Research paper

Behavioural outcomes of children exposed to antidepressants and unmedicated depression during pregnancy

Francesca Anns [a,b], Karen E. Waldie [a,c], Elizabeth R. Peterson [a,c], Caroline Walker [c,d], Susan M.B. Morton [c,d,f], Stephanie D'Souza [b,e,*]

[a] School of Psychology, The University of Auckland, Auckland, New Zealand
[b] Centre of Methods and Policy Application in the Social Sciences, University of Auckland, Auckland, New Zealand
[c] Centre for Longitudinal Research - He Ara ki Mua, The University of Auckland, Auckland, New Zealand
[d] School of Population Health, The University of Auckland, Auckland, New Zealand
[e] School of Social Sciences, The University of Auckland, Auckland, New Zealand
[f] INSIGHT, University of Technology Sydney, Sydney, Australia

A B S T R A C T

Background: Antenatal exposure to both antidepressants and maternal depression has been associated with child behavioural difficulties. However, previous research has not adequately distinguished between the effects of the antidepressants and the underlying maternal depression.
Methods: Child behavioural difficulties were assessed using the Strengths and Difficulties Questionnaire at 2-, 4.5-, and 8-years of age by mothers in the *Growing Up in New Zealand* study (N = 6233 at 2-years; N = 6066 at 4.5-years; N = 4632 at 8-years). Mothers were classified as either on antidepressants, unmedicated depression, or neither based on self-reported antidepressant intake during pregnancy and the Edinburgh Postnatal Depression Scale. Hierarchical multiple logistic regressions were used to examine whether antenatal exposure to antidepressants and unmedicated depression had a differential association with child behavioural outcomes relative to no exposure.
Results: When later life depression in the mother and a range of birth and sociodemographic variables were accounted for, neither antenatal exposure to unmedicated depression or antidepressants remained associated with an increased risk of behavioural difficulties at the ages investigated. However, maternal later life depression was associated with behavioural difficulties in the fully adjusted analyses at all three ages investigated.
Limitations: The current study relied on mother-report of child behaviour which may be susceptible to bias due to maternal mental health problems.
Conclusions: Adjusted results did not show an adverse association between antenatal antidepressant exposure or unmedicated depression in relation to child behaviour. Findings also suggest that efforts to improve child behaviour need to include more family-based approaches that support maternal wellbeing.

1. Introduction

During both pregnancy and postpartum, women are more vulnerable to experiencing mental health disorders relative to other stages of life (Mitchell and Goodman, 2018). For example, while the estimated global prevalence of depression for females is 5.1 % (World Health Organization [WHO], 2017), this doubles during pregnancy (Gentile, 2017; Grigoriadis et al., 2013). Antidepressants and psychological intervention remain the cornerstone of treatment for women experiencing depressive symptoms during pregnancy (Fitton et al., 2020; Kirby et al., 2019). For mild-to-moderate depression, psychological interventions such as cognitive behavioural therapy (CBT) are advised. For moderate-to-severe depression, a combination of psychological intervention and antidepressants are recommended when the mother feels capable of making an informed decision about the risks and benefits of treatment (Kirby et al., 2019). Selective serotonin reuptake inhibitors (SSRIs) are generally the main pharmacological treatment option for moderate-to-severe antenatal depression, except for paroxetine (Kirby et al., 2019; Molenaar et al., 2018).

Despite these treatment recommendations, depression of all

severities remains under-recognised and undertreated in pregnancy (Grigoriadis et al., 2013; Svardal et al., 2021). In addition to the limited accessibility of many treatment options, such as the time and cost of talking therapies (Kopelman et al., 2008), this undertreatment is in part due to concerns about the safety of antidepressant exposure on the foetus (Grigoriadis et al., 2013), which is reflected in the relatively low global prevalence of antenatal antidepressant use (3 %) (Molenaar et al., 2020). These concerns have been accentuated by studies demonstrating associations between gestational antidepressant exposure and a range of adverse outcomes for both the mother and child, such as increased risk of preterm birth (D'Onofrio and Sujan, 2017; Fitton et al., 2020; Gentile, 2017), low birthweight (Gentile, 2017), congenital defects (Fitton et al., 2020), and emotional and behavioural difficulties in childhood and adolescence (Casper et al., 2011; Hanley et al., 2013; Malm et al., 2016; Misri et al., 2006; Oberlander et al., 2007).

However, overall evidence regarding the safety of antidepressant use during pregnancy remains inconclusive, with some studies reporting significant associations between antidepressants and adverse outcomes (e.g., D'Onofrio and Sujan, 2017; Fitton et al., 2020; Gentile, 2017; Hanley et al., 2015; Hermansen et al., 2016; Oberlander et al., 2010) and others showing no significant association (e.g., Grzeskowiak et al., 2016; Misri et al., 2006; Pedersen et al., 2013). These mixed results could be because studies have not separated the effects of antidepressant exposure from underlying depression and its associated behaviours (e.g., concomitant medications, obesity, smoking, and substance abuse), which may act as confounding variables (Pearlstein, 2015). Indeed, antenatal depression is associated with a similar set of adverse outcomes to antidepressant use in pregnancy, such as an increased risk of preterm birth, low birth weight, and emotional and behavioural difficulties in the offspring (Becker et al., 2016; Gentile, 2017; Osborne et al., 2018). Additionally, antenatal depression is associated with several unique and longer-term outcomes such as poorer self-care and appetite, postnatal depression, reduced quality of mother-infant interactions (Bind et al., 2021), increased cortisol reactivity to stress in the offspring (Osborne et al., 2018), and a higher risk of smoking, alcohol, and other drug use in the mother (Mian, 2005). Given that unmedicated antenatal depression is associated with its own set of risks, it is important to understand whether risks associated with antidepressants outweigh those associated with antenatal depression. Separating these effects can help inform treatment options for women experiencing moderate-to-severe depression in pregnancy.

Behavioural difficulties are one of the longer-term outcomes associated with both antenatal antidepressant exposure and antenatal depression. These have included both internalising behaviours (i.e., depression and anxiety) and externalising behaviours (i.e., conduct problems and hyperactivity) (Willner et al., 2016). However, several reviews have noted mixed findings (Hermansen and Melinder, 2015; Millard et al., 2017; Oberlander et al., 2007; Oberlander et al., 2010; Olivier et al., 2015). As noted by Hermansen and Melinder (2015), studies with toddlers (Casper et al., 2011; Hanley et al., 2013) and pre-schoolers (Misri et al., 2006; Oberlander et al., 2007) have found associations with emotional and behavioural difficulties, whereas no negative effects have been observed in infants (e.g., Pedersen et al., 2010), suggesting a latent effect of SSRI exposure. As such, the evidence regarding the safety of antidepressant use while pregnant remains inconclusive.

