Associations between Consumption of Coffee and Caffeinated Soft Drinks and Late Stillbirth – Findings from the Midland and North of England Stillbirth Case-Control Study

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Abstract

Objective – The consumption of caffeinated drinks and soft drinks is widespread in society, including by pregnant women. Data regarding the association of caffeine intake and stillbirth are varied. We aimed to investigate the degree of consumption of caffeinated drinks or soft drinks in the last four weeks of pregnancy in women who experienced a late stillbirth compared to women with ongoing live pregnancies at similar gestation. Influences on maternal caffeine intake and soft drink consumption during pregnancy were also investigated.

Study Design – A case-control study undertaken in 41 maternity units in the United Kingdom. Cases were women who had a singleton non-anomalous stillbirth ≥28 weeks' gestation (n=290) and controls were women with an ongoing pregnancy at the time of interview (n=729). Data were collected using an interviewer-administered questionnaire which included questions regarding consumption of a variety of caffeinated drinks and soft drinks in the last four weeks of pregnancy as well as other behaviours (e.g. cigarette smoking).

Results - Multivariable analysis adjusting for co-existing demographic and behavioural factors found the consumption of instant coffee, energy drinks and cola were associated with increased risk of stillbirth. There was an independent association between caffeine intake and late stillbirth (adjusted Odds Ratio 1.27, 95% Confidence Interval (95%CI) 1.14, 1.43 for each 100mg increment/day). 15% of cases and 8% of controls consumed more than the World Health Organisation (WHO) recommendation (>300mg of caffeine/day; aOR 2.30, 95% CI 1.40, 4.24). The population attributable risk for stillbirth associated with >300mg of caffeine/day was 7.4%. The majority of respondents reduced caffeine consumption in pregnancy. Midwives and internet resources were the most frequently used sources of information which influenced maternal behaviour with regard to soft drinks and caffeine, and this did not differ between cases and controls.

Conclusions – Women should be informed that consumption of caffeine during pregnancy is associated with increased risk of stillbirth, particularly at levels greater than recommended by the

WHO (>300mg/day). Recommendations from midwives and internet-based resources are likely to be the most effective means to influence maternal behaviour.

Keywords

Caffeine, Perinatal Death, Stillbirth, Cola, Sweetened Soft Drinks.

Introduction

Stillbirth is an important public health problem with enduring impact not only in terms of lives lost but also with economic, psychological and social impacts upon affected families.[1,2] One approach to reducing stillbirth is to identify factors associated with increased risk so that their effects may be reduced. Epidemiological studies have identified risk factors for stillbirth, some of which are modifiable (e.g. cigarette smoking, drug misuse) and others which are not (e.g. maternal age, ethnicity).[3]

The Stillbirth Priority Setting Partnership identified a research need to ascertain modifiable risk factors for late stillbirth.[4] The Midland and North of England Stillbirth Study (MiNESS) was a case control study which aimed to identify modifiable risk factors for late stillbirth (≥28 weeks' gestation).[5] Due to their ubiquitous consumption, 80% of the UK population drinks instant coffee and on average 211.5 litres of soft drinks (many of which contain high levels of caffeine) were consumed per capita per year.[6] Accordingly, this study included questions about intake of caffeinated drinks and soft drinks during pregnancy. To date, the evidence linking caffeine intake and stillbirth shows variable effect size and some studies focus on coffee consumption rather than consumption of any source of caffeine.[7-9] Presently, the World Health Organisation recommends that high caffeine intake (>300mg/day) is decreased to reduce the risk of pregnancy loss and the National Health Service recommends caffeine intake is <200mg/day during pregnancy.[10] Given that caffeinated drinks, are widely consumed we aimed to investigate whether there is a relationship between consumption of these beverages and the risk of late stillbirth.

Methods

MiNESS was a prospective case-control study undertaken in 41 secondary and tertiary maternity units in the UK.[5] The methodology has been described in detail previously and was conducted in accordance with the published protocol.[5,11] Following ethical approval (Ref 13/NW/0174) and study

registration (NCT02025530) participants were recruited between April 2014 and March 2016. Cases were singleton stillbirths occurring ≥28 weeks' gestation with no evidence of congenital anomaly. Women who had a multiple pregnancy, who could not consent or who were <16 years of age were excluded. Controls were mothers who had an ongoing singleton pregnancy with no evidence of congenital anomaly. To achieve a similar distribution of gestational age between groups, controls were frequency matched to the distribution of stillbirths in the preceding four years at that maternity unit. Potential control participants were randomly selected from the booking lists and gestation for interview calculated; interviews for controls were contemporaneous with those for cases.

Information was collected by an interviewer-administered questionnaire and extracted from the mother's medical records; interviewers were not blinded to participants' status. This questionnaire included a wide range of self-reported social and demographic characteristics as well as behaviours. This included the frequency of intake in the preceding four weeks for different drinks including servings of coffee, tea, chocolate, cola, energy drinks and also recorded the sugar added to drinks as a potential confounding factor. In addition, respondents were asked whether they had altered their consumption of drinks during their pregnancy and if so, whether this was due to any advice and the sources of advice. The median gestation at interview for controls was 36 weeks 3 days (Interquartile Range (IQR) 32 weeks 6 days to 38 weeks 5 days). The median gestation at diagnosis of stillbirth was 37 weeks 4 days (IQR 33 weeks 4 days to 39 weeks 5 days) and the median time between diagnosis of stillbirth and the interview was 25 days (IQR 17-35).

Exposure Assessment

Total caffeine consumption per day was calculated based upon the reported frequency of consumption for instant coffee (81.5mg/serving), brewed/filter coffee (120.8mg/serving), decaffeinated coffee (3.5mg/serving), tea (54.9mg/serving), chai tea (100mg/serving), green tea (27mg/serving), drinking chocolate (5mg/serving), eating chocolate (10mg/serving), energy drinks

(103.9mg/serving) and cola (38.5mg/serving). These values were derived from searching established sources of data and where possible a mean value taken.[12-14] Caffeine consumption was assessed as continuous variable and categorically defined as individual servings of each drink / source of caffeine.

Statistical Methods

All statistical analyses were performed in R 3.6.2. Univariable logistic regression was initially carried out to determine the association between stillbirth and daily average consumption of each drink for which data were collected in the last month prior to stillbirth (cases) or interview (controls) as part of a univariable analysis. Drinks and sources of caffeine were included individually in the multivariable analysis to adjust for maternal biometric factors (ethnicity, age, body mass index), maternal smoking, maternal education, parity, fetal factors (gestation, birthweight centile) and maternal use of dietary supplements (folic acid, iron, multivitamins, multivitamins for pregnancy, vitamin D, omega 3 and others) in the last month prior to stillbirth (cases) or interview (controls). Chi-squared tests were used to analyse changes in maternal behaviour and influences on behaviour.

Results

During the recruitment period, 3490 women were identified as potentially eligible participants for MiNESS (660 cases and 2830 controls, Figure 1),760 women could not be contacted (77 cases (11%), and 683 controls (24%)) and 1700 women did not consent to participate (287 cases (43%) and 1413 controls (50%)). Six participants were excluded after data collection as five stillbirths had previously unidentified congenital abnormalities detected on post-mortem and one control participant had a stillbirth. Thus, there were 296 (44%) cases and 734 (26%) controls in the study population. Women who had a stillbirth were more likely to participate than controls ($p<0.0001$). Data on soft drink consumption was available on 290 cases and 729 controls (99.7% of cases and 99.4% of participants included in analysis of the main study respectively; Figure 1).

Detailed information about participants has been reported previously.[12] Briefly, the majority of participants, 80.4% of cases and 81% of controls, were of white ethnicity (Table 1), with a significant proportion of participants of South Asian (13.4% of cases and 13.0% controls) and Black ethnic groups (4.1% of cases and 4.0% of controls). Participants' ages were distributed from <20 years to over 40 years, with the largest group between 30-34 years of age in both groups (29.6% cases, 36.6% controls). The majority of women, 57.4% of cases and 40.4% of controls, were primiparous. There was no difference in mean body mass index (Cases 26.9 kg/m^2, Controls 26.0 kg/m^2). Stillbirth were most frequently associated with fetal growth restriction (45.2% of cases), placental insufficiency (16.4%), placental abruption (6.5%) or acute infection (4.5%).

