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The association between maternal occupation and down syndrome: A report from the national Down syndrome project

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ABSTRACT

Background: Among live births, Down syndrome (DS) due to trisomy 21 is the most commonly occurring autosomal trisomy, typically resulting from meiotic nondisjunction. Currently, advanced maternal age and altered recombination patterns are the only well-known risk factors for nondisjunction. Maternal occupation has not been investigated as a risk factor for maternally-derived cases of trisomy 21.

Objectives: This study explored the association between maternal occupation and chromosome 21 nondisjunction, stratified by the stage of maternal error – either Meiosis I (MI) or Meiosis II (MII). Additionally, we investigated specific toxic agents associated with occupation classes.

Methods: Using narrative job descriptions from the National Down Syndrome Project (NDSP), a population-based case-control study, occupation was coded using the 2010 Standard Occupational Classification (SOC). Odds ratios were calculated for the association between occupation class and having a child with DS, stratified by meiotic stage. An exposure analysis was performed within occupational classes that were statistically significant predictors of having a child with DS. Odds ratios were calculated to analyze associations between individual exposures and having a child with DS.

Results: The odds of MII nondisjunction were increased among Production Workers (OR = 3.15; 95%CI = 1.52,6.55). Women who worked as Life, Physical and Social Scientists or in Food Preparation and Serving-Related Occupations experienced greater likelihood of MI errors (OR = 5.72(1.80,18.20), and OR = 1.87(1.08,3.24), respectively). Exposure to solvents within the Production Worker group was a significant predictor ($p < 0.05$) for MI nondisjunction. No other environmental agents had a significant association with nondisjunction.

Discussion: Specific maternal occupation classes were associated with MI and MII chromosome 21 nondisjunction. These occupation classes were selected for an exposure analysis, which determined solvents as highly predictive of MI nondisjunction among Production Workers. Findings from this analysis will serve to further explore the relationship between maternal occupation and chromosome 21 nondisjunction.

1. Introduction

Down syndrome (DS) is the most frequently occurring human aneuploidy condition among live births, with an estimated prevalence in the United States of 1 in 700 (Parker et al., 2010). In the majority of infants with DS (approximately 95%), the aneuploidy is due to an extra full copy of chromosome 21, which typically results from maternal meiotic nondisjunction (Mutton et al., 1996). Meiotic nondisjunction can occur either during Meiosis I (MI) or Meiosis II (MII). MI errors involve failure of homologs to segregate or involve premature separation of sister chromatids (PSSC). These types of errors can occur as early as the mother's fetal lifetime or as late as the time of ovulation of that oocyte, when MI is resumed. The classic definition of an MII error occurs at the time of conception and is attributed to failure of chromatids of one homolog to separate. PSSC can also lead to two chromatids from the same homolog moving to the daughter cell, depending on the random segregation of the early separated chromatids. Due to the extended timeline over which these errors can occur—from the mother's

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fetal period throughout her lifetime until fertilization—the meiotic machinery is vulnerable to exposures that may influence nondisjunction errors.

Currently there are only two known risk factors associated with chromosome 21 nondisjunction: advanced maternal age and altered recombination patterns, with advanced maternal age being the strongest known risk factor to date (Sherman et al., 2013; Allen et al., 2009). Advanced maternal age has been associated with both stages of maternally-derived meiosis errors (Allen et al., 2009; Antonarakis et al., 1992; Muller et al., 2000; Yoon et al., 1996; Freeman et al., 2007). Specific altered recombination patterns have been observed for MI and MII errors (Allen et al., 2009; Oliver et al., 2008). Thorough research into the genetic etiology of chromosome 21 nondisjunction has shown that maternally-derived errors are complex, and that there is likely an age-related and an age-unrelated component to these mechanisms (reviewed in Sherman et al., 2013).

Several studies have demonstrated an association between maternal socioeconomic status (SES) and maternal chromosome 21 nondisjunction (Hunter et al., 2013; Torfs and Christianson, 2003; Christianson et al., 2004; Ghosh et al., 2014). All studies indicate that low SES is associated with MII nondisjunction. Given the specificity of SES as a predictor of MII nondisjunction errors reproduced, it is possible that SES is a proxy for environmental exposures associated with SES. Maternal occupation, exposure to toxic agents in the work environment, and their relationship with maternal chromosome 21 nondisjunction have yet to be explored.