As noted previously, the main confounding factor for studies examining the impact of antidepressant exposure on behavioural outcomes may be the underlying maternal depression, which is associated with a range of adverse outcomes for both the mother and child. In a review by Gentile (2017), it was noted that, in addition to numerous short-term effects on the foetus and new-born, untreated antenatal depression was associated with higher internalising and externalising problems in children (e.g., Ashman et al., 2002; Luoma et al., 2001). Similar findings have been reported in a review by Pearlstein (2015), noting that untreated antenatal depression is associated with altered neonatal

behavioural scores, internalising behaviours, externalising behaviours, and ADHD. Although concern exists regarding associations between antenatal antidepressant exposure and adverse childhood outcomes, untreated maternal depression comes with a similar set of risks. As such, women who experience severe, recurrent depression (and have a history of relapsing when they discontinue their antidepressant medication) should consider antidepressant treatment during pregnancy (Pearlstein, 2015).

An additional complication is that it is often difficult to separate the effects of the untreated antenatal depression from postnatal depression (Pearlstein, 2015), which may further affect childhood outcomes (Fitton et al., 2020). In addition to altering cortisol, serotonin, and dopamine levels in exposed children, antenatal depression may persist postnatally, having a range of indirect effects on the child by distorting communication and interactions between the mother and child (Hermansen and Melinder, 2015). Mothers experiencing depression often have affectively flat interactions with their infants and are more withdrawn, less sensitive, and more self-occupied in their parenting style (Hermansen and Melinder, 2015). Additionally, for depressed mothers, mother-infant interactions are generally characterised by longer periods of emotional mismatching when compared to non-depressed mothers (Hermansen and Melinder, 2015). It is perhaps not surprising, therefore, that postnatal depression is also associated with adverse child behavioural outcomes (Giallo et al., 2015). It is therefore imperative that studies investigating the impact of antenatal depression on child outcomes also control for the potential impact of maternal depression after birth.

Although research regarding the safety of antidepressant use during pregnancy remains inconclusive, antenatal exposure to antidepressants and unmedicated depression may influence the risk of adverse child outcomes. Research to date has largely failed to distinguish between the effects of antidepressants and underlying maternal depression on the offspring (Fitton et al., 2020) and it remains unclear whether the risk of behavioural difficulties differ between antidepressant and unmedicated depression exposure. Knowledge regarding the long-term effects of antenatal antidepressant exposure on the offspring also remains limited (Fitton et al., 2020). To address this, the present study investigated the effects of antenatal exposure to antidepressants and unmedicated depression, relative to exposure to neither, on child behavioural outcomes. This was examined while controlling for later life depression in the mother and a range of birth and sociodemographic factors. We predicted that antenatal exposure to unmedicated depression would be associated with greater odds of behavioural difficulties at the three ages investigated when compared to neither exposed children. Due to the conflicting findings of previous research, it was difficult to make a definitive hypothesis with regards to antidepressant exposure. If, however, there is an effect of both antidepressants and unmedicated depression on child behaviour in adjusted analyses, we planned to examine whether the risk varied across the two exposures.

2. Methods

2.1. Participants

Participants were mothers and children from the *Growing Up in New Zealand* (GUiNZ) longitudinal study. Mothers were recruited during pregnancy from three contiguous District Health Boards (DHBs) of Auckland, Counties-Manukau and Waikato, within which one-third of New Zealand's live births occur (Morton et al., 2013). These three DHB areas were chosen to maximise the socioeconomic and ethnic diversity of the participants. All pregnant women living within the three DHBs with an estimated delivery date between 25 April 2009 and 25 March 2010 were eligible for recruitment. For more information on the recruitment strategies, see Morton et al. (2013). Of the 6752 pregnancies included in the GUiNZ cohort, 6662 (99 %) were singleton births and 90 (1 %) were multiple births (twins and triplets) (Morton et al., 2010). The

resulting cohort was 6846 children (live births) (Morton et al., 2013).

Major face-to-face data collection waves (DCWs) have occurred during the antenatal period and when the child was 9-months, 2-years, 4.5-years, and 8-years of age. Computer Assisted Personal Interviews were used to collect information across six interconnected domains: societal context and neighbourhoods, family and whānau (extended family), psychological and cognitive development, culture and identity, education, and health and wellbeing. Ethics approval was granted from the Ministry of Health Northern Y Regional Ethics Committee (NTY/08/06/055) and all mothers provided written and informed consent for themselves and their children.

Data were collected from a total of 6327 (92.4 %) children at the 2-year DCW, 6156 (89.9 %) children at the 4-year DCW and 5556 (81.2 %) children at the 8-year DCW (Morton et al., 2014; Morton et al., 2017; Morton et al., 2020). In the current study, only one child was included from each mother in cases of multiple births to avoid violations to the assumption of independence.

2.2. Measures

2.2.1. Child behavioural difficulties

Childhood behavioural difficulties were measured using the parent-report Strengths and Difficulties Questionnaire (SDQ) (Goodman, 1997). The preschool version of the SDQ was used when the children were 2-years of age and the SDQ for ages 4–16 was used when the children were 4.5- and 8-years of age. These two versions have minor differences, as three items have been adjusted in the preschool version to be more appropriate for this age group (D'Souza et al., 2017).

The SDQ measures behavioural difficulties across four subscales: conduct problems; emotional symptoms; peer problems; and hyperactivity/inattention. A fifth prosocial behaviour subscale is also included. The four behavioural difficulties subscales can be added together to give a measure of total difficulties, which ranges from 0 to 40. Higher scores reflect greater difficulties. As previous studies have examined associations across both internalising and externalising outcomes, the total difficulties measure was the outcome of interest for the current study. Acceptable Cronbach's alphas (>0.75) were observed for the total difficulties measure at all ages.

The total difficulties score can be categorised into normal, borderline, and abnormal ranges, based on previously determined cut-offs (D'Souza et al., 2017; Youth in Mind, 2016). In clinical settings, the abnormal cut-off can be used to screen for children who may experience significant behavioural difficulties and require a specialist referral for a formal diagnosis (Ministry of Health, 2008). As we were interested in predictors of significant behavioural difficulties, the total difficulties score was recoded into high behavioural difficulties (abnormal ranges) and low behavioural difficulties (normal/borderline ranges).

