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Research Paper

An Individual Participant Data Meta-analysis of Maternal Going-to-Sleep Position, Interactions with Fetal Vulnerability, and the Risk of Late Stillbirth☆

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ABSTRACT

Background: Maternal supine going-to-sleep position has been associated with increased risk of late stillbirth (≥28 weeks), but it is unknown if the risk differs between right and left side, and if some pregnancies are more vulnerable.
Methods: Systematic searches were undertaken for an individual-level participant data (IPD) meta-analysis of case–control studies, prospective cohort studies and randomised trials undertaken up until 26 Jan, 2018, that reported data on maternal going-to-sleep position and stillbirth. Participant inclusion criteria included gestation ≥28 weeks', non-anomalous, singleton pregnancies. The primary outcome was stillbirth. A one-stage approach stratified by study and site was used for the meta-analysis. The interaction between supine going-to-sleep position and fetal vulnerability was assessed by bi-variable regression. The multivariable model was adjusted for a priori confounders. Registration number: PROSPERO, CRD42017047703.
Findings: Six case–control studies were identified, with data obtained from five (cases, n = 851; controls, n = 2257). No data was provided by a sixth study (cases, n = 100; controls, n = 200). Supine going-to-sleep position was associated with increased odds of late stillbirth (adjusted odds ratio [aOR] 2.63, 95% CI 1.72–4.04, p < 0.0001) compared with left side. Right side had similar odds to left (aOR 1.04, 95% CI 0.83–1.31, p = 0.75). There were no significant interactions between supine going-to-sleep position and assessed indicators of fetal vulnerability, including small-for-gestational-age infants (p = 0.32), maternal obesity (p = 0.08), and smoking (p = 0.86). The population attributable risk for supine going-to-sleep position was 5.8% (3.2–9.2).
Interpretation: This IPD meta-analysis confirms that supine going-to-sleep position is independently associated with late stillbirth. Going-to-sleep on left or right side appears equally safe. No significant interactions with our assessed indicators of fetal vulnerability were identified, therefore, supine going-to-sleep position can be considered a contributing factor for late stillbirth in all pregnancies. This finding could reduce late stillbirth by 5.8% if every pregnant woman ≥28 weeks' gestation settled to sleep on her side.

1. Introduction

Stillbirth, the loss of a baby during pregnancy, is a tragedy for individual families and a major public health problem [1,2]. Published studies of late stillbirth (≥28 weeks' gestation) risk factors have reported that when the pregnant mother goes-to-sleep in the supine position in the third trimester she has a 2.3 to 8.0 fold increase in odds of stillbirth [3–9]. Different biological mechanisms have been proposed. The

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Research in context

Evidence before this study

The 2011 Auckland Stillbirth Study was the first study to report an association between maternal supine going-to-sleep position and late stillbirth (≥28 weeks' gestation). This finding was biologically plausible and aligned with existing research on the effects of maternal supine position in the third trimester, including vena-caval and aortic compression. This study was considered hypothesis-generating and raised questions about the possibility of a chance finding, recall bias, and reverse causation. Further studies have subsequently investigated the association between supine going-to-sleep position and late stillbirth. However, the association of right side going-to-sleep position with late stillbirth was inconsistent across studies, and no individual study was large enough to investigate interactions between maternal sleep position and indicators of fetal vulnerability, such as small-for-gestational-age babies, maternal obesity, smoking or recreational drug use, pre-existing hypertension or diabetes, fetal movements, and term versus preterm gestation.

Added value of this study

We conducted the first individual participant data (IPD) meta-analysis on maternal going-to-sleep position and late stillbirth, assembling all the available world-wide data on the topic. Our IPD dataset comprises the largest database addressing this question, including data on confounders that have not been previously reported. Our study has shown that after adjustment for confounders, maternal supine going-to-sleep position compared with left side going-to-sleep position, was independently associated with a 2.6-fold increase in odds of late stillbirth. Right side going-to-sleep position had no increase in odds compared to left, therefore women can choose to go-to-sleep on either side. Furthermore, we found no significant interaction between the assessed indicators of fetal vulnerability and supine going-to-sleep position. We therefore conclude that supine going-to-sleep position is independently associated with late stillbirth in the general pregnant population, regardless of body size, baby size, smoking, recreational drug use, pre-existing hypertension or diabetes, fetal movements, or term versus preterm gestation. The population attributable risk for supine going-to-sleep position in this study was 5.8% (3.2–9.2).

Implications of all the available evidence

This study has important public health implications and could potentially reduce late stillbirth by approximately 6% if all women in the third trimester settled to sleep on their side. The message, that it is safer for baby if women from 28 weeks of pregnancy settle to sleep on either side is simple, and can be implemented by pregnant women.

increased odds of stillbirth associated with the supine position is considered to be due to haemodynamic changes from inferior vena-caval and aortic compression by the pregnant uterus, which reduces maternal-fetal blood flow and has the potential to compromise fetal wellbeing [10–19]. The position in which women first go-to-sleep has the longest duration overnight, compared with positions adopted later in the night [20], and may therefore have the greatest impact on the baby. The increased odds associated with the supine position may also be related to sleep-disordered breathing [21,22], which is exacerbated in the supine position [23] and by obesity [21], with both factors previously being associated with an increased risk of stillbirth [21].

Differences in the rates of late stillbirth between high-income countries [1] ranging from 1.3–8.8/1000 births, suggest that further reductions in late stillbirth are possible. However, stillbirth can only be reduced through identification and management of modifiable risk factors, with many factors unable to be changed during pregnancy. Findings from epidemiological studies and the physiological and anatomical evidence [11,19] suggest that the association between supine going-to-sleep position and late stillbirth is likely to be causal. Therefore, informing pregnant women about optimal going-to-sleep position in late pregnancy may be a feasible strategy [24] to reduce stillbirth. However, there is a need to assess the accumulated evidence from the existing studies to inform public health interventions. In particular, it is necessary to determine if there are specific groups of pregnant women who are more vulnerable when they go-to-sleep supine and if the odds of stillbirth differ between right and left side going-to-sleep position. This need is urgent, because pregnant women are already modifying their going-to-sleep position based on inconsistent advice [8,24].