The frequency of exposure to each type of drink, chocolate or sugar intake and their univariable odds ratios (OR) for their association with stillbirth are presented in Table 2. In the univariable analysis, the following variables were associated with stillbirth: caffeine intake per 100mg, cola, instant coffee, drinking chocolate, energy drinks and supplementary sugar in the preceding month. 62.8% of cases and 56.3% of controls had ≥100mg of caffeine per day, and a smaller proportion, 15.1% of cases and 8.3% of controls reported intake in excess of the WHO recommendations (>300mg per day).[10] When multivariable analysis was performed intake of cola (aOR 1.23, 95% CI 1.03, 1.48), instant coffee (aOR 1.34, 95% CI 1.09-1.71) and energy drinks (aOR 1.85, 95% CI 1.11, 3.58) were all independently associated with increased risk of stillbirth. We fitted a generalized additive model (GAM) and found the relationship between caffeine intake and stillbirth to be of a linear nature, no threshold level of association was observed (Supplementary File 1). For each 100mg caffeine intake the adjusted Odds Ratio (aOR) was 1.27 (95% Confidence Interval (95% CI) 1.14, 1.43). Caffeine intake greater than 300mg/day was associated with stillbirth aOR 2.30 (95% 1.40-4.24); the population attributable risk associated with this level of consumption was 7.4%. There was no relationship between caffeine intake and sleep duration in the preceding month (R=-0.01, p=0.78), but there was a weak negative relationship between caffeine intake and birthweight (R=-0.09, p=0.003).

In total, 607 women reported making alterations to their consumption of caffeinated and/or soft drinks during their pregnancy, 166 who had a stillbirth and 441 controls. The proportion of women who altered their caffeine consumption did not differ between cases and controls (Table 3), in both groups the majority of women who altered their consumption reported either reducing consumption of coffee, tea or energy drinks or changing to decaffeinated drinks (Table 3, 51.3% of cases, 56.1% of controls). In contrast, 3.8% of cases and 1.9% of controls increased their caffeine intake during pregnancy. With regard to fizzy drinks such as cola or soda, 1.4% of cases and 1.6% of controls reduced their intake and a smaller group of 0.7% of cases and 0.8% of controls increased their intake of this type of drinks. Most women made changes to their diet and caffeine intake following advice from a midwife (18.6% of cases and 21.4% of controls, Table 3). The next most frequently used source of information to change behaviour was the internet, pregnancy books and relatives, with a minority of women receiving advice from their family or hospital doctor.

Discussion

This study found an association between caffeine intake and late stillbirth; this appears to be mediated through an increased intake of instant coffee, cola and energy drinks in cases compared to controls. Tea consumption, the most widely consumed caffeinated drink (1.44 servings/day in controls) did not differ between cases and controls. Although the majority of participants (54.5%) reduced their caffeine intake during pregnancy, a small proportion (3%) increased it and over 15% of cases and 8% of controls consumed more than the WHO recommended limit of 300mg caffeine/day. Midwives and the internet were the most commonly used sources of information leading to change in maternal behaviour.

Strengths and Limitations

This study was strengthened by obtaining information about all possible sources of caffeine intake, not just coffee. Nevertheless, other sources of caffeine e.g. headache medication were not included,

meaning caffeine consumption may have been underestimated. As there is no standard calculation for the caffeine content of drinks average values were taken from different reliable sources.[12-14] The study was also strengthened by asking whether women's behaviour had changed during pregnancy; and if so, the sources of information that had driven this change. This study is limited by self-reported caffeine intake which may have led to errors in measurement of caffeine intake or recall bias, where women who had a stillbirth may recall exposures differently. However, there was no information about hypotheses regarding diet or caffeine intake in the study materials. There is also the potential for reverse causality i.e. caffeine consumption increased due to undetected fetal demise. However, this effect is likely small as the mean duration between diagnosis of stillbirth and presumed time of fetal death was always <7 days.

Significance of the association between caffeine consumption and stillbirth

To understand whether the association between caffeine intake and stillbirth is likely to be causal, we have applied the Bradford-Hill Criteria.[15] The association is only moderately strong, exceeding the WHO recommendation of <300mg/day has an aOR 2.30. Critically, the findings of this study are in agreement with the majority of studies investigating the effect of caffeine on pregnancy; a review of found 32 out of 42 studies reported caffeine increased the risk of miscarriage, stillbirth or low birth weight and/or small for gestational age neonate, with 10 studies reporting no or inconclusive associations.[16] There appears to be a biological gradient, as each increment of 100mg/day of caffeine was associated with a 27% increase in the risk of stillbirth, which is consistent with an early UK study conducted in 2004-2006 which demonstrated increased risk of stillbirth with increasing intake of caffeine.[17] In our population, the association was linear, meaning that we were unable to generate a threshold value over which risk increases markedly. The temporal relationship between caffeine consumption is appropriate (i.e. exposure to caffeine precedes the outcome) and interestingly, the risk to fetal growth and increased risk of pregnancy loss may extend to high periconceptual caffeine consumption.[18] An association between caffeine consumption and stillbirth is analogous to the

association of caffeine consumption with early miscarriage, neonatal death and sudden infant death syndrome ,[7,19] although the neonatal death also may relate to cigarette smoking, maternal age, education and parity.[20]

The association between caffeine consumption is biologically plausible, caffeine readily crosses the placenta with poor fetal clearance (levels are 30 times greater in the fetus than the mother).[21,22] Caffeine is metabolised by CYP1A2, the activity of which decreases by 65% in the third trimester,[23] resulting in an increase in the half-life of caffeine from 3 hours in non-pregnant women to 10.5 hours in the third trimester.[22] High maternal caffeine intake increases placental vasoconstriction and fetal catecholamine levels, potentially impairing fetal growth.[24] In agreement, we observed a weak negative correlation between caffeine intake and birthweight. However, another study of 100 women found no relationship between caffeine consumption and birthweight, although only 2 participants had daily caffeine intake >200mg.[25] High consumption of caffeine, especially in energy drinks, is associated with cardiac arrhythmias which can be fatal.[26] In an animal model, in utero exposure to caffeine alters gene expression in cardiomyocytes and the embryonic response to hypoxia.[27,28] Furthermore, exposure to energy drinks during pregnancy induces oxidative damage in fetal liver, kidney and brain in a murine model.[29] These experimental observations suggest excessive caffeine could lead to adverse fetal outcome.

It is important to note that other constituents of beverages may also be responsible for the observed associations with stillbirth. Sugar-sweetened soft drinks (such as cola) have been previously reported to be associated with poorer maternal diet quality[30] and increased risk of maternal obesity,[31] gestational diabetes,[32] preterm birth,[33] pre-eclampsia [34] and congenital heart defects.[35] Energy drinks are often supplemented with taurine, which is positively correlated with fetal size, and could augment the effect of sugar on fetal macrosomia.[36] Conversely, taurine supplementation is associated with reduced birthweight and increased neonatal mortality in rats.[37,38] Finally, the effects of sugar substitutes used in soft drinks are largely unknown; aspartame decreases placental weight,

impairs normal placental structure and increases rates of fetal growth restriction.[39,40] As soft drinks are frequently consumed by pregnant women, further studies are needed to determine whether caffeine, taurine or sweeteners exert direct negative effects on the placenta and/or fetus.