2.2.2. Antidepressants and unmedicated depression

To determine antenatal antidepressant use, mothers in the GUiNZ cohort were asked whether they took antidepressants during the first trimester and after the first trimester. This information was used to identify women who took antidepressants at any time during pregnancy. Antenatal depressive symptoms were measured using the 10-item, self-report Edinburgh Postnatal Depression Scale (EPDS) (Cox et al., 1987). The maximum score is 30 and mothers with a score of 13 or above are regarded as having significant antenatal depressive symptoms (Waldie et al., 2015). At this cut-off, the EPDS has a reported sensitivity of 0.83 and specificity of 0.90 for major depression in pregnancy (National Collaborating Centre for Mental Health, 2014).

A composite variable was then created using the antidepressant and EPDS data to indicate unmedicated antenatal depression. This was categorised as: antidepressants, unmedicated depression, and neither. Classification as on antidepressants meant that there was antidepressant use during pregnancy regardless of EPDS score. Unmedicated depression indicated that the woman met the EPDS criteria for significant depressive symptoms but was not taking antidepressants during pregnancy. Neither indicated that the woman was not taking antidepressants during pregnancy and did not meet the EPDS criteria for significant depressive symptoms.

2.2.3. Postnatal and later life depression

Information on postnatal and later life depression in the mother was obtained at the 9-month, 4.5-year and 8-year DCWs. Postnatal depression at 9-months was measured using the EPDS. Maternal depressive symptoms at the 4.5-year and 8-year DCWs were measured using the Patient Health Questionnaire (PHQ-9) (Kroenke et al., 2001). The PHQ-9 consists of nine self-report items and can yield a maximum score of 27. Continuous scores were used to assess postnatal and later life depression.

2.2.4. Birth and sociodemographic variables

In addition to maternal depression after birth, a range of birth and sociodemographic variables were also controlled for in the current study. Control variables from the antenatal DCW included: planned pregnancy (yes or no), mother's education (no secondary school qualification, secondary school qualification, diploma/trade certificate, bachelor's degree, higher degree), mother's age when pregnant, parity (first-born or subsequent), child's gender, pregnancy alcohol consumption (drinking or no-drinking, based on alcohol intake during and after the first trimester), smoking during pregnancy (smoking or no-smoking), mother's relationship status during pregnancy (no relationship, dating not cohabiting, cohabiting or married/civil union), mother's self-prioritised ethnicity (European, Māori, Pacific, Asian, Other), and child's gestational age/term (preterm or not preterm) and birthweight (low or not low). Rurality (urban or rural) and area-level deprivation (low, medium, high) were measured at the 2-year, 4.5-year, and 8-year DCWs.

2.3. Data analysis

A hierarchical multiple logistic regression was conducted for each SDQ outcome. Block 1 of the model included the antidepressants/unmedicated depression predictor variable. Block 2 incorporated the control variables from the antenatal DCW and the relevant area-level deprivation and rurality measures for each SDQ age. Later life depression in the mother at 9-months, 4.5-years and 8-years of age was added to Block 3 of the model for the 2-year, 4.5-year and 8-year SDQ outcomes, respectively. All analyses were conducted using SPSS Statistics v27 and statistical significance was given at an alpha level of 0.05.

3. Results

3.1. Descriptive information

Total difficulties scores were calculated for 98.5 % of children who participated in the 2- and 4.5-year DCWs (N = 6233 at 2-years; N = 6066 at 4.5-years) and 83.4 % of children at the 8-year DCW (N = 4632). Of those who participated in the 2-year DCW, 10.1 % had high behavioural difficulties; at 4.5-years, 11.5 % had high behavioural difficulties; and at 8-years, 10.9 % had high behavioural difficulties. Frequency distributions for the categorical variables across each SDQ outcome and for the three groupings of mothers are presented in Tables 1 and 2 respectively. Descriptive information for the continuous variables for each SDQ outcome and for the three groups of mothers are provided in Tables 3 and 4 respectively. These have been interpreted below.

As shown in Table 1, while most children with both low and high behavioural difficulties at each age were in the neither exposure group, a much larger proportion of children with high behavioural difficulties were exposed to unmedicated depression than the children with low behavioural difficulties. A slightly higher proportion of children with low behavioural difficulties were exposed to antidepressants antenatally at 2- and 4.5-years of age relative to those with high behavioural

Table 1
Frequency distributions of SDQ total difficulties for categorical variables.