The association between right side going-to-sleep position and late stillbirth has been inconsistent across studies. One study [6] showed increased odds of stillbirth in women who reported going-to-sleep on their right side compared to women going-to-sleep on their left, and another [8] reported a decreased odds with right side going-to-sleep position. Clarification by analysis of individual-level data is required, so that women can be advised whether to go-to-sleep on their left side or on either side in the last trimester of pregnancy. In addition, while an aggregate meta-analysis [22] of six studies [3–8] showed a significantly higher prevalence of stillbirth when women went to sleep in a supine position in late pregnancy, this review included studies with variable inclusion and exclusion criteria [3,5], and did not include unpublished studies [7]. Furthermore, as late stillbirth is a relatively rare event, individual studies are underpowered to investigate interactions between maternal going-to-sleep position and pregnancies with indicators of fetal vulnerability.

The Collaborative Individual Participant Data of Going-to-sleep and Stillbirth (CRIBSS) group was established to address the following main questions: 1) are supine and right side maternal going-to-sleep positions associated with late stillbirth, and 2) does maternal going-to-sleep position interact with indicators of fetal vulnerability (including small-for-gestational-age infants, maternal obesity, smoking, recreational drug and alcohol use, pre-existing hypertension or diabetes, and fetal movements), to influence the odds of late stillbirth?

2. Methods

2.1. Search Strategy and Selection Criteria

This study followed the published individual participant data (IPD) meta-analysis protocol [25]. The study was registered with the PROSPERO register of systematic reviews (CRD42017047703). The search strategy was developed prior to the systematic bibliographic search. We sought to assess the accumulated evidence in the first pooled IPD meta-analysis of randomised trials, prospective cohort studies, and case–control studies, to evaluate the relationship between maternal going-to-sleep position and late stillbirth, comprising all the available world-wide data on the topic. Systematic bibliographic searches of MEDLINE (Appendix A), Embase, LILACS, Web of Science, OpenGrey, Google Scholar, and the WHO International Clinical Trials Registry Platform of studies up until 26 January, 2018 (with no specified earliest date), using relevant terms (“stillbirth”, “fetal death”, “perinatal death” and “sleep”) and synonyms were tested prior to search commencement to check that the located articles were consistent with the inclusion criteria. Proceedings from International Stillbirth Alliance (ISA) conferences, the International Society for the Study and

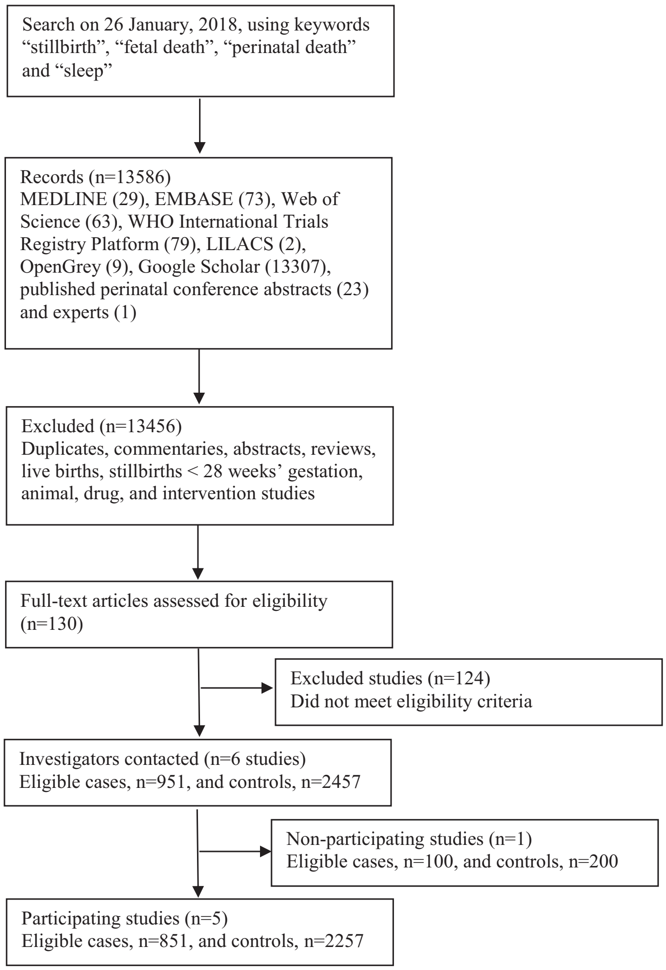

Fig. 1. Study selection.

Prevention of Perinatal and Infant Death (ISPID) conferences, and published perinatal conference abstracts were searched. Experts in the field were asked to identify any other studies. Reference lists of all retrieved articles were hand-searched. No language restriction was applied. Eligible participants (stillbirth cases and pregnant controls) were extracted from the identified studies that provided maternal going-to-sleep position and late stillbirth data.

Study eligibility was assessed independently by two reviewers (RC and TS). All potential study investigators were contacted to verify eligibility and invited to participate. If there was no response, co-authors and journal editors were approached. The included studies had a risk of bias assessment using the instrument tool "Risk Of Bias In Non-randomized Studies — of Exposures (ROBINS—E)" [26]. Participant level exclusion criteria (multiple pregnancy, major congenital abnormality, gestation <28 weeks' when going-to-sleep position data during pregnancy was collected, termination of pregnancy at ≥28 weeks', and receiving a study intervention that may have affected going-to-sleep position) were applied during the analysis. A detailed data management plan was agreed by CRIBSS investigators prior to the analysis [25]. For the primary analysis, the going-to-sleep position utilised was the last available going-to-sleep position recorded during pregnancy (within two weeks of when the women estimated their baby had died in cases). The position was categorised as left side, right side, variable sides, supine, prone, and propped. Left side was used as the reference group for the analysis. Going-to-sleep position was merged to supine versus non-supine groups in the analysis of interaction.