Clinical Implications

Our findings suggest that women should be advised to reduce their caffeine consumption during pregnancy. Women are likely already receiving some messaging; as in common with earlier studies we found the majority of participants reduced their caffeine consumption.[41,42] Although, WHO recommend limiting caffeine consumption, this is not reflected in the UK antenatal guidelines for uncomplicated pregnancies [43] and caffeine consumption is infrequently mentioned in antenatal consultations.[44]

Based on our findings, midwives may be best placed to deliver information about safe caffeine consumption and to signpost women to further online resources. This agrees with prior studies of maternal diet which found advice from healthcare professionals and the internet were the most widely used sources of information.[45,46] Thus, combining these two approaches may enhance communication and information provision which may increase adherence to recommendations. In addition, when delivering information to women about caffeine consumption, it is important to ensure that underpinning reasons for the recommendations are adequately explained, as messages about associated risks are often not communicated effectively.[47,48] Perceiving a low level of associated risk may act as a barrier to carrying out the target behaviour,[47] therefore training midwives and other health care professionals in effectively communicating information about the risks of caffeine consumption during pregnancy may improve women's adherence to advice.

Conclusions

This study demonstrates an independent association between caffeine consumption and stillbirth after 28 weeks' gestation. As there is also an increased risk of early pregnancy loss and neonatal

deaths reported with excessive caffeine consumption, clinicians should be aware of these associations and women should be informed about the benefits of reducing caffeine consumption in pregnancy. The most effective means is likely to be via interaction with midwives accompanied by signposting to internet-based resources.

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Disclosure of Interests

All authors declare that they have no competing interests.

Contribution to Authorship

AH, TS, BM, DR, EM & LM contributed to all aspects of the study design and obtained funding. AH had overall responsibility for the study. JB coordinated the running of the study. KT and LR analysed the data with input from AH. All authors were responsible for the drafting of the manuscript. All authors gave approval for the final version of the manuscript.

Details of Ethical Approval

This study was reviewed by NRES Committee North West - Greater Manchester Central Reference (13/NW/0874) on 24th January 2014.

Data Sharing Statement

No additional data from the MiNESS study are available from a repository. Anonymised data is available on request to the corresponding author.

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Figure Legends

Figure 1 - Flow diagram reporting the numbers of women eligible for the study, women who did not participate and those included in the final analysis of caffeine and soft drink consumption.

Supplementary Figure 1 – Output from Generalized Additive Model (GAM) showing the relationship between caffeine intake and probability of stillbirth has a close to linear relationship.

Table 1 – Demographic characteristics and sleep practices in 291 women who had a late stillbirth compared to 734 controls who participated in MiNESS. Data are presented as the number (percentage) or median (interquartile range).

Characteristic	Case (n=291)	Control (n=734)
Age (years)		
<20	7 (2.4)	15 (2.0)
20-24	48 (16.5)	81 (11.1)
25-29	82 (28.2)	219 (29.9)
30-34	86 (29.6)	268 (36.6)
35-39	52 (17.9)	125 (17.1)
40+	16 (5.5)	25 (3.4)
Ethnicity		
White	234 (80.4)	594 (81.0)
Black	12 (4.1)	29 (4.0)
South Asian	39 (13.4)	95 (13.0)
Others	6 (2.1)	15 (2.0)
Parity		
0	167 (57.4)	296 (40.4)
1-2	92 (31.6)	386 (52.7)
3+	32 (11.0)	51 (7.0)
Level of Education		
Graduate Education	99 (34.0)	326 (31.8)
Further Education	112 (38.5)	278 (27.2)
Secondary education to 16 years	56 (19.2)	100 (9.8)
No formal educational qualification	23 (7.9)	29 (2.8)
Body Mass Index	Median 26.9 (15.4- 47.9)	Median 26.0 (15.41-48.6)
Cause of Stillbirth		
Acute Infection	13 (4.5)	
Fetal-maternal haemorrhage	6 (2.1)	
Fetal Growth Restriction	132 (45.2)	
Umbilical Cord Prolapse	1 (0.3)	
Constricting loop or knot of cord	10 (3.4)	
Placental abruption	19 (6.5)	
Vasa Praevia	1 (0.3)	
Placental Insufficiency	48 (16.4)	
Chorioamnionitis	6 (2.1)	
Uterine rupture	1 (0.3)	
Diabetes	9 (3.1)	
Obstetric Cholestasis	1 (0.3)	
Intrapartum asphyxia	1 (0.3)	
No relevant condition identified	42 (14.4)	

Table 2 – Association between caffeinated and soft drink consumption and late stillbirth. Multivariate analysis adjusted for maternal biometric factors (ethnicity, age, body mass index), maternal smoking, maternal education, parity, fetal factors (gestation, birthweight centile) and maternal use of dietary supplements (folic acid, iron, multivitamins, multivitamins for pregnancy, vitamin D, omega 3 and others) in the last month prior to stillbirth (cases) or interview (controls).

	Stillbirth (Average number of servings/day) or n (%)	Control (Average number of servings/day) or n(%)	Odds Ratio (95% Confidence Interval)	Adjusted Odds Ratio (95% Confidence Interval)	P value
Tea **(Number of servings/day)** *Mean 54.9mg/serving*	1.66 (0-14)	1.44 (0-15)	1.07 (0.99, 1.15)	0.96 (0.85, 1.08)	0.53
Diet Soft Drinks **(Number of servings/day)** *Mean 38.5mg/serving*	>1	>1	0.51 (0.10, 3.69)	0.17 (0.02, 1.68)	0.104
Chocolate **(Number of servings/day)** *Mean 10mg/serving*	0.49 (0-6)	0.50 (0-16)	1.00 (0.85, 1.15)	0.94 (0.73, 1.16)	0.62
Cola **(330ml serving / day)** *Mean 38.5mg/serving*	0.53 (0-8)	0.37 (0-12)	**1.13 (1.01, 1.28)**	**1.23 (1.03, 1.48)**	**0.025**
Instant Coffee **(Number of servings/day)** *Mean 81.5mg/serving*	0.41 (0-10)	0.26 (0-10)	**1.18 (1.02, 1.36)**	**1.34 (1.09, 1.71)**	**0.009**
Decaffeinated Coffee **(Number of servings/day)** *Mean 3.5mg/serving*	0.18 (0-5)	0.23 (0-7.5)	0.95 (0.88, 1.00)	0.94 (0.63, 1.28)	0.72

Drinking chocolate (Number of servings/day) *Mean 5.0mg/serving*	0.11 (0-4)	0.07 (0-2)	**1.54 (1.00, 2.37)**	1.97 (0.92, 4.03)	0.07
Green Tea (Number of servings/day) *Mean 27mg/serving*	0.09 (0-3)	0.07 (0-5)	1.10 (0.80, 1.50)	1.03 (0.64, 1.79)	0.93
Filter Coffee (Number of servings/day) *Mean 120.8mg/serving*	0.08 (0-3)	0.05 (0-5)	1.29 (0.85,1.96)	1.54 (0.83, 1.17)	0.21
Energy drinks (Number of servings/day) *Mean 103.9mg/serving*	0.09 (0-8)	0.02 (0-3)	**2.06 (1.26, 3.96)**	**1.85 (1.11, 3.58)**	**0.037**
Chai Tea (Number of servings/day) *Mean 100mg/serving*	0.04 (0-2)	0.02 (0-2.5)	1.31 (0.70, 2.38)	1.45 (0.50, 3.25)	0.47
Teaspoons of sugar (Number of servings/day)	2.1 (0-30)	1.47 (0-24)	**1.07 (1.02, 1.12)**	1.00 (0.93, 1.08)	0.94
Caffeine intake (increments of 100mg/day)	1.74 (0-10.75)	1.33 (0-9.62)	**1.21 (1.10, 1.33)**	**1.27 (1.14, 1.43)**	**0.004**
Exceeded WHO guidelines (300mg Caffeine/day)	44 (15.1%)	60 (8.3 %)	**1.96 (1.30, 2.99)**	**2.30 (1.40, 4.24)**	**0.008**
Participant reports changing	216 (74.0%)	582 (79.4%)	1.4 (0.97, 1.83)	1.11 (0.66, 1.51)	0.70

their caffeine intake during pregnancy					

Table 3 – Changes to maternal behaviour regarding consumption of drinks in pregnancy

Behaviour	Case (n=290) N (%)	Control (n=729) N (%)	Total (n=1019) N (%)	P value
Reduced caffeine / switched to decaffeinated drinks	149 (51.3)	409 (56.1)	558 (54.8)	
Increased intake caffeinated drinks	11 (3.8)	14 (1.9)	25 (2.5)	0.12
No change to caffeinated drinks	130 (44.8)	306 (42.0)	436 (42.8)	
Reduced fizzy drinks (e.g. Cola, Soda)	4 (1.4)	12 (1.6)	16 (1.6)	
Increased fizzy drinks (e.g. Cola, Soda)	2 (0.7)	6 (0.8)	8 (0.8)	0.93
No change to fizzy drinks	284 (97.9)	711 (97.5)	995 (97.6)	

Table 4 – Sources of information reported to have led to altered behaviour regarding consumption of drinks in pregnancy.