	SDQ total difficulties age 2		SDQ total difficulties age 4.5		SDQ total difficulties age 8	
	Low difficulties n (%)	High difficulties n (%)	Low difficulties n (%)	High difficulties n (%)	Low difficulties n (%)	High difficulties n (%)
Antidepressants/unmedicated depression						
Neither	4412 (86.5)	407 (74.4)	4229 (86.7)	482 (77.0)	3312 (88.0)	359 (78.4)
Antidepressants	180 (3.5)	10 (1.8)	170 (3.5)	14 (2.2)	131 (3.5)	27 (5.9)
Unmedicated depression	506 (9.9)	130 (23.8)	478 (9.8)	130 (20.8)	322 (8.6)	72 (15.7)
Planned pregnancy						
Yes	3567 (63.9)	254 (40.6)	3458 (64.7)	292 (42.3)	2783 (67.7)	274 (54.8)
No	2011 (36.1)	372 (59.4)	1890 (35.3)	398 (57.7)	1328 (32.3)	226 (45.2)
Highest education						
No secondary school	303 (5.4)	99 (15.9)	268 (5.0)	107 (15.5)	178 (4.3)	42 (8.3)
Secondary school	1235 (22.1)	198 (31.7)	1134 (21.1)	236 (34.3)	825 (20.0)	133 (26.4)
Diploma/trade certificate	1660 (29.7)	237 (38.0)	1609 (30.0)	233 (33.8)	1165 (28.3)	173 (34.4)
Bachelor's degree	1396 (25.0)	64 (10.3)	1378 (25.7)	70 (10.2)	1144 (27.8)	88 (17.5)
Higher degree	996 (17.8)	26 (4.2)	973 (18.1)	43 (6.2)	807 (19.6)	67 (13.3)
Parity						
First born	2375 (42.4)	255 (40.6)	2270 (42.3)	279 (40.2)	1758 (42.6)	238 (47.2)
Subsequent	3222 (57.6)	373 (59.4)	3094 (57.7)	415 (59.8)	2364 (57.4)	266 (52.8)
Alcohol in pregnancy						
Drinking	1600 (28.6)	188 (30.0)	1543 (28.8)	191 (27.6)	1212 (29.5)	159 (31.7)
No drinking	3988 (71.4)	438 (70.0)	3812 (71.2)	501 (72.4)	2903 (70.5)	343 (68.3)
Smoking in pregnancy						
Smoking	432 (8.5)	125 (22.9)	385 (7.9)	135 (21.7)	243 (6.5)	87 (19.0)
No smoking	4657 (91.5)	420 (77.1)	4484 (92.1)	486 (78.3)	3513 (93.5)	371 (81.0)
Relationship status						
No relationship	233 (4.6)	55 (10.1)	201 (4.1)	69 (11.1)	131 (3.5)	48 (10.5)
Dating	160 (3.1)	60 (11.0)	150 (3.1)	50 (8.0)	105 (2.8)	21 (4.6)
Cohabiting	1375 (27.0)	186 (34.2)	1315 (27.0)	209 (33.6)	994 (26.4)	150 (33.0)
Married/civil union	3325 (65.3)	243 (44.7)	3206 (65.8)	294 (47.3)	2533 (67.3)	236 (51.9)
Ethnicity						
European	3322 (59.5)	154 (24.6)	3233 (60.4)	200 (28.8)	2705 (65.8)	285 (56.5)
Māori	674 (12.1)	160 (25.5)	646 (12.1)	156 (22.5)	442 (10.7)	89 (17.7)
Pacific	620 (11.1)	208 (33.2)	543 (10.1)	231 (33.3)	322 (7.8)	73 (14.5)
Asian	773 (13.8)	85 (13.6)	746 (13.9)	90 (13.0)	510 (12.4)	46 (9.1)
Other	198 (3.5)	20 (3.2)	186 (3.5)	17 (2.4)	135 (3.3)	11 (2.2)
Child gender						
Boy	2878 (51.4)	357 (56.7)	2727 (50.8)	404 (57.9)	2043 (49.5)	330 (65.2)
Girl	2725 (48.6)	273 (43.3)	2641 (49.2)	294 (42.1)	2083 (50.5)	176 (34.8)
Term						
Preterm	319 (5.7)	33 (5.3)	298 (5.6)	46 (6.6)	233 (5.7)	24 (4.8)
Not preterm	5275 (94.3)	595 (94.7)	5062 (94.4)	648 (93.4)	3889 (94.3)	480 (95.2)
Birthweight						
Low	241 (4.3)	27 (4.3)	222 (4.1)	37 (5.3)	160 (3.9)	23 (4.5)
Not Low	5358 (95.7)	602 (95.7)	5141 (95.9)	661 (94.7)	3965 (96.1)	483 (95.5)
Area-level deprivation						
Low	1581 (28.9)	83 (13.4)	1678 (33.1)	78 (11.9)	1480 (37.6)	126 (25.6)
Medium	2071 (37.9)	163 (26.3)	1903 (37.5)	162 (24.7)	1532 (38.9)	169 (34.3)
High	1815 (33.2)	373 (60.3)	1492 (29.4)	416 (63.4)	929 (23.6)	198 (40.2)
Rurality						
Urban	4996 (91.4)	596 (96.3)	4573 (90.1)	616 (93.9)	3448 (87.5)	429 (87.0)
Rural	473 (8.6)	23 (3.7)	500 (9.9)	40 (6.1)	493 (12.5)	64 (13.0)

Note: Total Ns for each bivariate crosstabulation will vary due to missing data for some variables.

Table 2
Frequency distributions of maternal antidepressants/unmedicated depression status for categorical variables.

	Neither n (%)	Antidepressants n (%)	Unmedicated depression n (%)
SDQ total difficulties age 2			
Low difficulties	4412 (91.6)	180 (94.7 %)	506 (79.6)
High difficulties	407 (8.4)	10 (5.3)	130 (20.4)
SDQ total difficulties age 4.5			
Low difficulties	4229 (89.8)	170 (92.4)	478 (78.6)
High difficulties	482 (10.2)	14 (7.6)	130 (21.4)
SDQ total difficulties age 8			
Low difficulties	3312 (90.2)	131 (82.9)	322 (81.7)
High difficulties	359 (9.8)	27 (17.1)	72 (18.3)
Planned pregnancy			
Yes	3296 (63.6)	105 (53.3)	286 (40.1)
No	1886 (36.4)	92 (46.7)	427 (59.9)
Highest education			
No secondary school	306 (5.9)	19 (9.6)	88 (12.3)
Secondary school	1184 (22.8)	56 (28.4)	210 (29.5)
Diploma/trade certificate	1538 (29.6)	60 (30.5)	267 (37.4)
Bachelor's degree	1260 (24.3)	35 (17.8)	94 (13.2)
Higher degree	902 (17.4)	27 (13.7)	54 (7.6)
Parity			
First born	2197 (42.3)	74 (37.6)	290 (40.6)
Subsequent	3003 (57.8)	123 (62.4)	425 (59.4)
Alcohol in pregnancy			
Drinking	1459 (28.1)	73 (37.2)	226 (31.6)
No drinking	3734 (71.9)	123 (62.8)	489 (68.4)
Smoking in pregnancy			
Smoking	461 (8.9)	25 (12.8)	148 (20.8)
No smoking	4722 (91.1)	171 (87.2)	564 (79.2)
Relationship status			
No relationship	226 (4.4)	23 (11.7)	78 (11.0)
Dating, not cohabiting	184 (3.5)	10 (5.1)	61 (8.6)
Cohabiting	1398 (26.9)	67 (34.0)	241 (33.8)
Married/civil union	3380 (65.2)	97 (49.2)	332 (46.6)
Ethnicity			
European	2899 (55.8)	157 (79.7)	245 (34.3)
Māori	679 (13.1)	20 (10.2)	140 (19.6)
Pacific	654 (12.6)	8 (4.1)	201 (28.2)
Asian	775 (14.9)	6 (3.0)	99 (13.9)
Other	184 (3.5)	6 (3.0)	29 (4.1)
Child gender			

Table 2 (*continued*)

