Coffee and Smoking as Risk Factors of Twin Pregnancies: The Danish National Birth Cohort

Maria M. Morales-Suárez-Varela,[1,2,6] Bodil Hammer Bech,[3] Kaare Christensen[4] and Jorn Olsen[3,5]

[1] Unit of Public Health and Environmental Care. Department of Preventive Medicine. University of Valencia, Spain
[2] Unit of Clinical Epidemiology, Dr. Peset University Hospital, Valencia, Spain
[3] The Danish Epidemiology Science Centre, University of Aarhus, Denmark
[4] Institute of Public Health, Epidemiology, University of Southern Denmark, Odense, Denmark
[5] Department of Epidemiology, School of Public Health, University of California Los Angeles, United States of America
[6] Research group CIBER CB06/02/0045, CIBER actions — Epidemiology and Public Health, Valencia, Spain

Twinning rates have changed substantially over time for reasons that are only partly known. In this study we studied smoking, coffee and alcohol intake, and their possible interaction with obesity as potential determinants of twinning rates using data from the Danish National Birth Cohort between 1996 and 2002. We identified 82,985 pregnancies: 81,954 singleton and 1031 twins. For the twins we had data to classify 121 as monozygotic, 189 dizygotic (same sex), 313 dizygotic (opposite sex) but, 408 were of the same sex but with unknown zygosity. All mothers were interviewed about their prepregnancy weight and height, coffee and alcohol intake, smoking habits, and potential confounding factors at early stages of pregnancy. We identified smoking (> 10 cigarettes/day) as a possible determinant of twinning, particularly for dizygotic twinning rates (same sex) and furthermore corroborated that obesity and the mother's age are strong correlates of twinning. Others have found coffee intake to increase twinning rates but that is not seen in these data.

Changes in the frequency of dizygotic (DZ) twins are among the best documented alterations in reproductive health in the second half of the last century (Belaisch-Allart et al., 1995; Botting et al., 1987). DZ twins declined over time in Denmark and in many other countries (Elwood, 1973; MacGillivray, 1970; Olsen et al., 1988) until the increasing use of certain types of infertility treatment changed that trend and the decline in natural twinning may even have stopped (Herskind et al., 2005). We do not know the causes of these changes in DZ twinning rates, nor do we know much in general about the determinants of DZ twinning, except that age and ethnicity play a role (Nylander, 1983). DZ twinning has been viewed as a marker of both reproductive failures and high fecundity (Bulmer, 1959; Eriksson & Fellman, 1967; Nylander, 1975; Pollard, 1969) and the decline in DZ twinning has been interpreted as a sign of declining fecundity. Monozygotic (MZ) twinning rates tend to remain constant over time.

Common lifestyle factors are the best causal candidates for these substantial changes in DZ twinning over time. Smoking, coffee intake, obesity and alcohol habit have increased in many countries as a result of female emancipation and related changes in lifestyles. Some of these factors have decreased again as people realized that these exposures may cause harm to the unborn child (Kapidaki et al., 1995; Parazzini et al., 1996). Dietary factors and physical activity have also changed over time (Flegal et al., 2002; Seidell & Flegal, 1997) followed by a widespread increase in obesity, especially in developed countries (Basso et al., 2004). In Denmark, the proportion of women with a body mass index (BMI) of 30 or more in the general population increased from 5.5% in 1987 to 9.5% in 2000 (Basso et al., 2004).

Caffeine and nicotine are among the most frequently used, self-administered, legal psychoactive drugs in western countries (Knight et al., 2004; Olsen et al., 1988), and caffeine is being consumed by a large part of the population (Bunker & McWilliams, 1979), with an average caffeine intake between 70 to 76 mg/person/day worldwide (Gilbert, 1981; Mandel, 2002). The highest caffeine intake is seen in the Nordic countries with an intake around 400 mg/person/day (Barone & Roberts, 1996; Debry, 1994; Gilbert, 1984).

There are several plausible biological pathways by which caffeine affects human reproduction (Burg,

Received 1 February, 2007; accepted 11 May, 2007.

Address for correspondence: María Morales Suárez-Varela, Unit of Public Health and Environmental Care, Department of Preventive Medicine, University of Valencia, Avda, Vicente Andrés Estellés s/n, 46100 Burjasot, Valencia, Spain. E-mail: maria.m.morales@uv.es

1975; Debry, 1994; Jensen et al., 1998; Olsen, 1991; Petridou, 1992; Viani, 1996), and possibly, the rate of twinning. Ovulation may be affected by caffeine-induced reduction of estradiol (London et al., 1991; Petridou et al., 1992), which may increase the levels of pituitary gonadotropins, and, accordingly, ovarian stimulation (Hack et al., 1970; Webster & Elwood, 1985; Wyshak, 1978). Transportation of the conceptus through the fallopian tube may also be affected by caffeine (Takizawa et al., 1983).