Source of Information	**Case (n=290) N (%)**	**Control (n=729) N (%)**	**Total (n=1,019)**	**P value**
Midwife	54 (18.6)	156 (21.4)	210 (20.1)	
General Practitioner / Family doctor	9 (3.1)	15 (2.1)	24 (2.4)	
Hospital doctor	7 (2.4)	16 (2.2)	23 (2.3)	
Relative	21 (7.2)	61 (8.4)	82 (8.0)	0.78
Internet	42 (14.5)	96 (13.2)	138 (13.5)	
Magazine	6 (2.1)	28 (3.8)	34 (3.3)	
Pregnancy book	23 (7.9)	53 (7.3)	76 (7.5)	
Television	4 (1.4)	11 (1.5)	15 (1.5)	
None given	124 (42.8)	293 (40.2)	417 (40.9)	

Supplementary Figure 1

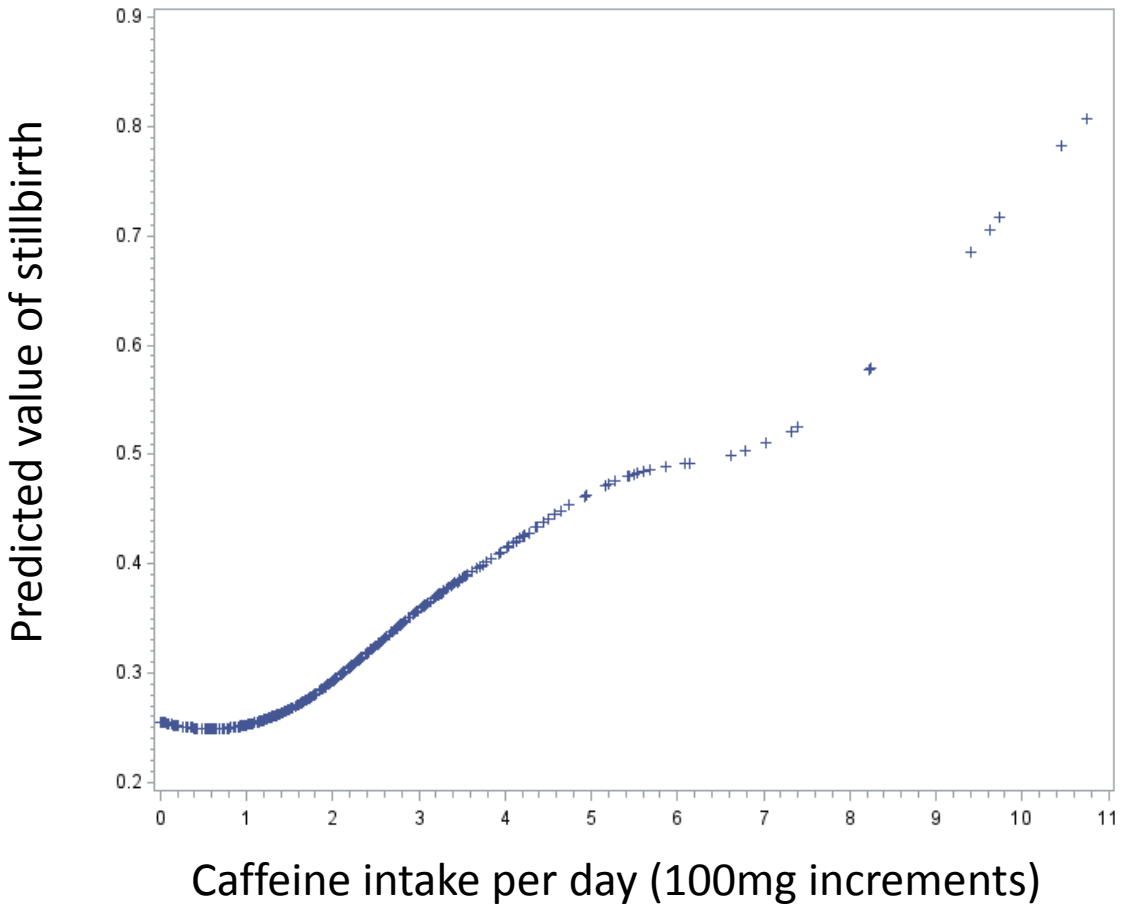
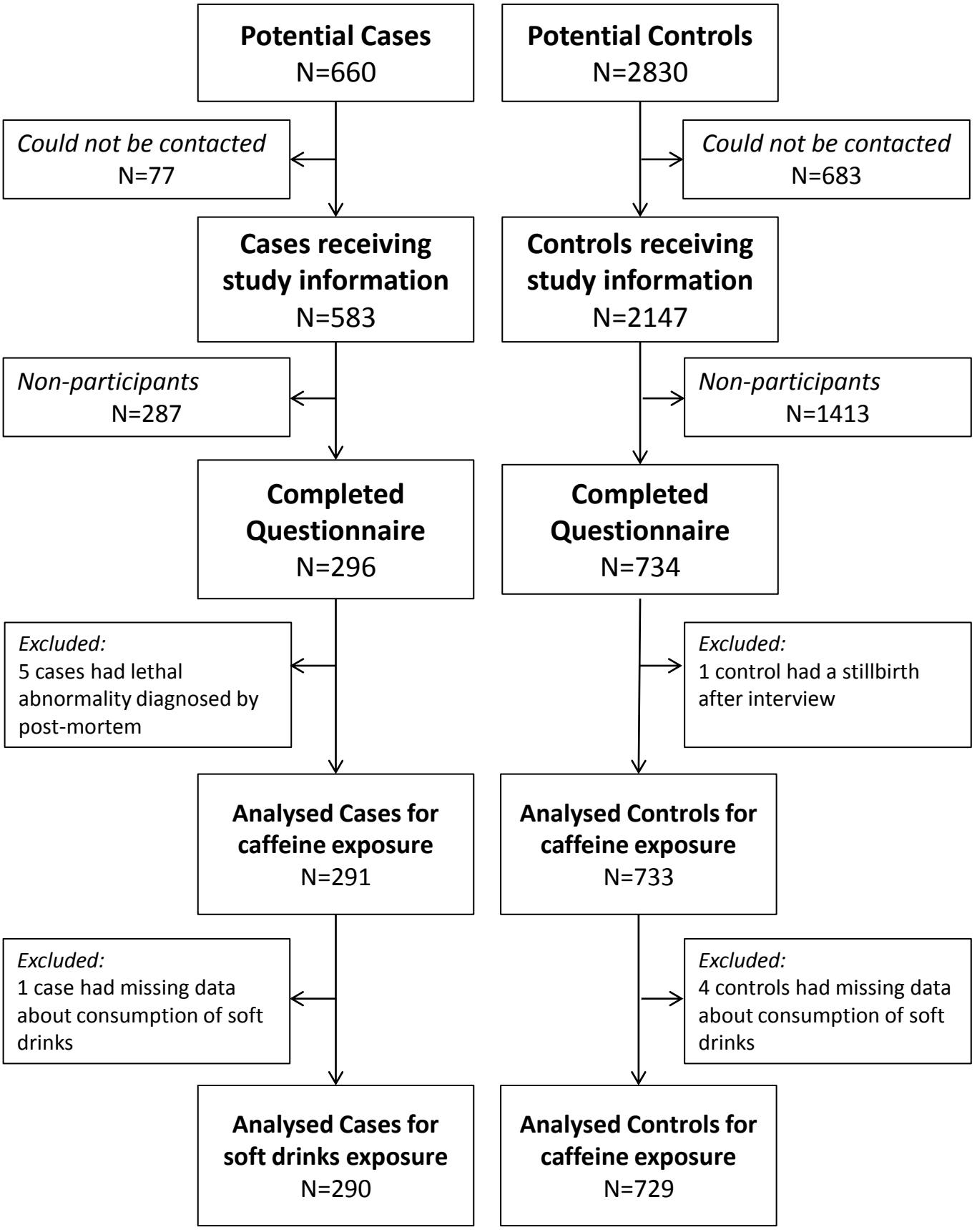


Figure 1

Figure 1 - Flow diagram reporting the numbers of women eligible for the study, women who did not participate and those included in the final analysis of social and demographic characteristics.