2.2. Outcome Measures

The primary outcome was late stillbirth, using the WHO international comparison definition of stillbirth: "a baby born with no signs of life at or after 28 weeks' gestation" [27]. Intrapartum stillbirth is included in the analysis with the rationale that supine going-to-sleep position may result in a vulnerable baby that is unable to tolerate labour. In addition, it is not always possible to be certain that the death occurred intrapartum. As the outcome (late stillbirth) is rare, odds ratio estimates rather than relative risk were used.

2.3. Risk of Bias

Two reviewers (RC and AG) independently rated the risk of bias for non-randomised studies using the ROBINS-E tool [26] and this was adjudicated by a third reviewer (ML) when required.

Table 1
Study level characteristics in participating IPD case–control studies.

Study level characteristics	TASS Stacey et al. (2011) [6]	SSS Gordon et al. (2015) [9]	MCSS McCowan et al. (2017) [4]	MiNESS Heazell et al. (2017) [8]	STARS O'Brien et al. (2018) [7]
Location	Auckland, New Zealand	Sydney, Australia	New Zealand	United Kingdom	International
Years of recruitment	July 2006 to June 2009	January 2006 to December 2011	February 2012 to December 2015	April 2014 to March 2016	September 2012 to August 2014
Study design	Prospective population-based case–control study	Prospective population-based case–control study	Prospective population-based case–control study	Prospective population-based case–control study	Nested case–control study with an uncontrolled cohort
Population	Non-anomalous singleton pregnancy, ≥28 weeks' gestation, from three health regions in Auckland, New Zealand	Non-anomalous singleton pregnancy, ≥32 weeks' gestation, from nine tertiary maternity facilities in metropolitan Sydney, Australia	Non-anomalous singleton pregnancy, ≥28 weeks' gestation, from seven health regions throughout New Zealand	Non-anomalous singleton pregnancy, ≥28 weeks' gestation, from 41 maternity facilities in the United Kingdom	Singleton pregnancy, ≥28 weeks' gestation, fluent in English, from 16 high, middle, and low income countries
Main outcome measure	Maternal snoring, daytime sleepiness (measured with the Epworth sleepiness scale), and sleep position at the time of going to sleep and on waking (left side, right side, back, and other)	To document risk factors for late-pregnancy stillbirth with a particular focus on those risks that are potentially modifiable	The adjusted odds of late stillbirth associated with self-reported going-to-sleep position, on the last night	Maternal sleep practices during pregnancy	To investigate, in an international cohort, whether maternal sleep practices are related to late stillbirth
Data collection	Interview and clinical records	Interview and clinical records	Interview and clinical records	Interview and clinical records	Online survey

TASS = The Auckland Stillbirth Study. SSS = Sydney Stillbirth Study. MCSS = New Zealand Multicentre Stillbirth Study. MiNESS = Midlands and North of England Stillbirth Study. STARS = Study of Trends and Associated Risks for Stillbirth Study.

Table 2
Participant level characteristics, late stillbirth risk factors, and going-to-sleep position in last two weeks in participating case–control studies and pooled IPD meta-analysis.