	Neither n (%)	Antidepressants n (%)	Unmedicated depression n (%)
Boy	2676 (51.5)	102 (51.8)	369 (51.6)
Girl	2524 (48.5)	95 (48.2)	346 (48.4)
Term			
Preterm	258 (5.0)	17 (8.6)	59 (8.3)
Not preterm	4933 (95.0)	180 (91.4)	655 (91.7)
Birthweight			
Low	198 (3.8)	9 (4.6)	44 (6.2)
Not low	4993 (96.2)	188 (95.4)	670 (93.8)
Area-level deprivation at 2 years			
Low	1350 (28.7)	56 (29.5)	113 (18.1)
Medium	1745 (37.1)	74 (38.9)	215 (34.5)
High	1613 (34.3)	60 (31.6)	295 (47.4)
Area-level deprivation at 4.5 years			
Low	1429 (32.1)	50 (27.9)	121 (21.2)
Medium	1619 (36.4)	86 (48.0)	172 (30.1)
High	1405 (31.6)	43 (24.0)	278 (48.7)
Area-level deprivation at 8 years			
Low	1460 (36.4)	53 (31.9)	119 (25.4)
Medium	1525 (38.0)	72 (43.4)	148 (31.6)
High	1029 (25.6)	41 (24.7)	202 (43.1)
Rurality at 2 years			
Urban	4302 (91.3)	161 (84.7)	583 (93.6)
Rural	408 (8.7)	29 (15.3)	40 (6.4)
Rurality at 4.5 years			
Urban	4006 (90.0)	151 (84.4)	528 (92.5)
Rural	447 (10.0)	28 (15.6)	43 (7.5)
Rurality at 8 years			
Urban	3516 (87.6)	140 (84.3)	423 (90.2)
Rural	498 (12.4)	26 (15.7)	46 (9.8)

Note: Total Ns for each bivariate crosstabulation will vary due to missing data for some variables.

difficulties. In contrast, a greater proportion of children with high behavioural difficulties were exposed to antidepressants relative to those with low behavioural difficulties at 8-years of age.

Table 1 also demonstrates that, when compared to children with low behavioural difficulties, children with high behavioural difficulties at each age were overrepresented in unplanned pregnancies, lower levels of maternal education, exposure to maternal smoking during pregnancy, and mothers who were not legally married or in a civil union. Additionally, they were more likely to be born to mothers who identified as Māori or Pacific compared to European and they were more likely to be males and live in highly deprived areas. Table 3 shows that children with

Table 3
Descriptive information for continuous variables at each SDQ total difficulties outcome.

	SDQ total difficulties age 2		SDQ total difficulties age 4.5		SDQ total difficulties age 8	
	Low difficulties M (SD)	High difficulties M (SD)	Low difficulties M (SD)	High difficulties M (SD)	Low difficulties M (SD)	High difficulties M (SD)
Mother's age	30.63 (5.75)	26.89 (6.13)	30.72 (5.70)	27.38 (6.21)	30.96 (5.57)	29.10 (6.16)
Later life depression[a]	5.03 (4.45)	7.67 (5.10)	3.23 (3.49)	6.12 (5.10)	3.50 (3.89)	6.39 (5.33)

[a] EPDS score at 9-months is given for total difficulties at 2-years, PHQ-9 score at 4.5- and 8-years is given for total difficulties at each age respectively.

Table 4
Descriptive information for continuous variables for the three groupings of mothers.

	Neither M (SD)	Antidepressants M (SD)	Unmedicated depression M (SD)
Mother's age	30.31 (5.85)	30.23 (5.59)	27.72 (6.20)
EPDS at 9 months	4.71 (4.18)	7.38 (5.49)	9.02 (5.40)
PHQ-9 at 4.5 years	3.17 (3.42)	5.80 (4.93)	5.63 (5.01)
PHQ-9 at 8 years	3.47 (3.87)	7.04 (5.95)	5.91 (5.37)

high behavioural difficulties at each age also tended to be born to younger mothers and mothers who experienced greater depressive symptoms in later life.

Table 2 shows that mothers with unmedicated depression had a higher proportion of children with high difficulties scores at 2 and 4.5 years along with higher rates of smoking during pregnancy, unplanned pregnancies, a greater proportion of Māori/Pacific ethnicities and a lower proportion of European ethnicity, and they were more greatly represented in areas with higher deprivation. Table 4 also shows that mothers with unmedicated depression tended to be younger and to have higher later life depression scores alongside mothers in the antidepressants group at each of the three ages investigated. A large proportion of mothers in the antidepressants category were of European ethnicity.

3.2. Total difficulties at age 2

The model containing only the antidepressants/unmedicated depression predictor was significant at 2-years of age (Model $X^2_{(2)} = 67.81, p < .001$).Children antenatally exposed to unmedicated depression had significantly greater odds of high behavioural difficulties than those exposed to neither ($OR = 2.70, p < .001$). There was no significant effect of antidepressants on behavioural difficulties.

The addition of the birth and sociodemographic covariates was also significant (Block $X^2_{(22)} = 413.43, p < .001$). The effect of unmedicated depression remained significant but was attenuated ($OR = 1.56; p < .001$). The effect of antidepressants remained non-significant.

The final addition of later life depression in the mother was also significant (Block $X^2_{(1)} = 51.68, p < .001$). Results for the fully adjusted model are given in Table 5. In the fully adjusted model, antenatal exposure to unmedicated depression was no longer significantly associated with increased odds of high behavioural difficulties at 2-years. However, a one-point increase in the mother's EPDS score at 9-months was associated with 1.08 times increase in the odds of high behavioural difficulties at age 2 ($p < .001$). As there was no significant risk observed from exposure to unmedicated depression or antidepressants during pregnancy in the fully adjusted model, we did not examine whether the risk of high behavioural difficulties varied between the two exposures.

3.3. Total difficulties at age 4.5

At 4.5-years, the model containing only the main antidepressants/ unmedicated depression predictor variable was significant (Model $X^2_{(2)} = 55.02, p < .001$). Children exposed to unmedicated depression had significantly greater odds of high behavioural difficulties than those

exposed to neither ($OR = 2.41, p < .001$). The effect of antidepressants on high behavioural difficulties was not significant.

The inclusion of the birth and sociodemographic covariates was also significant (Block $X^2_{(22)} = 463.53, p < .001$). Children exposed to unmedicated depression still had significantly greater odds of high behavioural difficulties than children exposed to neither, though the effect size was smaller ($OR = 1.37, p < .05$). Antenatal exposure to antidepressants did not significantly predict high behavioural difficulties.