***Conflict of Interest**

Declaration of interests

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

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

STROBE Statement—Checklist of items that should be included in reports of ***case-control studies***

	Item No	Recommendation	Location
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Page 1 Lines 1-2 + Page 3 Line 36
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 3-4 Lines 30-54
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 5 Lines 60-79
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 5 Lines 77-79
Methods			
Study design	4	Present key elements of study design early in the paper	Page 5-7 Lines 80-114
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 5-6 Lines 80-97 and Ref #6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	Page 6 Lines 85-92 and Ref #6
		(*b*) For matched studies, give matching criteria and the number of controls per case	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 6 Lines 85-95
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page 6 Lines 85-97
Bias	9	Describe any efforts to address potential sources of bias	Page 6 Lines 93-95 and Page 9 Lines 171-173
Study size	10	Explain how the study size was arrived at	In Ref #6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	N/A
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page 6-7 Lines 99 – 114
		(*b*) Describe any methods used to examine subgroups and interactions	N/A
		(*c*) Explain how missing data were addressed	N/A
		(*d*) If applicable, explain how matching of cases and controls was addressed	N/A

			(*e*) Describe any sensitivity analyses	N/A
Results				
Participants		13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Page 7 Lines 116-124, Figure 1 and Ref #12
			(b) Give reasons for non-participation at each stage	See above
			(c) Consider use of a flow diagram	Figure 1
Descriptive data		14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Page 7 Lines -124-126 & in Ref #12
			(b) Indicate number of participants with missing data for each variable of interest	Page 7 Lines 122-124 Table 1
Outcome data		15*	Report numbers in each exposure category, or summary measures of exposure	Page 7 Line 123
Main results		16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 1 Page 7-8 Lines 127-136
			(*b*) Report category boundaries when continuous variables were categorized	N/A
			(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses		17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion				
Key results		18	Summarise key results with reference to study objectives	Page 9 Lines 159-166
Limitations		19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page 9 Lines 168-174
Interpretation		20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 9-11 Lines 176-215
Generalisability		21	Discuss the generalisability (external validity) of the study results	Page 11-12 Lines 217-233
Other information				
Funding		22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 14 Lines 285-287

*Give information separately for cases and controls.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

Associations between Consumption of Coffee and Caffeinated Soft Drinks and Late Stillbirth – Findings from the Midland and North of England Stillbirth Case-Control Study

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Abstract

Objective – The consumption of caffeinated drinks and soft drinks is widespread in society, including by pregnant women. Data regarding the association of caffeine intake and stillbirth are varied. We aimed to investigate the degree of consumption of caffeinated drinks or soft drinks in the last four weeks of~~during~~ pregnancy in women who experienced a late stillbirth compared to women with ongoing live pregnancies at similar gestation. Influences on maternal caffeine intake and soft drink consumption during pregnancy were also investigated.

Study Design – A case-control study undertaken in 41 maternity units in the United Kingdom. Cases were women who had a singleton non-anomalous stillbirth ≥28 weeks' gestation (n=290) and controls were women with an ongoing pregnancy at the time of interview (n=729). Data were collected using an interviewer-administered questionnaire which included questions regarding consumption of a variety of caffeinated~~cafffeinated~~ drinks and soft drinks in the last four weeks of pregnancy as well as other behaviours (e.g. cigarette smoking).

Results - Multivariable analysis adjusting for co-existing demographic and behavioural factors found the consumption of instant coffee, energy drinks and cola were associated with increased risk of stillbirth. There was an independent association between caffeine intake and late stillbirth (adjusted Odds Ratio 1.27, 95% Confidence Interval (95%CI) 1.14, 1.43 for each 100mg increment/day). 15% of cases and 8% of controls consumed more than the World Health Organisation (WHO) recommendation (>300mg of caffeine/day; aOR 2.30, 95% CI 1.40, 4.24). The population attributable risk for stillbirth associated with >300mg of caffeine/day was 7.4%. The majority of respondents reduced caffeine consumption in pregnancy. Midwives and internet resources were the most frequently used sources of information which influenced maternal behaviour with regard to soft drinks and caffeine, and this did not differ between cases and controls.

Conclusions – Women should be informed that consumption of caffeine during pregnancy is associated with increased risk of stillbirth, particularly at levels greater than recommended by the

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WHO (>300mg/day). Recommendations from midwives and internet-based resources are likely to be the most effective means to influence maternal behaviour.

Keywords

Caffeine, Perinatal Death, Stillbirth, Cola, Sweetened Soft Drinks.

Introduction

Stillbirth is an important public health problem with enduring impact not only in terms of lives lost but also with economic, psychological and social impacts upon affected families.[1,2] One approach to reducing stillbirth is to identify factors associated with increased risk so that their effects may be reduced. Epidemiological studies have identified risk factors for stillbirth, some of which are modifiable (e.g. cigarette smoking, drug misuse) and others which are not (e.g. maternal age, ethnicity).[3] ~~Critically, only 19% of cases have established risk factors present at antenatal booking which hampers efforts to prevent stillbirth.~~[4]

The Stillbirth Priority Setting Partnership identified a research need to ascertain modifiable risk factors for late stillbirth.[5] The Midland and North of England Stillbirth Study (MiNESS) was a case control study ~~conducted from 2014-2016~~ which aimed to identify modifiable risk factors for late stillbirth (≥28 weeks' gestation).[6] Due to their ubiquitous consumption, 80% of the UK population drinks instant coffee and on average 211.5 litres of soft drinks (many of which contain high levels of caffeine) were consumed per capita per year.[6,7] Accordingly, this study included questions about intake of caffeinated drinks and soft drinks during pregnancy. To date, the evidence linking caffeine intake and stillbirth shows variable effect size and some studies focus on coffee consumption rather than consumption of any source of caffeine.[8-10] Presently, the World Health Organisation recommends that high caffeine intake (>300mg/day) is decreased to reduce the risk of pregnancy loss and the National Health Service recommends caffeine intake is <200mg/day during pregnancy.[11] Given that caffeinated drinks, are widely consumed we aimed to investigate whether there is a relationship between consumption of these beverages and the risk of late stillbirth.

Methods

MiNESS was a prospective case-control study undertaken in 41 secondary and tertiary maternity units in the UK.[6] The methodology has been described in detail previously and was conducted in

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accordance with the published protocol.[5,11] Following;[12] ~~briefly, following~~ ethical approval (Ref 13/NW/0174) and study registration (NCT02025530) participants were recruited between April 2014 and March 2016. ~~The study was conducted in accordance with the published protocol.~~ Cases were singleton stillbirths occurring ≥28 weeks' gestation with no evidence of congenital anomaly. Women who had a multiple pregnancy, who could not consent or who were <16 years of age were excluded. Controls were mothers who had an ongoing singleton pregnancy with no evidence of congenital anomaly. To achieve a similar distribution of gestational age between groups, controls were frequency matched to the distribution of stillbirths in the preceding four years at that maternity unit. Potential~~, potential~~ control participants were randomly selected from the booking lists and gestation for interview calculated; interviews for controls were contemporaneous with those for cases.