Characteristic	TASS Stacey et al. (2011) [6]		SSS Gordon et al. (2015) [9]		MCSS McCowan et al. (2017) [4]		MiNESS Heazell et al. (2017) [8]		STARS O'Brien et al. (2018) [7]		Collaborative Individual Participant Data of Going-to-sleep and Stillbirth (CRIBSS) analysis			
	Case	Control	Case	Control	Case	Control	Case	Control	Case	Control	Case	Control	Univariable odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Total participants	155 (33.8)	304 (66.2)	103 (34.9)	192 (65.1)	163 (22.5)	560 (77.5)	288 (28.2)	733 (71.8)	142 (23.3)	468 (76.7)	851 (27.4)	2257 (72.6)	Case n = 851 Control n = 2257 Total 3108	Case n = 826 Control n = 1953 Total 2779
Age (years)														
<20	10 (6.5)	24 (7.9)	3 (2.9)	1 (0.5)	9 (5.5)	17 (3.04)	7 (2.4)	15 (2.1)	9 (6.3)	21 (4.5)	38 (4.5)	78 (3.5)	1.50 (0.98–2.28)	1.33 (0.78–2.28)
20–24	29 (18.7)	44 (14.5)	4 (3.9)	14 (7.3)	23 (14.1)	79 (14.11)	47 (16.3)	81 (11.1)	12 (8.5)	56 (12.0)	115 (13.5)	274 (12.1)	1.33 (1.02–1.73)	1.04 (0.74–1.47)
25–29	40 (25.8)	75 (24.7)	25 (24.3)	43 (22.4)	40 (24.5)	157 (28.04)	82 (28.5)	219 (29.9)	41 (28.9)	137 (29.3)	228 (26.8)	631 (28.0)	1.12 (0.91–1.38)	0.98 (0.76–1.26)
30–34	44 (28.4)	92 (30.3)	39 (37.9)	66 (34.4)	48 (29.5)	191 (34.11)	85 (29.5)	268 (36.6)	49 (34.5)	177 (37.8)	265 (31.1)	794 (35.2)	1	1
35–39	29 (18.7)	57 (18.8)	25 (24.3)	51 (26.6)	29 (17.8)	96 (17.14)	51 (17.7)	125 (17.1)	26 (18.3)	67 (14.3)	160 (18.8)	396 (17.6)	1.19 (0.94–1.51)	1.23 (0.93–1.62)
≥40	3 (1.9)	12 (4.0)	7 (6.8)	17 (8.9)	14 (8.6)	20 (3.57)	16 (5.6)	25 (3.4)	5 (3.5)	10 (2.1)	45 (5.3)	84 (3.7)	1.60 (1.08–2.38)	1.47 (0.93–2.31)
Earliest pregnancy BMI (kg/m^2)	27.5 (23.2–33.3)	25.0 (22.2–30.8)	23.1 (21.2–28.3)	22.8 (20.8–26)	26.6 (23.1–33.5)	24.8 (22.0–29.6)	26.1 (22.5–30.3)	24.9 (22.1–28.8)	26.8 (22.8–32.5)	25.2 (22.5–31.1)	26.0 (22.5–31.4)	24.8 (22.0–29.3)	1.04 (1.03–1.05)	1.03 (1.01–1.05)
Ethnicity														
White	55 (35.5)	134 (44.1)	57 (55.3)	136 (70.8)	65 (39.9)	260 (46.4)	233 (80.9)	594 (81.0)	112 (78.9)	421 (90.0)	522 (61.3)	1545 (68.5)	1	1
Black	4 (2.6)	1 (0.3)	1 (1.0)	3 (1.6)	2 (1.3)	3 (0.5)	12 (4.2)	29 (4.0)	3 (2.1)	6 (1.3)	22 (2.6)	42 (1.9)	1.63 (0.94–2.84)	1.77 (0.92–3.42)
South Asian*	15 (9.7)	27 (8.9)	9 (8.7)	10 (5.2)	17 (10.4)	85 (15.2)	38 (13.2)	94 (12.8)	11 (7.8)	3 (0.6)	90 (10.6)	219 (9.7)	1.40 (1.04–1.88)	1.86 (1.32–2.63)
South East/East Asian	12 (7.7)	25 (8.2)	15 (14.6)	18 (9.4)	12 (7.4)	64 (11.4)	1 (0.4)	4 (0.6)	0	0	40 (4.7)	111 (4.9)	1.19 (0.8–1.79)	1.50 (0.94–2.39)
Maori	19 (12.3)	46 (15.1)	1 (1.0)	3 (1.6)	26 (16.0)	58 (10.4)	0	0	0	0	46 (5.4)	107 (4.7)	1.55 (1.04–2.32)	1.10 (0.68–1.78)
Pacific	48 (31.0)	65 (21.4)	4 (3.9)	4 (2.1)	38 (23.3)	84 (15.0)	0	0	1 (0.7)	1 (0.2)	91 (10.7)	154 (6.8)	2.25 (1.60–3.16)	1.88 (1.23–2.88)
Others	2 (1.3)	6 (2.0)	16 (15.5)	18 (9.4)	3 (1.8)	6 (1.1)	4 (1.4)	12 (1.6)	15 (10.6)	37 (7.9)	40 (4.7)	79 (3.5)	1.47 (0.97–2.22)	1.74 (1.06–2.86)
Parity														
Nulliparous	75 (48.4)	138 (45.4)	53 (51.5)	104 (54.2)	77 (47.2)	241 (43.0)	165 (57.3)	296 (40.4)	76 (53.5)	151 (32.3)	446 (52.4)	930 (41.2)	1.77 (1.49–2.11)	1.70 (1.38–2.09)
1–2	56 (36.1)	138 (45.4)	35 (34.0)	83 (43.2)	66 (40.5)	283 (50.5)	91 (31.6)	386 (52.7)	44 (31.0)	220 (47.0)	292 (34.3)	1110 (49.2)	1	1
3–4	17 (11.0)	26 (8.6)	14 (13.6)	4 (2.1)	14 (8.6)	30 (5.4)	25 (8.7)	45 (6.1)	17 (12.0)	71 (15.2)	87 (10.2)	176 (7.8)	1.99 (1.48–2.67)	1.67 (1.15–2.40)
≥ 5	7 (4.5)	2 (0.7)	1 (1.0)	1 (0.5)	6 (3.7)	6 (1.1)	7 (2.4)	6 (0.8)	5 (3.5)	26 (5.6)	26 (3.1)	41 (1.8)	2.63 (1.57–4.42)	2.29 (1.18–4.44)
Education														
Primary	42 (27.1)	68 (22.4)	10 (9.7)	13 (6.8)	49 (30.1)	118 (21.07)	84 (29.2)	137 (18.7)	2 (1.4)	12 (2.6)	187 (22.0)	348 (15.4)	1.88 (1.49–2.38)	1.39 (1.02–1.88)
Secondary	48 (31.0)	73 (24.0)	24 (23.3)	33 (17.2)	18 (11.0)	63 (11.25)	40 (13.9)	84 (11.5)	31 (21.8)	90 (19.2)	161 (18.9)	343 (15.2)	1.49 (1.18–1.89)	1.22 (0.91–1.64)
University	40 (25.8)	103 (33.9)	60 (58.3)	143 (74.5)	73 (44.8)	318 (56.79)	85 (29.5)	292 (39.8)	70 (49.3)	213 (45.5)	328 (38.5)	1069 (47.4)	1	1
Post–graduate degree	0	0	0	0	2 (1.2)	6 (1.07)	37 (12.9)	106 (14.5)	34 (23.9)	128 (27.4)	73 (8.6)	240 (10.6)	1.00 (0.73–1.37)	1.13 (0.78–1.64)
Non–university trade	25 (16.1)	60 (19.7)	2 (1.9)	1 (0.5)	20 (12.3)	52 (9.29)	41 (14.2)	114 (15.6)	5 (3.5)	22 (4.7)	93 (10.9)	249 (11.0)	1.30 (0.98–1.72)	1.14 (0.81–1.59)
Marital status														
Single	17 (11.0)	23 (7.6)	8 (7.8)	7 (3.7)	20 (12.3)	29 (5.18)	40 (13.9)	71 (9.7)	7 (4.9)	13 (2.8)	92 (10.8)	143 (6.3)	1.90 (1.43–2.52)	1.29 (0.91–1.84)
Married/cohabitating	138 (89.0)	281 (92.4)	91 (88.4)	183 (95.3)	143 (87.7)	531 (94.82)	248 (86.1)	662 (90.3)	135 (95.1)	455 (97.2)	755 (88.7)	2112 (93.6)	1	1
Pre-existing														

