substance use outcomes, demonstrating negligible impacts of nonrandom missingness on the ITT estimates. As a result, it would require extreme and unlikely scenarios for nonrandom missingness in order to change statistical significance results, as shown by the large TP values in Table 7. For instance, a TP (tipping point to change statistical significance result) value of -8.4 for cigarette use means an extreme scenario such that a participant with cigarette use has an increase of $e^{8.4}$-fold (≈4447-fold) in the odds of being observed relative to a participant without cigarette use and the same values on observed predictors for missingness. A TP value of this large size is not meant to capture the exact tipping point precisely, but merely means that one has to consider extreme cases of non-random missingness to find sensitivity. Given the very small ISNI values and large TP values for all substance use outcomes, we conclude the ITT estimation results are robust to the violation of the MAR assumption.

Table 7. Sensitivity analysis of the intention-to-treat treatment effect estimation to the assumption of missing at random

	ISNI	Tipping Point (TP)
Cigarette (%)	0.05	-8.4
Alcohol (%)	0.00036	-88.9
Cannabis (%)	0.0097	146.4
Street Drug (%)	0.00016	-12.5
Any Substance Use (%)	0.0047	-19.1

Note: ISNI (Index of Local Sensitivity to Nonignorability) estimates the change in ITT intervention effect estimates listed in the column "Treatment Effect" in Table 5 for a moderate size of nonrandom missingness where a participant with the binary outcome = Yes has an increase of e^1=2.7-fold in the odds of being missing relative to a participant with the outcome = No, given that both participants have the same values of observed predictors for missingness (baseline covariate values, visit dummy variables, randomization groups, LHA and HA, missingness status in prior visit); TP (Tipping Point) approximates the threshold size of nonrandom missingness required to change statistical significance results, where the size of nonrandom missingness is described by the log odds ratio of being missing for a participant with the outcome = Yes relative to a participant with the outcome = No and the same values on the aforementioned predictors for missingness.[9,10,11]

Appendix 1 References

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11. Xie H, Qian Y. Measuring the impact of nonignorability in panel data with non-monotone nonresponse. *J App Econom* 2012;27:129–59.

2. Unanticipated problems

The British Columbia Healthy Connections Project (BCHCP) Data and Safety Monitoring Committee (DSMC) includes five independent members with experience and expertise in child health, maternal health, ethics, epidemiology and public health, including one clinician and one statistician. The purpose of the BCHCP DSMC is to safeguard the interests of the trial's participants, potential participants and investigators, and to monitor the trial's overall conduct, validity and credibility. Since the trial commenced in late 2013, no major protocol deviations or unanticipated problems have been reported for the BCHCP. An unanticipated problem is defined as any incident, experience or outcome (including an unanticipated serious adverse event) that meets all the following criteria:

- Unexpected regarding nature, severity or frequency given: a) the research procedures as described in the protocol-related documents; and b) the characteristics of the participant population being studied; and
- Related or possibly related to participation in the research (possibly related meaning there is a reasonable chance that the incident, experience or outcome may have been caused by the investigational intervention or by the research procedures); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, mental, economic or social harm) than was previously known or recognized.