~~.~~ Information was collected by an interviewer-administered ~~a~~ questionnaire and extracted from the mother's medical records; interviewers were not blinded to participants' status.~~administered by clinically trained researchers.~~ This questionnaire included a wide range of self-reported social and demographic characteristics as well as behaviours. This included the frequency of intake in the preceding four weeks for different drinks including servings of coffee, tea, chocolate, cola, energy drinks and also recorded the sugar added to drinks ~~in the preceding month~~ as a potential confounding factor. In addition, respondents were asked whether they had altered their consumption of drinks during their pregnancy and if so, whether this was due to any advice and the sources of advice. The median gestation at interview for controls was 36 weeks 3 days (Interquartile Range (IQR) 32 weeks 6 days to 38 weeks 5 days). The median gestation at diagnosis of stillbirth was 37 weeks 4 days (IQR 33 weeks 4 days to 39 weeks 5 days) and the median time between diagnosis of stillbirth and the interview was 25 days (IQR 17-35).

Exposure Assessment

Total caffeine consumption per day was calculated based upon the reported frequency of consumption for instant coffee (81.5mg/serving), brewed/filter coffee (120.8mg/serving),

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decaffeinated coffee (3.5mg/serving), tea (54.9mg/serving), chai tea (100mg/serving), green tea (27mg/serving), drinking chocolate (5mg/serving), eating chocolate (10mg/serving), energy drinks (103.9mg/serving) and cola (38.5mg/serving). These values were derived from searching established sources of data and where possible a mean value taken.[12-14] Caffeine consumption was assessed as continuous variable and categorically defined as individual servings of each drink / source of caffeine.

Statistical Methods

All statistical analyses were performed in R 3.6.2. Univariable logistic regression was initially carried out to determine the association between stillbirth and daily average consumption of each drink for which data were collected in the last month prior to stillbirth (cases) or interview (controls) as part of a univariable analysis. Drinks~~Consumption of solid chocolate was included due to its caffeine content. Total caffeine consumption per day was calculated based upon the reported frequency of consumption for instant coffee (81.5mg/serving), brewed/filter coffee (120.8mg/serving), decaffeinated coffee (3.5mg/serving), tea (54.9mg/serving), chai tea (100mg/serving), green tea (27mg/serving), drinking chocolate (5mg/serving), eating chocolate (10mg/serving), energy drinks (103.9/serving)~~ and ~~cola (38.5mg/serving). These values were derived from searching established~~ sources of caffeine were included individually in the ~~data and where possible a mean value taken.[13-15] Drinks which reached or neared statistical significance (p<0.1) in the univariable analysis were included in~~ multivariable analysis to adjust~~which also adjusted~~ for maternal biometric factors (ethnicity, age, body mass index), maternal smoking, maternal education, parity, fetal factors (gestation, birthweight centile) and maternal use of dietary supplements (folic acid, iron, multivitamins, multivitamins for pregnancy, vitamin D, omega 3 and others) in the last month prior to stillbirth (cases) or interview (controls). Chi-squared tests~~Descriptive statistics~~ were used to analyse changes in maternal behaviour and influences on behaviour.

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Results

During the recruitment period, 3490 women were identified as potentially eligible participants for MiNESS (660 cases and 2830 controls, Figure 1)~~,~~. ~~)~~760 women could not be contacted (77 cases (11%), and 683 controls (24%)) and 1700 women did not consent to participate (287 cases (43%) and 1413 controls (50%)). Six participants were excluded after data collection as five stillbirths had previously unidentified congenital abnormalities detected on post-mortem and one control participant had a stillbirth. Thus, there were 296 (44%) cases and 734 (26%) controls in the study population. Women who had a stillbirth were more likely to participate than controls (p<0.0001). Data on ~~caffeinated drink and~~ soft drink consumption was available on 290 cases and 729 controls (99.7% of cases and 99.4% of participants included in analysis of the main study respectively; Figure 1).

Detailed information about participants has been reported previously.[12] Briefly, the majority of participants, 80.4% of cases and 81% of controls, were of white ethnicity (Table 1), with a significant proportion of participants of South Asian (13.4% of cases and 13.0% controls) and Black ethnic groups (4.1% of cases and 4.0% of controls). Participants' ages were distributed from <20 years to over 40 years, with the largest group between 30-34 years of age in both groups (29.6% cases, 36.6% controls). The majority of women, 57.4% of cases and 40.4% of controls, were primiparous. There was no difference in mean body mass index (Cases 26.9 kg/m^2, Controls 26.0 kg/m^2). Stillbirth were most frequently associated with fetal growth restriction (45.2% of cases), placental insufficiency (16.4%), placental abruption (6.5%) or acute infection (4.5%).

The frequency of exposure to each type of drink, chocolate or sugar intake and their univariable odds ratios (OR) for their association with stillbirth are presented in Table 2~~1~~. In the univariable analysis, the following variables were associated with stillbirth: caffeine intake per 100mg, cola, instant coffee, drinking chocolate, energy drinks and supplementary sugar in the preceding month. 62.8% of cases and 56.3% of controls had ≥100mg of caffeine per day, and a smaller proportion, 15.1% of cases and 8.3% of controls reported ~~an~~ intake in excess of the WHO recommendations (>300mg per day).[11] When multivariable ~~Multivariable~~ analysis was performed intake~~to adjust for~~

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~~the effects of maternal biometric factors (ethnicity, age, body mass index), maternal smoking, maternal education, parity, use of dietary supplements and fetal factors (gestation, birthweight centile). Intake~~ of cola (aOR 1.23, 95% CI 1.03, 1.48), instant coffee (aOR 1.34, 95% CI 1.09-1.71) and energy drinks (aOR 1.85, 95% CI 1.11, 3.58) were all independently associated with increased risk of stillbirth. We fitted a generalized additive model (GAM) and found the relationship between caffeine intake and stillbirth to be of a linear nature, no threshold level of association was observed (Supplementary File 1). For each 100mg caffeine intake the adjusted Odds Ratio (aOR) was 1.27 (95% Confidence Interval (95% CI) 1.14, 1.43). Caffeine intake greater than 300mg/day was associated with stillbirth aOR 2.30 (95% 1.40-4.24); the population attributable risk associated with this level of consumption was 7.4%. There was no relationship between caffeine intake and sleep duration in the preceding month (R=-0.01, p=0.78), but there was a weak negative relationship between caffeine intake and birthweight (R=-0.09, p=0.003).

In total, 607 women reported making alterations to their consumption of caffeinated and/or soft drinks during their pregnancy, 166 who had a stillbirth and 441 controls. The~~There was no difference in the~~ proportion of women who altered their caffeine consumption did not differ between cases and controls (Table 3), in both groups the~~1). The~~ majority of women who altered their consumption reported ~~reducing their caffeine intake by~~ either reducing consumption of coffee, tea or energy drinks or changing to decaffeinated drinks (Table 3, 51~~2, 50~~.3% of cases, 56.1~~55.7~~% of controls). In contrast, 3.8% of cases and 1.9% of controls increased their caffeine intake during pregnancy. With regard to fizzy drinks such as cola or soda, 1.4% of cases and 1.6% of controls reduced their intake and a smaller group of 0.7% of cases and 0.8% of controls increased their intake of this type of drinks. Most women made changes to their diet and caffeine intake following advice from a midwife (18.6% of cases and 21.4% of controls, Table 3). The next most frequently used source of information to change behaviour was the internet, pregnancy books and relatives, with a minority of women receiving advice from their family or hospital doctor.

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Discussion

This study found an association between caffeine intake and late stillbirth; this appears to be mediated through an increased intake of instant coffee, cola and energy drinks in cases compared to controls. Tea consumption, the most widely consumed caffeinated drink (1.44 servings/day in controls) did not differ between cases and controls~~, however is the major contributor to caffeine intake in both groups.~~ Although the majority of participants (54.5%) reduced their caffeine intake during pregnancy, a small proportion (3%) increased it and over 15% of cases and 8% of controls consumed more than the WHO recommended limit of 300mg caffeine/day. Midwives and the internet were the most commonly used sources of information leading to change in maternal behaviour.