The addition of later life depression in the mother was significant (Block $X^2_{(1)} = 126.52, p < .001$). Results for the fully adjusted model are given in Table 5. Antenatal exposure to unmedicated depression was no longer a significant predictor of high behavioural difficulties. However, children exposed to antidepressants now had significantly reduced odds of high behavioural difficulties when compared to those exposed to neither ($OR = 0.52, p < .05$). The mother's PHQ-9 score at 4.5-years was shown to significantly predict high behavioural difficulties at age 4.5 ($OR = 1.13, p < .001$). As we saw no adverse risk of high behavioural difficulties associated with either antenatal antidepressant or unmedicated depression exposure, no further analyses were conducted to determine whether the risk varied between the two exposures.

3.4. Total difficulties at age 8

The model containing only the main antidepressants/unmedicated depression predictor variable was significant (Model $X^2_{(2)} = 27.41, p < .001$). Children antenatally exposed to unmedicated depression had significantly greater odds of high behavioural difficulties relative to children exposed to neither ($OR = 2.14, p < .001$). Additionally, children exposed to antidepressants had 1.83 times greater odds of high behavioural difficulties than children exposed to neither ($p < .01$).

The inclusion of the birth and sociodemographic covariates was also significant at 8-years of age (Block $X^2_{(22)} = 179.48, p < .001$). Children exposed to unmedicated depression still had significantly greater odds of high behavioural difficulties than children exposed to neither, though this effect was attenuated ($OR = 1.55, p < .01$). The effect of exposure to antidepressants now reached marginal significance ($OR = 1.59, p = .057$).

The final addition of later life depression in the mother was significant (Block $X^2_{(1)} = 97.92, p < .001$). Results for the fully adjusted model are given in Table 5. In the final model, neither unmedicated depression nor antidepressant exposure was associated with significantly increased odds of high behavioural difficulties at 8-years. However, a one-point increase in the mother's PHQ-9 score at 8-years was associated with 1.12 times greater odds of high behavioural difficulties ($p < .001$). As above, no further analyses were conducted to examine whether the risk of high behavioural difficulties varied across those exposed to unmedicated depression and antidepressants.

4. Discussion

The present study examined the effects of antenatal exposure to antidepressants and unmedicated depression on child behavioural outcomes at 2-, 4.5- and 8-years of age. While unadjusted analyses showed a strong effect of unmedicated depression on behavioural difficulties at the three ages investigated, this effect was attenuated and no longer

Table 5

Associations between predictor and control variables and SDQ total difficulties at 2-, 4.5-, and 8-years.

	SDQ total difficulties age 2				SDQ total difficulties age 4.5				SDQ total difficulties age 8			
	B (SE)	OR	95 % CI	Wald	*B* (SE)	OR	95 % CI	Wald	*B* (SE)	OR	95 % CI	Wald
Antidepressants/ unmedicated depression Neither												
Antidepressants	−0.54 (0.35)	0.58	0.29–1.15	2.43	−0.66 (0.32)	0.52	0.28–0.97	4.18*	0.01 (0.26)	1.01	0.61–1.68	0.00
Unmedicated depression	0.15 (0.14)	1.16	0.89–1.52	1.22	0.04 (0.13)	1.04	0.80–1.36	0.10	0.22 (0.17)	1.25	0.89–1.74	1.66
Later life depression[a]	0.08 (0.01)	1.08	1.06–1.10	52.84***	0.12 (0.01)	1.13	1.11–1.15	128.90***	0.11 (0.01)	1.12	1.10–1.14	101.96***
Planned pregnancy Yes												
No	0.04 (0.12)	1.04	0.83–1.31	0.13	0.04 (0.11)	1.04	0.83–1.29	0.10	−0.04 (0.14)	0.96	0.74–1.25	0.10
Highest education Higher degree												
No secondary school	1.03 (0.28)	2.80	1.61–4.86	13.27***	0.84 (0.25)	2.32	1.42–3.81	11.18***	0.28 (0.27)	1.32	0.77–2.26	1.03
Secondary school	0.78 (0.25)	2.19	1.35–3.54	10.14** (0.001)	0.68 (0.21)	1.97	1.31–2.98	10.52***	0.19 (0.19)	1.21	0.83–1.76	0.95
Diploma/trade certificate	0.91 (0.24)	2.48	1.56–3.94	14.71***	0.44 (0.21)	1.55	1.04–2.32	4.59*	0.05 (0.18)	1.05	0.73–1.50	0.06
Bachelor's degree	0.38 (0.26)	1.46	0.89–2.41	2.20	0.07 (0.22)	1.08	0.69–1.66	0.10	−0.19 (0.19)	0.83	0.58–1.20	0.96
Mother age (years)	−0.06 (0.01)	0.94	0.93–0.96	32.02***	−0.03 (0.01)	0.97	0.95–0.99	10.55***	−0.01 (0.01)	0.99	0.97–1.01	1.39
Parity First born												
Subsequent	0.14 (0.11)	1.15	0.92–1.44	1.57	−0.05 (0.11)	0.95	0.77–1.18	0.21	−0.19 (0.012)	0.83	0.66–1.05	2.39
Alcohol in pregnancy No drinking												
Drinking	−0.08 (0.12)	0.93	0.73–1.17	0.40	−0.09 (0.12)	0.91	0.73–1.15	0.63	−0.01 (0.12)	0.99	0.78–1.26	0.00
Smoking in pregnancy No smoking												
Smoking	0.37 (0.15)	1.44	1.08–1.92	6.29*	0.31 (0.14)	1.36	1.03–1.81	4.65*	0.61 (0.17)	1.84	1.31–2.59	12.35***
Relationship status Married/civil union												
No relationship	0.20 (0.21)	1.23	0.82–1.84	0.97	0.38 (0.20)	1.46	0.99–2.14	3.72	0.65 (0.24)	1.91	1.20–3.03	7.48**
Dating	0.49 (0.21)	1.63	1.08–2.46	5.51*	0.10 (0.22)	1.11	0.72–1.70	0.23	−0.16 (0.29)	0.85	0.48–1.51	0.31
Cohabiting	0.17 (0.13)	1.19	0.91–1.54	1.63	0.05 (0.13)	1.05	0.82–1.35	0.13	0.09 (0.14)	1.10	0.83–1.44	0.42
Ethnicity European												
Māori	0.75 (0.15)	2.11	1.56–2.84	23.78***	0.61 (0.15)	1.85	1.38–2.47	17.26***	0.09 (0.17)	1.10	0.78–1.54	0.30
Pacific	1.14 (0.15)	3.14	2.33–4.24	56.01***	1.19 (0.15)	3.30	2.48–4.39	66.86***	0.24 (0.20)	1.27	0.85–1.87	1.38
Asian	0.76 (0.17)	2.15	1.53–3.00	19.94***	0.68 (0.17)	1.97	1.42–2.72	16.52***	−0.42 (0.23)	0.66	0.42–1.03	3.41
Other	0.81 (0.27)	2.25	1.32–3.83	8.89**	0.30 (0.31)	1.35	0.73–2.50	0.93	−0.30 (0.37)	0.74	0.36–1.52	0.68
Gender Girl												
Boy	0.19 (0.10)	1.21	0.99–1.47	3.46	0.34 (0.10)	1.41	1.16–1.71	12.14***	0.83 (0.12)	2.29	1.82–2.87	50.74***
Term Not preterm												
Preterm	−0.32 (0.28)	0.73	0.42–1.25	1.34	0.02 (0.24)	1.02	0.63–1.63	0.00	−0.73 (0.32)	0.48	0.26–0.90	5.28*
Birthweight Not low												
Low	0.27 (0.29)	1.32	0.75–2.31	0.91	0.12 (0.27)	1.13	0.67–1.92	0.21	0.51 (0.32)	1.66	0.89–3.10	2.53
NZDep Low												
Medium	−0.01 (0.16)	0.99	0.72–1.36	0.00	0.19 (0.16)	1.21	0.89–1.65	1.44	0.01 (0.14)	1.01	0.76–1.32	0.00