Previous studies on these lifestyle factors and twinning have given ambiguous results perhaps because most studies either rely on retrospective recall over longer time periods or they have used small sample sizes. In 1988, Olsen et al. observed an association between smoking and twinning, but Kapidaki et al. (1995) considered this finding to be confounded by coffee intake and reported that a higher twinning rate rather correlated with coffee intake. Furthermore, Parazzini et al. found similar results in 1996, although with different associations between MZ and DZ twins. Since then, the role of coffee and smoking on twinning rates has been unsettled. Recently in 2004 and 2005, Basso et al. and Reddy et al. found an association between maternal BMI and twinning rates and it is possible that the effect of coffee on twinning rates could be modified by maternal BMI.

This study presents data from the Danish National Birth Cohort (DNBC; Olsen et al., 2001) and includes lifestyle data that have been collected prospectively early in pregnancy before a twin pregnancy was diagnosed. Our aim was to estimate the association between coffee and tobacco intake and zygosity-specific twinning occurrence by taking maternal prepregnancy BMI and alcohol consumption into consideration.

Material and Methods

Study Population

The study was carried out within the DNBC, which is a study of pregnant women and their offspring. From March 1996 to November 2002, a total of about 100,000 pregnant women gave written informed consent to participate in the DNBC. Women were recruited from their general practitioners and around 60% of those invited by about half of all Danish practitioners in Denmark gave consent. The pregnant women received a written report about the DNBC at their first antenatal visit, usually scheduled at 6 to 10 weeks of gestation. The study population comprised of women who gave birth to live-born singletons or twins and who had participated in the first pregnancy interview in the DNBC (n = 88,719), which took place at approximately 16 weeks of gestation. The interview was classified as missing if we could not reach the woman at the scheduled time after three additional attempts to make contact, or if the woman was no longer pregnant at the time of the interview. Women who reported receiving infertility treatment were furthermore excluded from the study (n = 5734). The study was approved by all the Ethic Committees in the country and by the Danish Data Protection Board.

Outcome Assessment

For the main analysis, we had data on 81,954 singleton and 1031 twin births. We categorized twin births into MZ, DZ same sex (DZ-SS), DZ opposite sex (DZ-OS) and unknown zygosity same sex (UZ). Zygosity classification was made according to a standardized questionnaire on 'likeness' by linkage to the Twin Register which updated zygosity information until the year 2000, see Skytthe et al., 2002. Zygosity assessment was based on an established similarity questionnaire, (Christiansen et al., 2003) administered in 2003 when the twins were 3 to 5 years of age. The questions were: (1) Are/were you and your twin as like as two peas in a pod or as ordinary siblings? (2) Are/were you mistaken by family and friends? (3) Are/were you mistaken by kindergarten teachers and mates? (4) Do/did you have the same eye and hair color? The questionnaires were answered by the twins' parents. Twins described as being as alike as two peas in a pod, with the same eye and hair color, were classified as MZ if at least one of the questions about being mistaken was answered 'yes'. Twins described as alike as ordinary siblings and answering 'yes' to all the other questions were also classified as MZ. The rest were classified as DZ. All inconsistent answers were classified as having unknown zygosity.

Exposure Assessment

The main exposures of interest were coffee and smoking. Participants were asked about daily coffee intake. We coded the answers according to the number of cups or mugs per day; a mug was coded as two cups. Similar questions were asked about tea consumption. We asked women for details about their smoking habits at the time of the interview and throughout pregnancy. Information on parity, socioeconomic status, alcohol consumption and prepregnancy BMI was also collected in the first interview based on self-reported information about prepregnancy data. All interviews are available at http://www.ssi.dk/sw9653.asp.

Statistical Analyses

We estimated odds ratios (OR) for twinning rates according to coffee intake and smoking by unconditional logistic regressions separately for MZ, DZ-SS, DZ-OS and UZ twins. The unit of observation was a confinement.