hypertension or diabetes														
No	152 (98.1)	300 (98.7)	101 (98.1)	191 (99.5)	158 (96.9)	549 (98.04)	272 (94.4)	728 (99.3)	140 (98.6)	454 (97.0)	823 (96.7)	2222 (98.5)	1	1
Yes	3 (1.9)	4 (1.3)	2 (1.9)	1 (0.5)	5 (3.1)	11 (1.96)	16 (5.6)	5 (0.7)	2 (1.4)	14 (3)	28 (3.3)	35 (1.6)	2.03 (1.21–3.41)	1.86 (0.97–3.58)
Maternal smoking														
Smoking (beyond first trimester)	34 (21.9)	47 (15.5)	10 (9.7)	18 (9.4)	25 (15.3)	40 (7.1)	67 (23.3)	79 (10.8)	9 (6.3)	21 (4.5)	145 (17.0)	205 (9.1)	2.05 (1.61–2.6)	1.62 (1.18–2.23)
Non–smoker	121 (78.1)	257 (84.5)	93 (90.3)	174 (90.6)	138 (84.7)	520 (92.9)	221 (76.7)	654 (89.2)	130 (91.6)	437 (93.4)	703 (72.6)	2042 (90.5)	1	1
Recreational drug use (during pregnancy)														
No	142 (91.6)	292 (96.1)	100 (97.1)	188 (97.9)	160 (98.2)	549 (98.0)	280 (97.2)	727 (99.2)	138 (97.2)	436 (93.7)	820 (96.4)	2192 (97.1)	1	1
Yes	13 (8.4)	12 (4.0)	3 (2.9)	4 (2.1)	3 (1.8)	11 (2.0)	8 (2.8)	6 (0.8)	2 (1.4)	18 (3.9)	29 (3.4)	51 (2.3)	1.49 (0.93–2.38)	1.15 (0.64–2.06)
Infant birthweight customised centile														
<10th	56 (36.1)	27 (8.9)	21 (20.4)	15 (7.8)	42 (25.8)	67 (12.0)	118 (41.0)	82 (11.2)	41 (28.9)	21 (4.5)	278 (32.7)	212 (9.4)	5.70 (4.14–7.83)	5.14 (3.61–7.31)
10–24.9th	21 (13.6)	42 (13.8)	20 (19.4)	29 (15.1)	26 (16.0)	77 (13.8)	43 (14.9)	121 (16.5)	24 (16.9)	25 (5.3)	134 (15.8)	294 (13.0)	1.89 (1.36–2.64)	1.82 (1.26–2.63)
25–49.9th	31 (20.0)	77 (25.3)	18 (17.5)	49 (25.5)	34 (20.9)	136 (24.3)	55 (19.1)	193 (26.3)	23 (16.2)	58 (12.4)	161 (18.9)	513 (22.7)	1.36 (0.99–1.86)	1.49 (1.06–2.11)
50–74.9th	20 (12.9)	79 (26.0)	14 (13.6)	60 (31.6)	35 (21.5)	132 (23.6)	43 (14.9)	153 (20.9)	15 (10.6)	58 (12.4)	127 (14.9)	482 (21.4)	1.14 (0.82–1.57)	1.28 (0.9–1.83)
75–89.9th	13 (8.4)	44 (14.5)	14 (13.6)	21 (10.9)	11 (6.8)	100 (17.9)	18 (6.3)	110 (15.0)	18 (12.7)	41 (8.8)	74 (8.7)	316 (14.0)	1	1
≥90th	14 (9.0)	27 (8.9)	16 (15.5)	18 (9.4)	15 (9.2)	48 (8.6)	10 (3.5)	71 (9.7)	18 (12.7)	26 (5.6)	73 (8.6)	190 (8.4)	1.58 (1.09–2.31)	1.57 (1.03–2.38)
Going-to-sleep position (last two weeks)														
Left side	42 (27.1)	129 (42.4)	32 (31.1)	48 (25.0)	78 (47.9)	324 (57.9)	138 (47.9)	383 (52.3)	69 (48.6)	190 (40.6)	359 (42.2)	1074 (47.6)	1	1
Supine	15 (9.7)	14 (4.6)	10 (9.7)	4 (2.1)	19 (11.7)	20 (3.6)	19 (6.6)	24 (3.3)	4 (2.8)	11 (2.4)	67 (7.9)	73 (3.2)	2.89 (2.01–4.14)	2.63 (1.72–4.04)
Right side	49 (31.6)	83 (27.3)	14 (13.6)	25 (13.0)	43 (26.4)	186 (33.2)	72 (25.0)	220 (30.0)	43 (30.3)	110 (23.5)	221 (26.0)	624 (27.7)	1.10 (0.90–1.34)	1.04 (0.83–1.31)
Prone	0	0	0	0	0	0	3 (1.0)	4 (0.6)	0 (0.0)	4 (0.9)	3 (0.4)	8 (0.4)	1.15 (0.30–4.45)	0.63 (0.12–3.25)
Variable sides	9 (5.8)	23 (7.6)	38 (36.9)	110 (57.3)	14 (8.59)	20 (3.57)	32 (11.1)	76 (10.4)	9 (6.3)	36 (7.7)	102 (12.0)	265 (11.7)	0.92 (0.69–1.23)	0.97 (0.70–1.35)
Propped up	4 (2.6)	7 (2.3)	0	0	4 (2.45)	9 (1.61)	9 (3.1)	15 (2.1)	3 (2.1)	15 (3.2)	20 (2.4)	46 (2.0)	1.28 (0.74–2.23)	1.30 (0.68–2.49)
Don't remember	36 (23.2)	48 (15.8)	9 (8.7)	5 (2.6)	5 (3.07)	1 (0.18)	15 (5.2)	11 (1.5)	14 (9.9)	102 (21.8)	79 (9.3)	167 (7.4)	1.40 (1.03–1.91)	2.26 (1.48–3.46)
Fetal movement frequency (last two weeks)														
Increased	13 (8.4)	85 (28.0)	6 (5.8)	17 (8.9)	21 (12.9)	217 (38.8)	36 (12.5)	254 (34.7)	7 (4.9)	75 (16.0)	83 (9.8)	648 (28.7)	0.33 (0.26–0.43)	0.29 (0.22–0.38)
Decreased	45 (29.0)	36 (11.8)	9 (8.7)	13 (6.8)	61 (37.4)	82 (14.6)	84 (29.2)	63 (8.6)	66 (46.5)	74 (15.8)	265 (31.1)	268 (11.9)	2.74 (2.22–3.37)	2.49 (1.96–3.16)
No change or unsure	97 (62.6)	183 (60.2)	88 (85.4)	162 (84.4)	81 (49.7)	261 (46.6)	168 (58.3)	416 (56.8)	63 (44.4)	225 (48.1)	497 (58.4)	1247 (55.3)	1	1