Table 5 (*continued*)

	SDQ total difficulties age 2				SDQ total difficulties age 4.5				SDQ total difficulties age 8			
	B (SE)	OR	95 % CI	Wald	*B* (SE)	OR	95 % CI	Wald	*B* (SE)	OR	95 % CI	Wald
High	0.24 (0.17)	1.27	0.92–1.76	2.13	0.70 (0.16)	2.01	1.47–2.74	18.99***	0.29 (0.16)	1.34	0.97–1.84	3.23
Rurality												
Rural												
Urban	0.51 (0.25)	1.67	1.02–2.74	4.08*	−0.07 (0.19)	0.93	0.64–1.37	0.13	0.26 (0.16)	1.29	0.94–1.77	2.49

* *p* < .05.
** *p* < .01.
*** *p* ≤ .001.
^a EPDS score at 9-months is given for total difficulties at 2-years, PHQ-9 score at 4.5- and 8-years is given for total difficulties at each age respectively.

significant in the fully adjusted model, particularly once later life depression in the mother was accounted for. Maternal later life depression significantly predicted high behavioural difficulties at all three ages investigated.

Antenatal exposure to unmedicated depression was not associated with greater odds of high behavioural difficulties at the three ages investigated, inconsistent with previous research using both continuous and categorical measures of behavioural difficulties (Ashman et al., 2002; Giallo et al., 2015; Glover, 2014; Grzeskowiak et al., 2016; Luoma et al., 2001; Mäki et al., 2003). One possibility for these differential findings could be that the current study did not utilise a clinical diagnosis of depression and so the EPDS cut-off used may not always signal a severity of depression that would produce clinical impairment (Osborne et al., 2018). It may also be due to the fact that the current study controlled for postnatal and later life depression in the mother, whereas earlier research did not always adjust for this. The importance of controlling for postnatal depression when examining adverse childhood outcomes such as behaviour has been highlighted by previous work (Hay et al., 2008; Van Batenburg-Eddes et al., 2013). Van Batenburg-Eddes et al. (2013) found that the association between antenatal depressive symptoms and offspring attention problems at 3-years of age attenuated considerably when depressive symptoms after birth (around when the child's behaviour was assessed) were accounted for. These results suggest that either the development or persistence of maternal depressive symptoms postnatally may drive associations found between antenatal depressive symptoms and child behaviour, rather than this being the result of an intrauterine mechanism (Van Batenburg-Eddes et al., 2013). As such, it is imperative that studies investigating the impact of antenatal depression on child outcomes such as behaviour also control for the potential impact of maternal depression after birth.

Despite this, results remain mixed and other studies have found a significant effect of antenatal depression on behavioural difficulties even when controlling for postnatal depression and when using the same measures (EPDS and SDQ) and scoring cut-offs as the current study (e.g., Giallo et al., 2015; Grzeskowiak et al., 2016; O'Donnell et al., 2014). It is also worth noting that at all three ages, we found a much greater frequency of children with high behavioural difficulties amongst mothers with antenatal depression alone than mothers with both antenatal and postnatal depression and postnatal depression alone (data not shown). This may signal a relationship between antenatal depression and child behaviour that the current study was unable to detect, perhaps due to the highly correlated nature between antenatal and postnatal depression. Indeed, antenatal depression has been widely shown to be the best predictor of postnatal depression (Beck, 1996; Underwood et al., 2017). The mixed findings across extant literature highlight the complicated nature of the relationship between antenatal and postnatal depression and later childhood outcomes, signalling the need for more research on antenatal depression and childhood behavioural outcomes with ample control of confounding variables including maternal depression after birth.

Antenatal exposure to antidepressants was not associated with

increased odds of high behavioural difficulties at 2-, 4.5-, or 8-years of age. Further, results at 4.5-years indicated reduced odds of high behavioural difficulties amongst those exposed to antidepressants. Several previous studies have reported no significant adverse association between gestational antidepressant exposure and later behavioural difficulties in childhood (Grzeskowiak et al., 2016; Misri et al., 2006; Pedersen et al., 2013). It is possible that exposure to antidepressants may not be associated with behavioural difficulties, as treating maternal depressive symptoms may reduce the offspring's likelihood of being exposed to other risk factors for behavioural difficulties associated with untreated maternal depression (e.g., tobacco and other substance use and postnatal depression) (Mian, 2005). Furthermore, if antidepressants reduce depressive symptoms and improve maternal mood, they may improve interactions between the mother and child, yielding a better postnatal environment for the child than that which follows medically untreated depression, which is likely to persist postnatally if left untreated (Hermansen and Melinder, 2015).