In the analysis, we categorized coffee intake according to the number of cups per day (0, 1–3, 4–8, and 9+), and we used the number of cups when testing for trend. If coffee intake was less than one cup per day but more than zero, we coded it as one cup of coffee per day. We also analyzed data according to caffeine intake by using average levels of 100 mg of caffeine for a cup of coffee and 50 mg for a cup of tea

https://doi.org/10.1375/twin.10.4.597 Published online by Cambridge University Press

Table 1

Odds Ratio (OR) and Adjusted* Odds Ratio (ORa) for All Twins, Monozygotic and Dizygotic (Same Sex and Opposite Sex) After Spontaneous Ovulations in Relation to BMI, Coffee, Smoking and Alcohol Habits

	Singleton	All twins			Monozygotic (MZ)			Dizygotic same sex (DZ-SS)			Dizygotic opposite sex (DZ-OS)			Unknown zygosity same sex (UZ)		
		N	OR	ORa (95% CI)	*N*	OR	ORa (95% CI)	*N*	OR	ORa (95% CI)	*N*	OR	ORa (95% CI)	*N*	OR	ORa (95% CI)
All 82,985	81,954	1031			121			189			313			408		
Prepregnancy BMI#																
< 18.5	3691	39	0.87	0.89 (0.64,1.23)	4	0.73	0.75 (0.27,2.03)	10	1.22	1.26 (0.66,2.41)	9	0.65	0.66 (0.34,1.30)	16	0.91	0.95 (0.57,1.58)
18.6–24.9	54,882	666	1.00	1.00 (Reference)	81	1.00	1.00 (Reference)	121	1.00	1.00 (Reference)	203	1.00	1.00 (Reference)	261	1.00	1.00 (Reference)
25.0–29.9	15,544	201	1.06	1.06 (0.90,1.24)	23	1.00	0.99 (0.62,1.58)	33	0.96	0.94 (0.64,1.39)	67	1.16	1.13 (0.86,1.50)	78	1.05	1.08 (0.83,1.39)
≥ 30	6472	110	1.40	1.37 (1.11,1.68)	9	0.95	0.93 (0.46,1.86)	23	1.61	1.55 (0.98,2.44)	32	1.33	1.24 (0.85,1.81)	46	1.50	1.52 (1.10,2.10)
Age (years)																
< 24	5222	40	1.00	1.00 (Reference)	7	1.00	1.00 (Reference)	6	1.00	1.00 (Reference)	10	1.00	1.00 (Reference)	17	1.00	1.00 (Reference)
25–29	26,015	323	1.62	1.40 (0.71, 2.79)	50	1.43	1.22 (0.54,2.74)	56	1.87	2.51 (0.33,18.72)	83	1.67	1.93 (0.46,8.08)	134	1.58	0.77 (0.32,1.81)
≥ 30	48,557	668	1.80	1.65 (0.84,3.25)	64	0.98	1.00 (0.44,2.26)	127	2.27	3.11 (0.42,22.78)	220	2.36	2.71 (0.66,11.18)	257	1.62	0.87 (0.37,2.01)
Parity																
1	30,890	427	1.00	1.00 (Reference)	48	1.00	1.00 (Reference)	82	1.00	1.00 (Reference)	134	1.00	1.00 (Reference)	163	1.00	1.00 (Reference)
2	11,150	165	1.06	1.02 (0.85,1.23)	15	0.86	0.94 (0.52,1.72)	29	0.98	0.94 (0.60,1.45)	47	0.97	0.87 (0.80,1.93)	74	1.26	1.23 (0.92,1.64)
≥ 3	2598	45	1.55	1.08 (0.78,1.51)	4	1.00	1.17 (0.41,3.34)	11	1.59	1.43 (0.74,2.74)	14	1.24	0.90 (0.49,1.63)	16	1.17	1.05 (0.71,2.06)
Coffee intake (cups/day)																
0	45,232	596	1.00	1.00 (Reference)	83	1.00	1.00 (Reference)	109	1.00	1.00 (Reference)	166	1.00	1.00 (Reference)	238	1.00	1.00 (Reference)
1–3	25,846	293	0.86	0.84 (0.72,0.97)	21	0.44	0.47 (0.29, 0.77)	56	0.89	0.84 (0.60,1.17)	103	1.08	1.05 (0.82,1.35)	113	0.83	0.80 (0.64,1.01)
4–8	9337	114	0.92	0.86 (0.70,1.06)	15	0.87	0.96 (0.54,1.68)	20	0.88	0.79 (0.49,1.29)	340	0.99	0.84 (0.58,1.24)	45	0.91	0.88 (0.64,1.23)
≥ 9	1484	28	1.43	1.29 (0.87,1.91)	2	0.73	0.84 (0.20,3.46)	4	1.11	0.73 (0.23,2.33)	10	1.83	1.50 (0.78,2.86)	12	1.53	1.56 (0.86,2.81)
Tea intake (cups/day)																
0	30,448	386	1.00	1.00 (Reference)	50	1.00	1.00 (Reference)	61	1.00	1.00 (Reference)	111	1.00	1.00 (Reference)	164	1.00	1.00 (Reference)