Data are number (percentage) or median (IQR). TASS = The Auckland Stillbirth Study. SSS = Sydney Stillbirth Study. MCSS = New Zealand Multicentre Stillbirth Study. MiNESS = Midlands and North of England Stillbirth Study. STARS = Study of Trends and Associated Risks for Stillbirth Study. CRIBSS = Collaborative IPD of Sleep and Stillbirth. Multivariable models are adjusted for matching terms (gestation at interview in controls and at diagnosis of stillbirth for cases) and study and site, and all the other variables in the table. Participants with missing data were excluded from the multivariable model. No imputation for missing data. *South Asian includes India, Pakistan, Sri Lanka, Bangladesh, Nepal, Bhutan, the Maldives, and Afghanistan ethnicities.

2.4. Data analysis

A detailed statistical analysis plan for the main questions was published [25] prior to the analysis. Potential confounders were all prespecified (maternal age, earliest pregnancy body mass index (BMI kg/m2), ethnicity, parity, education level, marital status, pre-existing hypertension or diabetes, smoking, recreational drug use, going-to-sleep position, fetal movements, and infant birthweight by customised centiles). A one-stage approach to IPD meta-analysis was used, so that the data from all the eligible studies were included in a single model. Logistic regression models were used for the binary outcome. A fixed study effect and study site effect were included in the model specification as strata. Univariable analysis was performed to evaluate the association between going-to-sleep position and the odds of late stillbirth. During data acquisition, one prespecified confounder, alcohol intake during pregnancy, was found to be inconsistently collected across the studies and unable to be merged, and consequently omitted from the analysis. A multivariable model was developed incorporating prespecified confounders available in all the studies.

Three confounders (going-to-sleep duration, frequency of overnight toilet use, and day-time napping) were only available in some of the studies, and were therefore analysed in sensitivity models. A sensitivity analysis was also conducted after exclusion of controls who reported their pregnancy going-to-sleep position after they had given birth. The interaction between going-to-sleep position and prespecified factors indicating a vulnerable pregnancy were assessed in bi-variable regression models. Estimates of risk of late stillbirth were reported as odds ratio (OR) with 95% confidence intervals.

For missing data in each individual study, no imputation was undertaken. The population attributable risk (PAR) was calculated using the unadjusted OR for the primary outcome for supine going-to-sleep position and for other modifiable risk factors that were significant in multivariable analysis. Statistical analyses were performed using SAS, version 9.4 (SAS Institute Inc., Cary NC USA).

Ethics approval was obtained by each individual study. Additional approval for the IPD meta-analysis was obtained from the New Zealand Health and Disability Ethics Committee (NTX/06/05/054/AM06).

3. Results

Six eligible case–control studies were identified [3,4,6–9] (Fig. 1). Five studies provided individual-level data, the Auckland Stillbirth Study [6], the Sydney Stillbirth Study [9], the New Zealand Multicentre Stillbirth Study [4], the Midlands and North of England Stillbirth Study [8], and the International Study of Trends and Associated Risks for Stillbirth (STARS) Study [7] (Table 1). No contact was able to be made, despite repeated attempts, with the authors or journal editors of the sixth study [3]. Eligible participants comprised 851 cases and 2257 controls. The risk of bias (ROBINS-E) [26] tool is summarised (Appendix B).

There were a number of differences in maternal and pregnancy characteristics, infant size, and going-to-sleep practices between cases and controls in univariable and multivariable analysis (Table 2). The proportion of women reporting a supine going-to-sleep position was 67 cases (7.9%) and 73 controls (3.2%). In multivariable analysis, compared with

Table 3
Analysis for interaction between supine going-to-sleep position and prespecified indicators of fetal vulnerability.

Prespecified indicators of fetal vulnerability	Supine	Non–supine	Bi-variable regression
	Univariable odds ratio (95% CI)	Univariable odds ratio (95% CI)	P for interaction
Small-for-gestational-age infant (<10th infant birthweight customised centile)			
Yes	15.66 (6.96–35.25)	3.98 (3.17–4.99)	0.32
No	2.45 (1.6–3.75)	1	
Infant birthweight customised centile			
<50th centile	4.85 (3.12–7.53)	1.97 (1.64–2.38)	0.34
≥50th centile	3.62 (1.87–7.01)	1	
Earliest pregnancy BMI (kg/m^2)			
BMI <25.0	3.69 (2.26–6.01)	1	0.30
BMI 25–29.9	4.96 (2.33–10.57)	1.4 (1.13–1.74)	
BMI 30–34.9	3.61 (1.40–9.27)	1.71 (1.3–2.24)	
BMI >35.0	2.99 (1.09–8.21)	2.2 (1.66–2.91)	
Obesity			
Obese	3.52 (2.34–5.3)	1.69 (1.38–2.07)	0.08
Non–obese	2.90 (1.45–5.8)	1	
Recreational drug use (during pregnancy)			
Yes	–	1.40 (0.83–2.37)	0.97
No	2.92 (2.05–4.15)	1	
Smoking			
Smoking (beyond first trimester)	6.32 (2.31–17.32)	1.99 (1.54–2.58)	0.86
Non-smoking	2.88 (1.98–4.2)	1	
Pre-existing hypertension or diabetes			
Yes	3.12 (0.19–51.78)	2.23 (1.28–3.88)	0.62
No	2.90 (2.04–4.12)	1	
Fetal movement frequency (last two weeks)			
Increased	2.49 (1.03–6.00)	1	0.40
Decreased	16.94 (7.60–37.76)	8.50 (6.19–11.67)	
Same/unsure	10.50 (6.19–17.81)	2.91 (2.19–3.85)	
Term (≥37 weeks') versus preterm (<37 weeks') infant			
Term	2.79 (1.72–4.53)	1	0.88
Preterm	2.78 (1.69–4.57)	0.95 (0.79–1.13)	

left side going-to-sleep position, the last available supine going-to-sleep position during pregnancy (aOR [adjusted odds ratio] 2.63, 95% Confidence Interval [CI] 1.72–4.04, $p < 0.0001$) and being unable to recall going-to-sleep position (2.26, 1.48–3.46, $p = 0.0002$) remained significantly associated with the odds of late stillbirth. However, there was no increase associated with right side going-to-sleep position (aOR 1.04, 95% CI 0.83–1.31, $p = 0.75$) compared to left side.