However, findings regarding the impact of antidepressant exposure on child behavioural outcomes remain mixed, with some studies reporting significant associations between antidepressant exposure and adverse behavioural outcomes (Hanley et al., 2015; Hermansen et al., 2016; Oberlander et al., 2010). This inconsistency across studies may in part be due to limitations within and variability between study designs, such as small and unrepresentative samples (Grigoriadis et al., 2013; Hermansen and Melinder, 2015) and an inability to distinguish between the effects of the antidepressants and the underlying maternal depression (Fitton et al., 2020). This may be complicated by the fact that women who take antidepressants during pregnancy may suffer from more severe symptoms of depression, the effects of which can be difficult to disentangle from psychotropic treatment (Fitton et al., 2020). These limitations in the literature to date highlight the need for more research employing large, representative samples with the ability to distinguish between the effects of the treatment and depression to determine the risks associated with gestational antidepressant use on later childhood behaviour. Indeed, this is the main strength of the present study.

Overall, the current study adds a significant contribution to the literature regarding the effects of antenatal exposure to antidepressants on child behavioural outcomes in showing no significant adverse effect of exposure on later risk of high behavioural difficulties using a large, diverse, population-based sample. Our findings may aid both mothers-to-be and their clinicians in making an informed decision about the relative safety of medically treating antenatal depression (compared to leaving the depression medically untreated). Particularly with replication, our findings will help decisions regarding the best course of action for both the mother and child.

Postnatal and later-life depression in the mother significantly predicted high behavioural difficulties at 2-, 4.5-, and 8-years of age. These findings are consistent with previous research that has demonstrated associations between maternal depression after birth and a range of adverse child behavioural outcomes (Giallo et al., 2015). While our results cannot speak to causation, this link between maternal depression

after pregnancy and poor behavioural outcomes for the child may be due to distorted communication and altered interactions between the mother and child resulting from the maternal depression, such as reduced attentiveness and responsiveness to children's needs (Hermansen and Melinder, 2015). Evidence suggests that mothers experiencing depression may also model negative mood regulation and may be less likely to set and follow-through on limits with their children, which may contribute to the development of behavioural difficulties (Bernard-Bonnin, 2004).

4.1. Strengths and limitations

The current study has several limitations that should be noted. To begin with, data collection for the GUiNZ sample occurred through self-report measures of variables, such as antidepressant intake, depressive symptoms, smoking, and alcohol consumption. Such measures may be impacted by social-desirability bias, particularly due to the social stigma surrounding such issues and the sensitive nature of the questions (Krumpal, 2013; Lauber and Rössler, 2007). Additionally, we did not obtain information on the quantity or dosage of antidepressant intake or investigate an effect of timing, which may impact the development of behavioural difficulties. The relatively low number of mothers in the antidepressants group, particularly for children with high behavioural difficulties, should also be considered as this may have impacted the current study's statistical power. Future research could benefit by utilising large administrative datasets such as Statistics New Zealand's Integrated Data Infrastructure (Milne et al., 2019; Milne et al., 2022) to increase cell counts and statistical power, clinical measures of depression rather than a screening instrument, detailed prescription information, and obtaining information on any other forms of treatment received (e.g., talking therapies). Similarly, our study relies solely on mother-report of child behavioural difficulties, which may be susceptible to bias due to maternal mental health problems. Depressed and/or anxious mothers may have less accurate perceptions of their children and may overreport child emotional and behavioural problems (Fergusson et al., 1993). However, associations have been reported between maternal depression and child emotional and behavioural problems independent of the effects of maternal depression on reporting errors (Fergusson et al., 1993). To combat this, future research could employ a multi-informant approach by including both parent-report and teacher-report of child behavioural outcomes (e.g. Fihrer et al., 2009).

In addition, prior research investigating the GUiNZ cohort at 2-, 4.5- and 8-years found a reduction in the sample representativeness resulting from attrition (D'Souza et al., 2019; Theunissen et al., 2022) namely differences in maternal health and sociodemographic measures. However, sample attrition is not uncommon in longitudinal studies and the study's analytic sample still showed considerable diversity on key sociodemographic factors at all ages. Further, the GUiNZ study has demonstrated high retention rates compared to other birth cohorts (Teague et al., 2018).

There are several strengths to the current study. Firstly, the study utilises a large, diverse, population-based sample. Secondly, the multidisciplinary nature of the GUiNZ study allowed us to investigate the effects of antenatal antidepressant use and unmedicated depression on child behavioural outcomes while controlling for later life depression in the mother and a range of important birth and sociodemographic factors linked to behavioural outcomes. Furthermore, the longitudinal nature of GUiNZ allowed us to measure the effect of these variables on child behaviour across several time points, to evaluate whether any effects persist long-term. Another key strength of the current study is the prospective study design, which allowed antenatal data to be gathered without being subject to significant recall bias. Many other studies in the field have relied on retrospective recall for medication exposures and the severity of depressive symptoms, leaving this data vulnerable to recollection bias (Singal et al., 2016).

5. Conclusions

Using a large and diverse sample, the present study examined whether exposure to antidepressants and unmedicated depression was adversely associated with high behavioural difficulties at 2-, 4.5- and 8-years of age, while controlling for a range of birth and sociodemographic factors and later life maternal depression. Despite finding a strong association between unmedicated depression and high behavioural difficulties in the unadjusted analyses, this effect was attenuated and no longer statistically significant in the fully adjusted analyses. Later life depression in the mother was significantly associated with high behavioural difficulties at all three of the ages investigated. Results contribute to evidence on the safety of antenatal antidepressant exposure for children's long-term outcomes. Although in the adjusted analyses unmedicated depression was no longer significantly associated with high behavioural difficulties, the experience of depressive symptoms during pregnancy can be harmful and extremely unpleasant for mothers-to-be and can persist after birth if left untreated. As such, adequate mental health support is vital to ensure the best outcomes for both the mother and child. It is also noteworthy that high behavioural difficulties at each age also seemed to be associated with adverse sociodemographic and familial circumstances which may impact both child behavioural outcomes and maternal mental health. If considering intervention strategies, these results also signal the need for not only targeting children exhibiting high behavioural difficulties but also utilising a more holistic family-systems approach to address the various facets in a child's life and to support others in the family and wider community.

CRediT authorship contribution statement

Anns was responsible for statistical analyses and writing the original draft. Waldie, Peterson, Walker and Morton all contributed to study conceptualisation, data collection, funding acquisition, and assisted with reviewing and editing the manuscript. D'Souza was involved in study conceptualisation, supervised statistical analyses and writing, contributed to key intellectual content in the manuscript, and reviewed and edited the writing.

Declaration of competing interest

All authors declare no conflict of interest.

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