1–3	23,317	297	1.00	1.02 (0.87,1.19)	31	0.81	0.80 (0.51,1.27)	66	1.41	1.47 (1.03,2.09)	88	1.03	1.06 (0.80,1.41)	112	0.89	0.89 (0.69,1.13)
4–8	12,951	150	0.91	0.90 (0.74,1.10)	20	0.94	0.98 (0.58,1.67)	31	1.19	1.18 (0.76,1.84)	49	1.03	1.02 (0.72,1.43)	50	0.71	0.70 (0.50,0.97)
≥ 9	1662	15	0.71	0.70 (0.41,1.18)	1	0.36	0.39 (0.05,2.85)	4	1.20	1.20 (0.43,3.31)	8	1.32	1.26 (0.61,2.59)	2	0.22	0.22 (0.05,0–88)
Caffeine intake (mg/day)*																
0	5477	77	1.00	1.00 (Reference)	28	1.00	1.00 (Reference)	15	1.00	1.00 (Reference)	18	1.00	1.00 (Reference)	35	1.00	1.00 (Reference)
1–299	52,427	654	0.86	0.85 (0.67,1.09)	81	0.94	0.89 (0.44,1.78)	114	0.79	0.77 (0.45,1.32)	195	1.13	1.07 (0.66,1.74)	264	0.78	0.76 (0.53,1.10)
300–699	19,327	250	0.98	0.84 (0.65,1.10)	25	0.78	0.81 (0.37,1.75)	51	0.96	0.85 (0.48,1.53)	85	1.33	1.15 (0.69,1.93)	89	0.72	0.68 (0.45,1.02)
> 699	4723	50	0.77	0.66 (0.45,0.95)	6	0.77	0.83 (0.29,2.35)	9	0.69	0.54 (0.22,1.28)	15	0.96	0.72 (0.35,1.46)	20	0.66	0.65 (0.37,1.13)
Smoking habits (cigarettes/day)																
0	60,625	727	1.00	1.00 (Reference)	88	1.00	1.00 (Reference)	142	1.00	1.00 (Reference)	235	1.00	1.00 (Reference)	262	1.00	1.00 (Reference)
1–9	16,180	219	0.72	1.17 (1.00,1.36)	28	1.19	1.27 (0.81,2.00)	33	0.87	0.70 (0.59,1.29)	49	0.78	0.80 (0.59,1.10)	109	1.56	1.66 (1.32,2.10)
≥ 10	5149	85	0.82	1.12 (1.03,1.79)	5	0.66	0.80 (0.32,2.03)	14	1.16	1.15 (0.66,2.02)	29	1.45	1.35 (0.91,2.02)	37	1.66	1.86 (1.31,2.65)
Alcohol consumption (g/week) before pregnancy																
0	50,553	649	1.00	1.00 (Reference)	71	1.00	1.00 (Reference)	122	1.00	1.00 (Reference)	208	1.00	1.00 (Reference)	248	1.00	1.00 (Reference)
< 20	5015	67	1.04	1.01 (0.78,1.31)	10	1.42	1.31 (0.65,2.64)	13	1.07	1.07 (0.60,1.90)	16	0.77	0.77 (0.46,1.29)	28	1.13	1.10 (0.74,1.64)
21–40	9928	125	0.98	0.96 (0.78,1.16)	18	1.29	1.25 (0.73,2.13)	20	0.83	0.83 (0.52,1.34)	36	0.88	0.89 (0.62,1.27)	51	1.04	0.99 (0.72,1.36)
≥ 40	16,458	190	0.89	0.92 (0.78,1.08)	22	0.95	0.99 (0.61,1.61)	34	0.85	0.88 (0.60,1.30)	53	0.78	0.79 (0.58,1.08)	811	1.00	1.02 (0.79,1.33)

Note: *The sum may not add up to the total because of missing values; †OR: Odds ratio; ‡ORa: Adjusted for socioeconomic status and other variables as seen in the table; § 95% CI: 95% confidence interval; #BMI, body mass index; calculated as weight in kilograms divided by the square of height in meters; **Caffeine intake included coffee (1 cup = 100 mg.), tea (1 cup = 50 mg.) †Change in alcohol consumption between prepregnancy consumption and consumption during pregnancy

https://doi.org/10.1375/twin.10.4.597 Published online by Cambridge University Press

(Bunker & McWilliams, 1979), and disregarding caffeine intake from other sources. We went on to categorize smoking (using nonsmoking as a reference) into 1 to 9 and more than 10 cigarettes per day on average during the peri-conceptional period (before and during the first pregnancy period). Finally, we converted alcohol consumption into a daily number of drinks. In Denmark, a standard drink contains an average of 12 g of alcohol (one glass of wine, one beer or 4 cl of spirits).