Other maternal risk factors significant in multivariable analysis included: parity, with an increased odds of stillbirth associated with nulliparity (aOR 1.70, 95% CI 1.38–2.09 $p < 0.0001$), parity 3–4 (1.67, 1.15–2.4, $p = 0.001$), and parity ≥5 (2.29, 1.18–4.44, $p = 0.01$) compared to parity of 2; primary-level education compared to university (1.39, 1.02–1.88, $p = 0.04$); BMI (1.03, 1.01–1.05, $p = 0.0004$) with a 3% increase in odds for every unit increase in BMI; South Asian (1.86, 1.32–2.63, $p = 0.0004$), Pacific (1.88, 1.23–2.88, $p = 0.004$), and other (1.74, 1.06–2.86, $p = 0.03$) ethnicities compared to white; and smoking beyond the first trimester (1.62, 1.18–2.23, $p = 0.003$).

Significant risk factors related to the baby were: maternal perception of reduced fetal movements (aOR 2.49, 95% CI 1.96–3.16, $p < 0.0001$) compared to women who reported no change in movements or were unsure; and customised birthweight centile of 10.0–24.9 (1.82, 1.26–2.63, $p = 0.002$), 25.0–49.9 (1.49, 1.06–2.11, $p = 0.02$), and ≥90.0th centile (1.57, 1.03–2.38, $p = 0.03$), compared with centile 75.0–89.9. Small-for-gestational-age infants <10th customised centile (aOR 5.14, 95% CI 3.61–7.31, $p < .0001$) had the greatest risk (Table 2).

We evaluated the interaction between supine going-to-sleep position and pregnancies with prespecified indicators of fetal vulnerability to identify the OR for the combined effect of supine going-to-sleep position in women with indicators of fetal vulnerability (Table 3). The prespecified indicators of fetal vulnerability included infants <50th birthweight centile, due to our finding of an increased risk of late stillbirth in this group compared to infants ≥50th birthweight centile. None of the assessed indicators of fetal vulnerability significantly modified the overall effect between the risk of the combination of supine going-to-sleep position and indicators of fetal vulnerability. The p value for interactions, assessed using bi-variable regression, were small-for-gestational-age infant ($p = 0.32$), infant <50th birthweight customised centile ($p = 0.34$), earliest pregnancy BMI ($p = 0.30$), maternal obesity ($p = 0.08$), recreational drug use ($p = 0.97$), smoking beyond the first trimester ($p = 0.86$), pre-existing hypertension or diabetes ($p = 0.62$), reduced fetal movements ($p = 0.40$), and term (≥37 weeks') versus preterm gestation ($p = 0.88$). The PAR for supine going-to-sleep position was 5.8% (3.2–9.2) (Table 4).

Our prespecified sensitivity analyses (Appendix C) were conducted to include variables that were only available in some studies: sleep duration, frequency of overnight toilet use, and daytime napping. Short sleep duration (<6 hours), not getting up to the toilet overnight, and daily napping during the last two weeks, were associated with late stillbirth. Sensitivity analyses were also conducted without controls who reported their pregnancy going-to-sleep position after they had given birth (Appendix C). The relationship between supine going-to-sleep position and other risk factors associated with late stillbirth in these models remained similar to those reported in the main model.

4. Discussion

Our individual participant-level data meta-analysis confirms that maternal supine going-to-sleep position during the last two weeks of pregnancy is independently associated with late stillbirth. Importantly, we observed no difference in odds of late stillbirth between women who reported they went to sleep on their left or right side. Women who were unable to recall their going-to-sleep position also had increased odds of late stillbirth, although this is likely to reflect a combination of going-to-sleep positions and other factors. These associations between going-to-sleep position and late stillbirth were independent of maternal age, ethnicity, parity, education level, marital status, BMI, pre-existing hypertension or diabetes, smoking, recreational drug use, perception of fetal movements, customised birthweight centiles (small-for-gestational-age infants), and gestation.

The effect of ethnicity in the adjusted model requires further research to understand why some ethnic groups appear to have an increased risk of late stillbirth or whether these effects reflect residual confounding. Pathways may be related to less favourable pre-pregnancy social and environmental factors and differential access to optimal maternity care [28]. However, these factors were not measured in the individual studies.

Our findings regarding going-to-sleep position are biologically plausible, as maternal supine position in late pregnancy is associated with compression of the inferior vena cava [10,13], and aorta [10,19], with reported 85% reduction in blood flow through the vena cava at its origin and around 30% reduction through the aorta at the level of bifurcation. This compression diverts blood into the collateral venous circulation [15,19], with a reported compensatory 220% increase in flow through the dominant azygos venous pathway [19]. However, this increase in collateral flow does not fully offset the compression, resulting in an 11–25% decrease in stroke volume [10,13,19] and 9–29% decrease in cardiac output [10,13,19]. In turn, this may reduce uterine [17] and placental perfusion [16,18] and decrease fetal oxygenation [14], demonstrated by increased fetal quiescence in the maternal supine position [11,14]. Individual variations in the woman's collateral venous circulation [19], autonomic response to positional change [29], the duration of supine position exposure [12], and the presence of sleep-disordered breathing [21–23] may contribute to this process.