Strengths and Limitations

This study was strengthened by obtaining information about all possible sources of caffeine intake, not just coffee. Nevertheless, other sources of caffeine e.g. headache medication were not included, meaning caffeine consumption may have been underestimated. As there ~~However, there~~ is no standard calculation for the caffeine content of drinks ~~so~~ average values were taken from different reliable sources.[13-15] The study was also strengthened by asking whether women's behaviour had changed during pregnancy; and if so, ~~what were~~ the sources of information that had driven this change. This study is limited by self-reported caffeine intake which may have led to errors in measurement of caffeine intake or recall bias, where women who had a stillbirth may recall exposures differently. However, there was no information about hypotheses regarding diet or caffeine intake in the study materials. There is also the potential for reverse causality i.e. caffeine consumption increased due to undetected fetal demise. However, this effect is likely small as the mean duration between diagnosis of stillbirth and presumed time of fetal death was always <7 days.

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Significance of the association between caffeine consumption and stillbirth

~~To understand whether the association between caffeine intake and stillbirth is likely to be causal, we have applied the Bradford-Hill Criteria.[16] The association is only moderately strong, but the effect size of exceeding the WHO recommended amount of caffeine in pregnancy (≥300mg/day)[11] was consistent with other studies (aOR 2.30) and there appears to be a biological gradient, as each increment of 100mg/day of caffeine was associated with a 27% increase in the risk of stillbirth. The association was linear, meaning that we were unable to generate a threshold value over which risk increases markedly.~~ The temporal relationship between caffeine consumption is appropriate (i.e. To understand whether the association between caffeine intake and stillbirth is likely to be causal, we have applied the Bradford-Hill Criteria.[15] The association is only moderately strong, exceeding the WHO recommendation of <300mg/day has an aOR 2.30. Critically, the findings of this study are in agreement with the majority of studies investigating the effect of caffeine on pregnancy; a review of found 32 out of 42 studies reported caffeine increased the risk of miscarriage, stillbirth or low birth weight and/or small for gestational age neonate, with 10 studies reporting no or inconclusive associations.[16] There appears to be a biological gradient, as each increment of 100mg/day of caffeine was associated with a 27% increase in the risk of stillbirth, which is consistent with an early UK study conducted in 2004-2006 which demonstrated increased risk of stillbirth with increasing intake of caffeine.~~exposure to caffeine precedes the outcome) and interestingly, the risk to fetal growth and increased risk of pregnancy loss may extend to high periconceptual caffeine consumption.~~[17] In our population, the association was linear, meaning that we were unable to generate a threshold value over which risk increases markedly. ~~An association between caffeine consumption and stillbirth is analogous to the association of caffeine consumption with early miscarriage, neonatal death and sudden infant death syndrome ,The temporal relationship between caffeine consumption is appropriate (i.e. exposure to caffeine precedes the outcome) and interestingly, the risk to fetal growth and increased risk of pregnancy loss may extend to high periconceptual caffeine consumption.[8,18]~~ An association between caffeine consumption and stillbirth is analogous to the

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association of caffeine consumption with early miscarriage, neonatal death and sudden infant death syndrome ,[7,19] although the neonatal death also may relate to cigarette smoking, maternal age, education and parity.[20] ~~although the neonatal death also may relate to cigarette smoking, maternal age, education and parity.[19]~~

The association between caffeine consumption is biologically plausible, caffeine readily crosses the placenta with poor fetal clearance (levels are 30 times greater in the fetus than the mother).[20,21] Caffeine is metabolised ~~to paraxanthine, theophylline and theobromine~~ by CYP1A2, the activity of which decreases by 65% in the third trimester,[23~~22~~] resulting in an increase in the half-life of caffeine from 3 hours in non-pregnant women to 10.5 hours in the third trimester ~~of pregnancy~~.[22~~21~~] High maternal caffeine intake increases~~may increase~~ placental vasoconstriction and fetal catecholamine levels, potentially~~thus~~ impairing fetal growth ~~and oxygenation~~.[24~~23~~] In agreement, we observed a weak negative correlation between caffeine intake and birthweight. However~~, however~~, another study of 100 women found no relationship between caffeine consumption and birthweight ~~or neonatal length, head or chest circumference~~, although only 2 participants had daily caffeine intake >200mg~~, limiting the conclusions which can be drawn the effect of excessive caffeine consumption and fetal growth~~.[24] High ~~In addition, high~~ consumption of caffeine, especially in energy drinks, is associated with cardiac arrhythmias which can be fatal.[25] In an animal model, in utero exposure to caffeine alters gene expression in ~~embryonic~~ cardiomyocytes and the embryonic response to hypoxia.[26,27] Furthermore, exposure to energy drinks during pregnancy induces oxidative damage in fetal liver, kidney and brain in a murine model.[28] These experimental observations suggest excessive caffeine could lead to adverse fetal outcome.

It is important to note that other constituents of beverages may also be responsible for the observed associations with stillbirth. Sugar-sweetened soft drinks (such as cola) have been previously reported to be associated with poorer maternal diet quality[29] and increased risk of maternal obesity,[30] gestational diabetes,[32~~31~~] preterm birth,[32] pre-eclampsia [33] and congenital heart defects.[34] Energy

drinks are often supplemented with taurine, which is positively correlated with fetal size, and could augment the effect of sugar on fetal macrosomia.[36~~35~~] Conversely, taurine supplementation is associated with reduced birthweight and increased neonatal mortality in rats~~rat pregnancies~~.[36,37] Finally, the effects of sugar substitutes used in soft drinks are largely unknown; aspartame decreases placental weight, impairs normal placental structure and increases rates of fetal growth restriction.[38,39] ~~Although saccharin crosses to the fetus, it's direct effects on the placenta are unknown.~~ As soft drinks are frequently consumed by pregnant women, further~~scientific~~ studies are needed to determine whether caffeine, taurine or sweeteners exert direct negative effects on the placenta and/or fetus.

Clinical Implications

Our findings suggest that women should be advised to reduce their caffeine consumption during pregnancy. Women are likely already receiving some messaging; as in common with earlier studies we found the majority of participants reduced their caffeine consumption.[40,41] Although, WHO recommend limiting caffeine consumption, this is not reflected in the UK antenatal guidelines for uncomplicated pregnancies[43] and~~.[42] Importantly, studies show that~~ caffeine consumption is infrequently mentioned in antenatal consultations.[43]

Based on our findings, midwives may be best placed to deliver information about safe caffeine consumption and to signpost women to further online resources. This agrees~~Previous research yielded similar findings,~~ with prior studies of maternal diet which found advice from healthcare professionals and the internet were~~, amongst~~ the most widely used sources of information.[44,45] Thus, combining~~ Combining~~ these two approaches may enhance communication and information provision which may increase adherence to recommendations. In addition, when delivering information to women about caffeine consumption, it is important ~~for midwives~~ to ensure that underpinning reasons for the recommendations are adequately explained, as messages about associated risks are often not communicated effectively.[46,47] Perceiving a low level of associated risk

may act as a barrier to carrying out the target behaviour,[47~~46~~] therefore training midwives and other health care professionals in effectively communicating information about the risks of caffeine consumption during pregnancy may improve women's adherence to advice.

Conclusions

This study demonstrates an independent association between caffeine consumption and stillbirth after 28 weeks' gestation. As there is also an increased risk of early pregnancy loss and neonatal deaths reported with excessive caffeine consumption, clinicians should be aware of these associations and women should be informed about the benefits of reducing caffeine consumption in pregnancy. The most effective means is likely to be via interaction with midwives accompanied by signposting to internet-based resources.

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Disclosure of Interests

All authors declare that they have no competing interests.

Contribution to Authorship

AH, TS, BM, DR, EM & LM contributed to all aspects of the study design and obtained funding. AH had overall responsibility for the study. JB coordinated the running of the study. KT and LR analysed the data with input from AH. All authors were responsible for the drafting of the manuscript. All authors gave approval for the final version of the manuscript.

Details of Ethical Approval

This study was reviewed by NRES Committee North West - Greater Manchester Central Reference (13/NW/0874) on 24th January 2014.