We classified BMI as underweight, normal weight, overweight, or obese (< 18.4, 18.5–25, 25.1–29.9, ≥ 30, respectively), according to the World Health Organization definitions.

We used likelihood ratio tests to assess whether the associations between coffee intake and smoking on twinning were modified by alcohol or BMI. We used the SPSS software (version 12.0; SPSS Inc, Chicago, Ill) to perform all the analyses. We deleted all the personal identification numbers after register linkage.

Results

A total of 82,985 pregnant women fulfilled the inclusion criteria of this study; 81,954 (98.75%) of the pregnancies resulted in a singleton pregnancy, and 1031 (1.24%) in a twin pregnancy. Of the 1031 twins that had been notified to the Danish Twin Registry at the time of study, we could classify 121 as MZ, 189 as DZ-SS, and 313 as DZ-OS. It was not possible to classify the remaining 408 same-sex twins (UZ) because infants were still very young during the study period.

Women with a high intake of coffee had a high crude twinning rate, especially for DZ-OS and UZ. However after adjustment for potential confounders, this odds ratio attenuated and was no longer statistically significant (Table 1). We found no association between tea intake and the rate of twinning. Using caffeine intake from both coffee and tea showed no association with multiple pregnancies.

Smokers presented a statistically significant adjusted odds ratio (ORa) of twinning rates, especially for DZ. We found no significant associations with twinning rates for prepregnancy alcohol consumption, alcohol consumption recorded at the time of pregnancy, or for changes in alcohol habits from before pregnancy to early pregnancy (data not shown). In addition, we noted a relation between obesity (BMI ≥ 30) and twinning rates, especially for DZ-SS twins (see Table 2) and twinning rates were high for obese smoking mothers. Age increased twinning rates in general, although we saw no association with MZ.

Discussion

Common lifestyle factors may modify twinning rates and are perhaps partly responsible for the secular changes in twinning rates over time. We found DZ twinning to be associated with smoking habits and the multiplicative effect measure was not modified by BMI. We saw no association between caffeine and DZ twinning when we adjusted for confounding factors. Other studies have shown that nutritional components also correlate with twinning rates (Mills et al., 1993).

The strength of this study is its large sample size and the prospectively collected data on lifestyle factors. At the time of the first interview, women were unaware of a possible twin pregnancy and it is thus unlikely that reporting lifestyle factors correlates with twinning rates. Our results further indicate that changes in alcohol consumption in early pregnancy are the same for both twin and singleton pregnancies. We believe this assumption also holds for smoking, but it could be different for coffee intake if adhesion to coffee drinking habits is related to the higher estrogen level seen in twin pregnancies (Bunker & McWilliams, 1979; Gavaler & Van Thiel, 1987; Mills et al., 1993). Our negative results for coffee intake can, therefore, be explained by differential misclassification.

Previous studies on coffee and twinning rates conducted by Kapidaki et al. (1995) and Parazzini et al. (1996) showed an increased twinning rate related to coffee intake. Kapidaki et al. found an OR for coffee intake of 1.31 for DZ twinning while our study gave an OR for coffee intake of 1.83 for DZ-OS, which approaches the finding in the study by Parazzini et al. with an OR of 1.7. However, our adjustments removed the association between coffee intake and multiple pregnancies. Coffee intake was higher in our data than that found in the aforementioned papers.

Smoking and alcohol consumption during early pregnancy may reflect peri-conceptional consumption better than consumption before pregnancy for those who planned their pregnancy, and a total of 88% of all pregnancies were planned in our study. It is reasonable to believe that women consume less fetotoxic substances during the period when they try to conceive. We did not find results that differ much from those presented in the tables when we restricted our analyses to pregnancy planners only (n = 72,458).

Changes in lifestyle factors vary in different countries and smoking frequencies have changed substantially over time as have the chemical contents of cigarettes and types of tobacco used (blond, black). If our associations are causal, we would expect to see twinning rates continue to vary over time due to changes in smoking, obesity, and the age of reproduction. It is of interest that some of these lifestyle factors, like obesity and smoking (Table 2), are also strong determinants of subfecundity, as described by Olsen (1991). A similar finding was found by Basso et al. (2004), using an early segment of data from the DNBC.