The triple risk model for unexplained late stillbirth [30] hypothesises that stillbirth may result from an inter-relationship of three groups of factors: a vulnerable baby (e.g. small-for-gestational-age), an adverse maternal factor (e.g. obesity) and an additional stressor (e.g. reduced uterine blood flow associated with supine going-to-sleep position). Although, we found no statistically significant interactions between these factors and supine going-to-sleep position, our bi-variable regression models found the effect of vulnerable pregnancies and supine position was independent and additive, and this is important information for practicing clinicians. For example, in our interaction analysis (Table 3), we found the combined effect of supine going-to-sleep position with a small-for-gestational-age baby resulted in significantly increased odds of late stillbirth (aOR 15.66, 95% CI 6.96–35.25) compared to supine position with an appropriately grown or large baby (2.45, 1.6–3.75), and non-supine position with a small-for-gestational-age baby (3.98, 3.17–4.99).

Table 4
Population attributable risk of modifiable risk factors for late stillbirth in pooled IPD population.

Variables	Prevalence of the exposure in controls	Relative risk unadjusted	Population attributable risk
<10th birthweight customised centile	9.4%	5.7	30.6% (22.8–39.1)
Decreased fetal movements (last two weeks)	11.9%	2.7	17.1% (12.6–22.0)
Obesity (BMI >30 kg/m^2)	22.2%	1.62	12.1% (7.2–17.4)
Smoking (beyond first trimester)	9.1%	2.1	8.7% (5.2–12.7)
Overweight (BMI 25–29.9 kg/m^2)	25.4%	1.4	8.2% (2.5–14.2)
Supine going-to-sleep position (last two weeks)	3.2%	2.9	5.8% (3.2–9.2)

Other maternal sleep practices associated with late stillbirth during the last two weeks in the sensitivity analysis were short sleep duration (<6 h), not getting up to the toilet overnight, and daily napping (Appendix C), which are consistent with findings from the individual studies [4,6,8]. Short sleep duration in pregnancy has been associated with an increased risk of preterm labour [31], depression [32], gestational hypertension [33], hyperglycaemia, and gestational diabetes [34]. This may be a result of increased systemic inflammatory responses, oxidative stress, and sympathetic activity, which could contribute to placental dysfunction and metabolic derangements [32,34]. Similarly, daytime napping during pregnancy has been associated with nocturnal sleep-disordered breathing and abnormal glucose metabolism [34]. A possible explanation for the increased risk associated with not getting up to the toilet overnight is that prolonged periods of undisturbed sleep, with unrelieved inferior vena cava compression, may result in reduced uterine [17] and placental perfusion [16,18], and decreased oxygenation [14], from which the fetus is unable to recover.

There are limitations to our study. First, the time lapse between interview and stillbirth may have influenced the accuracy of recall by cases, however, this would not be systematically biased towards the exposure of supine going-to-sleep position [35,36]. Secondly, there were no randomised trials or eligible prospective cohort studies identified for this IPD, and a Ghanaian cross-sectional study [5] that reported an association between supine sleep and late stillbirth was ineligible due to the study design. Therefore, the exposure data and data about a number of prespecified confounders were collected retrospectively in the included case–control studies and subject to potential recall bias. Thirdly, the small differences between each individual study design limited our ability to control for all a priori confounders, emphasising the importance of prospective planning for future IPDs whenever possible. Fourthly, although we had no language restriction, and the participating studies included women of many ethnicities, only one participating study included women from low and middle-income countries [7].

This is the largest dataset assembled on maternal going-to-sleep position and late stillbirth, comprising to our knowledge all the available data world-wide on the topic. A strength of our IPD meta-analysis is that combining the data has increased the sample size and statistical power. Furthermore, all data underwent additional data cleaning by the CRIBSS data centre [25], resulting in a reduced number of eligible participants compared to the individual studies [4,6–9]. Sensitivity analysis was conducted to compare odds estimates where an important confounder was not available in all studies. A further strength is that some factors not previously reported in the individual studies were made available and were included in the IPD meta-analysis e.g. recreational drug use, pre-existing hypertension or diabetes, and maternal perception of fetal movement.

This IPD meta-analysis comprises the best available data for making policy decisions on maternal going-to-sleep position in order to reduce the risk of late stillbirth. Our findings have major implications for clinical practice and policy development. It may now be timely to advise women that going-to-sleep on the side in the third trimester is associated with an approximate halving of the odds of late stillbirth compared to going-to-sleep on the back. Swapping from the supine to the side-lying going-to-sleep position in late pregnancy is a simple intervention that women report can be self-managed by women with minimal difficulty in the home [8,24], requires no technology or equipment [24], is not known to cause harm, is applicable to all pregnant women, and most importantly could reduce late stillbirth.

We conclude that supine going-to-sleep position is a risk factor for late stillbirth, with a 2.6-fold increase in odds, independent of other common stillbirth risk factors. Going-to-sleep on the left or right side appears equally safe, therefore women in the third trimester can choose to settle to sleep on either side. Furthermore, as we did not identify significant interactions with our indicators of fetal vulnerability, supine going-to-sleep position can be considered a contributing factor for late stillbirth in all third trimester pregnancies. This study has important public health implications and could potentially reduce late stillbirth by approximately 6% if all women ≥28 weeks' gestation settled to sleep on their side. The message, that it is safer for baby if women from 28 weeks of pregnancy settle to sleep on either side is simple, and can be implemented by pregnant women.

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Authors Contributions

RC participated in conception, study design, protocol development, data collection, data analysis, data interpretation, and drafted the manuscript. ML, JT, AG, CRG, AH, TS, EM, and LM participated in conception, study design, protocol development, data collection, data analysis, data interpretation, and edited the manuscript. LA participated in study design, protocol development, data analysis, data interpretation, and edited the manuscript. VB and VC participated in protocol development, data interpretation, and edited the manuscript. LO participated in data collection, data interpretation, and edited the manuscript. NA participated in data interpretation and edited the manuscript. LM developed the IPD collaboration research team and led the application to fund the study. All members of the CRIBSS group saw and approved the final version.

Conflict of Interest

Mrs. Cronin reports grants from Health Research Council of New Zealand (12/372); Cure Kids (5357); Mercia Barnes Trust; Nurture Foundation; University of Auckland Faculty Research Development Fund (3700696)., grants from 2016 TransTasman Red Nose/Curekids (6601), grants from Sir John Logan Campbell Medical Trust, during the conduct of the study;

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.eclinm.2019.03.014.

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