335 **Data Sharing Statement**

336 No additional data from the MiNESS study are available from a repository. Anonymised data is
337 available on request to the corresponding author.

338

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Figure Legends

Figure 1 - Flow diagram reporting the numbers of women eligible for the study, women who did not participate and those included in the final analysis of caffeine and soft drink consumption.

Supplementary Figure 1 – Output from Generalized Additive Model (GAM) showing the relationship between caffeine intake and probability of stillbirth has a close to linear relationship.

Table 1 – Demographic characteristics and sleep practices in 291 women who had a late stillbirth compared to 734 controls who participated in MiNESS. Data are presented as the number (percentage) or median (interquartile range).

Characteristic	Case (n=291)	Control (n=734)
Age (years)		
<20	7 (2.4)	15 (2.0)
20-24	48 (16.5)	81 (11.1)
25-29	82 (28.2)	219 (29.9)
30-34	86 (29.6)	268 (36.6)
35-39	52 (17.9)	125 (17.1)
40+	16 (5.5)	25 (3.4)
Ethnicity		
White	234 (80.4)	594 (81.0)
Black	12 (4.1)	29 (4.0)
South Asian	39 (13.4)	95 (13.0)
Others	6 (2.1)	15 (2.0)
Parity		
0	167 (57.4)	296 (40.4)
1-2	92 (31.6)	386 (52.7)
3+	32 (11.0)	51 (7.0)
Level of Education		
Graduate Education	99 (34.0)	326 (31.8)
Further Education	112 (38.5)	278 (27.2)
Secondary education to 16 years	56 (19.2)	100 (9.8)
No formal educational qualification	23 (7.9)	29 (2.8)
Body Mass Index	Median 26.9 (15.4- 47.9)	Median 26.0 (15.41-48.6)
Cause of Stillbirth		
Acute Infection	13 (4.5)	
Fetal-maternal haemorrhage	6 (2.1)	
Fetal Growth Restriction	132 (45.2)	
Umbilical Cord Prolapse	1 (0.3)	
Constricting loop or knot of cord	10 (3.4)	
Placental abruption	19 (6.5)	
Vasa Praevia	1 (0.3)	
Placental Insufficiency	48 (16.4)	
Chorioamnionitis	6 (2.1)	
Uterine rupture	1 (0.3)	
Diabetes	9 (3.1)	
Obstetric Cholestasis	1 (0.3)	
Intrapartum asphyxia	1 (0.3)	
No relevant condition identified	42 (14.4)	

Table 2 – Association between caffeinated and soft drink consumption and late stillbirth. Multivariate analysis adjusted for maternal biometric factors (ethnicity, age, body mass index), maternal smoking, maternal education, parity, fetal factors (gestation, birthweight centile) and maternal use of dietary supplements (folic acid, iron, multivitamins, multivitamins for pregnancy, vitamin D, omega 3 and others) in the last month prior to stillbirth (cases) or interview (controls).

	Stillbirth (Average number of servings/day) or n (%)	Control (Average number of servings/day) or n(%)	Odds Ratio (95% Confidence Interval)	Adjusted Odds Ratio (95% Confidence Interval)	P value
Tea **(Number of servings/day)** *Mean 54.9mg/serving*	1.66 (0-14)	1.44 (0-15)	1.07 (0.99, 1.15)	0.96 (0.85, 1.08)	0.53
Diet Soft Drinks **(Number of servings/day)** *Mean 38.5mg/serving*	>1	>1	0.51 (0.10, 3.69)	0.17 (0.02, 1.68)	0.104
Chocolate **(Number of servings/day)** *Mean 10mg/serving*	0.49 (0-6)	0.50 (0-16)	1.00 (0.85, 1.15)	0.94 (0.73, 1.16)	0.62
Cola **(330ml serving / day)** *Mean 38.5mg/serving*	0.53 (0-8)	0.37 (0-12)	**1.13 (1.01, 1.28)**	**1.23 (1.03, 1.48)**	**0.025**
Instant Coffee **(Number of servings/day)** *Mean 81.5mg/serving*	0.41 (0-10)	0.26 (0-10)	**1.18 (1.02, 1.36)**	**1.34 (1.09, 1.71)**	**0.009**
Decaffeinated Coffee **(Number of servings/day)** *Mean 3.5mg/serving*	0.18 (0-5)	0.23 (0-7.5)	0.95 (0.88, 1.00)	0.94 (0.63, 1.28)	0.72

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Drinking chocolate (Number of servings/day) *Mean 5.0mg/serving*	0.11 (0-4)	0.07 (0-2)	**1.54 (1.00, 2.37)**	1.97 (0.92, 4.03)	0.07
Green Tea (Number of servings/day) *Mean 27mg/serving*	0.09 (0-3)	0.07 (0-5)	1.10 (0.80, 1.50)	1.03 (0.64, 1.79)	0.93
Filter Coffee (Number of servings/day) *Mean 120.8mg/serving*	0.08 (0-3)	0.05 (0-5)	1.29 (0.85,1.96)	1.54 (0.83, 1.17)	0.21
Energy drinks (Number of servings/day) *Mean 103.9mg/serving*	0.09 (0-8)	0.02 (0-3)	**2.06 (1.26, 3.96)**	**1.85 (1.11, 3.58)**	**0.037**
Chai Tea (Number of servings/day) *Mean 100mg/serving*	0.04 (0-2)	0.02 (0-2.5)	1.31 (0.70, 2.38)	1.45 (0.50, 3.25)	0.47
Teaspoons of sugar (Number of servings/day)	2.1 (0-30)	1.47 (0-24)	**1.07 (1.02, 1.12)**	1.00 (0.93, 1.08)	0.94
Caffeine intake (increments of 100mg/day)	1.74 (0-10.75)	1.33 (0-9.62)	**1.21 (1.10, 1.33)**	**1.27 (1.14, 1.43)**	**0.004**
Exceeded WHO guidelines (300mg Caffeine/day)	44 (15.1%)	60 (8.3 %)	**1.96 (1.30, 2.99)**	**2.30 (1.40, 4.24)**	**0.008**
Participant reports changing	216 (74.0%)	582 (79.4%)	1.4 (0.97, 1.83)	1.11 (0.66, 1.51)	0.70

their caffeine intake during pregnancy					

Table 32 – Changes to maternal behaviour regarding consumption of drinks in pregnancy

Behaviour	Case (n=290) N (%)	Control (n=729) N (%)	Total (n=1019) N (%)	P value
Reduced caffeine / switched to decaffeinated drinks	149 (51.3)	409 (56.1)	558 (54.85)	0.12
Increased intake caffeinated drinks	11 (3.8)	14 (1.9)	25 (2.5)	
No change to caffeinated drinks	130 (44.8)	306 (42.0)	436 (42.8)	
Reduced fizzy drinks (e.g. Cola, Soda)	4 (1.4)	12 (1.6)	16 (1.6)	0.93
Increased fizzy drinks (e.g. Cola, Soda)	2 (0.7)	6 (0.8)	8 (0.8)	
No change to fizzy drinks	284 (97.9)	711 (97.5)	995 (97.6)	

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Table 43 – Sources of information reported to have led to altered behaviour regarding consumption of drinks in pregnancy.

Source of Information	Case (n=290) N (%)	Control (n=729) N (%)	Total (n=1,019)	P value
Midwife	54 (18.6)	156 (21.4)	210 (20.1)	0.78
General Practitioner / Family doctor	9 (3.1)	15 (2.1)	24 (2.4)	
Hospital doctor	7 (2.4)	16 (2.2)	23 (2.3)	
Relative	21 (7.2)	61 (8.4)	82 (8.0)	
Internet	42 (14.5)	96 (13.2)	138 (13.5)	
Magazine	6 (2.1)	28 (3.8)	34 (3.3)	
Pregnancy book	23 (7.9)	53 (7.3)	76 (7.5)	
Television	4 (1.4)	11 (1.5)	15 (1.5)	
None given	124 (42.8)	293 (40.2)	417 (40.9)	

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