Epidemiologic studies over the years have identified smoking as an important hazard for reproductive health. We believe DZ twinning may be one of the reproductive factors that is modified by smoking. This study showed that BMI, smoking habits and the mother's age may play an important role in the occurrence of twin pregnancies.

Table 2

Adjusted* Odds Ratio (ORa) (and 95% Confidence Intervals) for all Twins, Monozygotic, Dizygotic Same Sex, Dizygotic Opposite Sex and Unknown Zygosity Same Sex According to Smoking and Prepregnancy BMI (PP BMI)

		PP BMI#				
All twins	Smoking	18.5–25.0	< 18.5	25.0–29.9	> 30	Smoking
		ORa (95%CI)	ORa (95%CI)	ORa (95%CI)	ORa (95%CI)	ORa (95%CI)
	0	1 (Reference)	0.72 (0.49, 1.07)	0.90 (0.64, 1.27)	0.84 (0.58, 1.22)	1 (Reference)
	1–9	1.02 (0.68, 1.54)	0.69 (0.40, 1.19)	0.87 (0.59, 1.30)	1.26 (0.78,2.01)	1.13 (0.95, 1.35)
	≥ 10	1.94 (1.11, 3.40)	1.01 (0.58, 1.75)	1.23 (0.82, 1.85)	1.42 (0.87, 2.33)	1.47 (1.14, 1.90)
	PP BMI ORa 95%CI)	1 (Reference)	0.25 (1.01, 1.54)	1.23 (0.96, 1.58)	1.73 (1.31, 2.29)	
Monozygosity (MZ)						
	0	1 (Reference)	0.40 (0.11, 1.44)	1.01 (0.36, 2.82)	0.92 (0.31, 2.76)	1 (Reference)
	1–9	1.03 (0.31, 3.48)	1.82 (0.51, 6.46)	0.95 (0.29, 3.10)	1.30 (0.32, 5.22)	1.21 (0.78, 1.87
	≥ 10	0.88 (0.99, 7.94)	1.42 (0.31, 6.41)	1.26 (0.37, 4.34)	0.91 (0.16, 4.99)	0.73 (0.29, 1.82)
	PP BMI ORa (95%CI)	1 (Reference)	1.41 (0.80, 2.46)	1.34 (0.70, 2.57)	1.26 (0.55, 2.88)	
Dizygosity same sex (DZ-SS)						
	0	1 (Reference)	1.82 (0.63, 5.28)	1.55 (0.56, 4.28)	1.33 (0.45, 3.87)	1 (Reference)
	1–9 (0.72, 6.50)	2.16 (0.03, 2.91)	0.32 (0.39, 3.88)	1.23 (0.23, 4.60)	1.03 (0.59, 1.29)	0.87
	≥ 10	2.84 (0.63, 12.74)	1.41 (0.31, 6.33)	2.32 (0.75, 7.14)	3.16 (0.92, 10.84)	1.15 (0.66, 2.02)
	PP BMI ORa (95%CI)	1 (Reference)	1.06 (0.70, 1.60)	1.00 (0.60, 1.64)	1.66 (0.96, 2.88)	
Dizygosity opposite sex (DZ-OS)						
	0 (Reference)	1 (0.28, 1.05)	0.55 (0.47, 1.41)	0.82 (0.46, 1.51)	0.84 (Reference)	1
	1–9	0.867 (0.84, 1.67)	0.27 (0.08, 0.95)	0.44 (0.21, 0.93)	1.16 (0.54, 2.48)	0.84 (0.59, 1.20)
	≥ 10	1.04 (0.34, 3.17)	0.73 (0.28, 1.90)	0.80 (0.40, 1-62)	0.59 (0.21, 1.65)	1.53 (0.99, 2.38)
	PP BMI ORa (95%CI)	1 (Reference)	1.34 (0.94, 1.89)	1.50 (1.01, 2.23)	1.72 (1.08, 2.75)	
Unknown zygosity same sex (UZ)						
	0	1 (Reference)	0.70 (0.38, 1.31)	0.79 (0.45, 1.38)	0.714 (0.38, 1.30)	1 (Reference)
	1–9	0.88 (0.45, 1.73)	0.88 (0.39, 1.99)	1.19 (0.64, 2.20)	1.44 (1.69, 2.99)	1.62 (1.21, –2.15)
	>10	2.99 (0.35, 6.62)	1.09 (0.45, 2.60)	1.38 (0.72, 2.63)	1.98 (0.95, 4.13)	2.04 (1.35, 3.09)
	PP BMI ORa (95%CI)	1 (Reference)	1.11 (0.83, 1.48)	1.15 (0.82, .62)	1.63 (1.11, 2.40)	

Note: *Register with complete information on covariates used in the adjusted analysis
†ORa Adjusted for: maternal age, parity, coffee intake and socioeconomic status
‡ 95% CI: 95% confidence interval
§ Smoking: Cigarettes/day

Acknowledgments

The project was supported by grants from the Danish Research Agency (No. 1105-93 and 11099-96). The Danish National Research Foundation has established the Danish Epidemiology Science Center that initiated and created the Danish National Birth Cohort. The Cohort is a result of a major grant from this Foundation. Additional support for the Danish National Birth Cohort is obtained from the Pharmacy Foundation, the Egmont Foundation, the March of Dimes Birth Defects Foundation and the Augustinus Foundation.

References

Barone, J. J., & Roberts, M. R. (1996). Caffeine consumption. *Food and Chemical Toxicology, 34*, 119–129.

Basso, O., Olsen, J., Christensen, K., & Olsen J. (2004). Risk of twinning as a function of maternal height and body mass index. *Journal of the American Medical Association, 291,* 1564–1566.

Belaisch-Allart, J., Elaoufir, A., Mayenga, J. M., Segard, L., Bernard, J. P., Plachot, M., Mandelbaum, J., Cohen, J., & Labbe, F. (1995). Monozygotic triplet pregnancy following transfer of frozen-thawed embryos. *Human Reproduction, 10*, 3064–3066.

Botting, B. J., Macdonald, I., & Macfarlane, A. J. (1987). Recent trends in the incidence of multiple births and associated mortality. *Archives of Disease in Childhood, 62,* 941–950.

Bulmer, M. G. (1959). Twinning rate in Europe during the war. *British Medical Journal, 1,* 29–30.

Bunker, M. L., & McWilliams, M. (1979). Caffeine content of common beverages. *Journal of the American Dietetic Association, 74,* 28–32.

Burg, A. W. (1975). Physiological disposition of caffeine. *Drug Metabolism Reviews, 4,* 199–228.

Christiansen, L., Frederiksen, H., Schousboe, K., Skytthe, A., von Wurmb Schwark, N., Christensen, K., & Kyvik, K. (2003). Age- and sex-differences in the validity of questionnaire-based zygosity in twins. *Twin Research, 6,* 275–278.

Debry, G. (1994). *Coffee and health* (pp. 1–538). Paris: John Libbey.

Elwood, T. M. (1973). Changes in the twinning rate in Canada in 1926–70. *British Journal of Preventive and Social Medicine, 27,* 236–241.

Eriksson, A. W., & Fellman, J. (1967). Twinning in relation to the marital status of the mother. *Human Heredity, 17, 385–398.*

Flegal, K. M., Carroll, M. D., Ogden, C. L., & Johnson, C. L. (2002). Prevalence and trends in obesity among US adults, 1999–2000. *Journal of the American Medical Association, 288*, 1723–1727.

Gavaler, J. S., & Van Thiel, D. H. (1987). International Commission for Protection against Environmental Mutagens and Carcinogens. ICPEMC Working Paper No. 15/7. Reproductive consequences of alcohol abuse: Males and females compared and contrasted. *Mutation Research, 186*, 269–277.

Gilbert, R. M. (1981). Caffeine: Overview and anthology. In S. Miller S. (Ed.), *Nutrition and behavior* (pp. 146–266). Philadelphia: The Franklin Institute.

Gilbert, R. M. (1984). *Caffeine consumption. The methilxantine beverages and foods. Chemistry, consumption and health effects* (pp. 185–213). New York: Liss.

Hack, M., Brish, M., Serr, D. M., Insler, V., & Lunenfeld, B. (1970). Outcome of pregnancy after introduced ovulation. *Journal of the American Medical Association, 211*, 791–797.

Herskind, A. M., Basso, O., Olsen, J., Skytthe, A., & Christensen, K. (2005). Is natural twinning rate still declining? *Epidemiology, 16,* 591 (Letter).

Jensen, T. K., Henriksen, T. B., Hjollund, N. H., Scheike, T., Kolstad, H., Giwercman, A., Ernst, E., Bonde, J. P., Skakkebaek, N. E., & Olsen, J. (1998). Caffeine intake and fecundability: A follow-up study among 430 Danish couples planning their first pregnancy. *Reproductive Toxology, 12,* 289–295.

Kapidaki, M., Roupa, Z., Sparos, L., Tzonou, A., Olsen, J., & Trichopoulos, D. (1995). Coffee intake and other factors in relation to multiple deliveries: A study in Greece. *Epidemiology, 3*, 294–298.

Knight, C. A., Knight, I., Mitchell, D. C., & Zepp, J. E. (2004). Beverage caffeine intake in US consumers and subpopulations of interest: Estimates from the Share of Intake Panel survey. *Food and Chemical Toxicology, 42,* 1923–1930.

London, S., Willett, W., Longcope, C., & McKinlay, S. (1991). Alcohol and other dietary factors in relation to serum hormone concentrations in women at climacteric. *American Journal of Clinical Nutrition, 53*, 166–171.

MacGillivray, I. (1970). Changing incidence of twinning in Scotland in 1939–68. *Acta Geneticae Medicae et Gemellologiae, 19,* 26–29.

Mandel, H. G. (2002). Update on caffeine consumption, disposition and action. *Food and Chemical Toxicology, 40,* 1231–1234.

Mills, J. K., Holmes, L. B., Aarons, J. H., Simpson, J. L., Brown, Z. A., Jovanovic-Peterson, L. G., Conley, M. R., Graubard, B. I., Knopp, R. H., & Metzger, B. E. (1993). Moderate caffeine use and the risk of spontaneous abortion and intrauterine growth retardation. *Journal of the American Medical Association, 269, 593–597.*

Nylander, P. P. S. (1975). Frequency of multiple births. *Human Multiple Reproduction, 87*, 97.

Nylander, P. P. S. (1983). The phenomenon of twinning. *Obstetrical Epidemiology*, 143–165.

https://doi.org/10.1375/twin.10.4.597 Published online by Cambridge University Press

Olsen, J., Bonnelykke, B., & Nielsen, J. (1988). Tobacco smoking and twinning. *Acta Medica Scandinavica, 224*, 491–494.

Olsen, J. (1991). Cigarette smoking, tea and coffee drinking, and subfecundity. *American Journal of Epidemiology, 133*, 734–739.

Olsen, J., Melbye, M., Olsen, S. F., Sørensen, T. I., Aaby, P., Andersen, A. M., Taxbøl, D., Hansen, K. D., Juhl, M., Schow, T. B., Sørensen, H. T., Andresen, J., Mortensen, E. L., Olesen, A. W., & Søndergaard, C. (2001). The Danish National Birth Cohort: Its background, structure and aim. *Scandinavian Journal of Public Health, 29,* 300–307.

Parazzini, F., Chatenoud, L., Benzi G., Di Cintio, E., Dal Pino, D., Tozzi, L., & Fedele, L. (1996). Coffee and alcohol intake, smoking and risk of multiple pregnancy. *Human Reproduction, 10*, 2306–2309.

Petridou, E. (1992). Pregnancy estrogens in relation to coffee and alcohol intake. *Annals of Epidemiology, 2*, 241–247.

Pollard, G. N. (1969). Multiple births in Australia 1944–1963. *Journal of Biosocial Science, 1,* 389–404.

Reddy, U. M., Branum, A. M., & Klebanoff, M. A. (2005). Relationship of maternal body mass index and height to twining. *Obstetrics and Gynecology, 106*, 411–412.

Seidell, J. C., & Flegal, K. M. (1997). Assessing obesity: Classification and epidemiology. *British Medical Bulletin, 53*, 238–252.

Skytthe, A., Kyvik, K., Holm, N. V., Vaupel, J. W., & Christensen, K. (2002). The Danish twin registry: 127 cohorts of twins. *Twin Research, 5*, 352–357.

Takizawa, K., Kun, K., & Matison, D. (1983). Female reproduction. *American Journal of Industrial Medicine, 4*, 17–20.

Viani, R. (1996). Caffeine consumption. Proceedings of the Caffeine Workshop. Thai FDA and ISCI, Bangkok.

Webster, F., & Elwood, J. M. (1985). A study of the influence of ovulation stimulants and oral contraception on twin births in England. *Acta Geneticae Medicae et Gemellologiae, 34*, 105–108.

Wyshak, G. (1978). Statistical findings on the effects of fertility drugs on plural births. *Biology and Epidemiology, 24*, 17–33.

https://doi.org/10.1375/twin.10.4.597 Published online by Cambridge University Press