In the United States there are more women in the workforce than ever before. Working environments are thought to affect physical, chemical, and psychosocial factors influential to fetal development. Previous literature has found that environmental toxicity and occupational stressors harm fetal development in addition to increasing the risk of adverse pregnancy outcomes including spontaneous abortion, preterm delivery, low birth weight, birth defects, and stillbirth (Burdorf et al., 2011; Figa-Talamanca, 2006; Thulstrup and Bonde, 2006; Ahmed and Jaakkola, 2007; Herdt-Losavio et al., 2010; Rocheleau et al., 2011; Lin et al., 2013). Some research has hypothesized that the increased risk of nondisjunction could be related to an accumulation of toxic elements from the environment that has damaged meiotic machinery and reduced oocyte quality (Nagaoka et al., 2012; Pacchierotti and Eichenlaub-Ritter, 2011; Susiarjo et al., 2007; Sherman et al., 2013).

Thus, maternal occupational exposure could be an important risk factor contributing to nondisjunction in humans. However, no study to date has investigated the association between maternal occupational exposure and DS exclusively. Furthermore, maternal occupational exposure and stage of meiotic origin in maternally derived cases of DS have not been examined. This study has two main objectives: (1) to determine the association between maternal occupational exposure and maternal nondisjunction, stratified by meiotic stage of origin; (2) to evaluate exposure to environmental agents accrued through the work environment in occupations that are found to be associated with nondisjunction to test their potential association with nondisjunction.

2. Methods

2.1. Study population

The National Down Syndrome Project (NDSP), based at Emory University in Atlanta, Georgia, served as the data source for this project. The study design, recruitment and ascertainment protocols have previously been described (Freeman et al., 2007). In brief, this was a population-based case-control study enrolling at six sites across the U.S. between 2000 and 2004 and is representative of approximately 11% of the annual births in the U.S. NDSP enrolled 907 infant cases and 977 infant controls (Freeman et al., 2007). Cases were defined as having standard or mosaic trisomy 21 (excluding translocations), and controls were defined as having no chromosomal abnormality or major birth defect(s). For this study, case and control definitions were based on the mother's outcome where cases were defined as those with a confirmed maternal MI or MII nondisjunction error. We excluded cases that were considered to be mitotic errors (i.e., errors where the extra chromosome 21 appears to be a duplicate of the other), as they are thought to be post-zygotic events. We included cases that were mosaic trisomy 21 and had evidence for maternal nondisjunction, as the mosaic euploid cells are thought to be a post-zygotic “rescue” after the meiotic nondisjunction event. The designation of the type of error is detailed in Freeman et al. (2007) and was based on the contribution of chromosome 21 genetic markers from parent to child with DS. Controls were defined as mothers of the control infants described above.

All participating national sites obtained IRB approval and informed consent from all study participants.

The study population and data analyzed in the current study were essentially the same sample as those studied in Hunter et al. (2013), with the exception of 4 control mothers for whom occupation information was not available or who were in an occupation that could not be analyzed.

2.2. Questionnaire

Mothers were asked to complete a structured, self-report questionnaire with a trained interviewer either by telephone or in person in Spanish or English, depending on the mother's primary language. As part of this questionnaire, mothers were asked about their employment history up to three months prior to date-of-conception (DOC). If respondents indicated they had a paid job for a total of six months or longer over the course of their lifetime up until three months prior to DOC (“Over your lifetime up until [DOC – 3 months], did you ever have a paid job for a total of six months or longer? Please include part-time and full-time work done in the workplace, at home, or during active military duty.“) Additional information was gathered on their job title or occupation, the type of company or industry, and usual activities associated with the job they held the longest. If the respondent indicated that they did not have a paid job for six months or longer during their lifetime up to three months DOC, they were grouped together as ‘unemployed.’

Mothers were also asked about a range of demographic factors, including maternal age, household income, proband sex, parity, preferred language, and race/ethnicity. Additionally, mothers were asked about smoking history and alcohol consumption.

2.3. Occupational exposures

Occupational information (job title, industry, and daily activities associated with this job) from mothers who indicated they were employed three months prior to DOC for six months or longer was entered into the National Institute for Occupational Safety and Health (NIOSH) Industry and Occupation Computerized Coding System (NIOCCS) version 3.0. Occupation was coded using the Standard Occupational Classification (SOC) system. SOC codes are classified into major, minor, broad and detailed occupation groupings, with the level of specificity often dependent upon the level of specificity of information from the respondent. If a study participant's occupation could not be auto-coded through NIOCCS, participant responses to questionnaire items were analyzed individually in accordance with NIOSH guidelines to assign an SOC code. All coding was done blind to case/control status. Most participants could be assigned a detailed occupation code, but due to limited sample sizes, participants were collapsed into broad occupational groups for analysis.

2.4. Exposure analysis

Occupation groups that were found to significantly predict either maternal MI or MII nondisjunction were prioritized for an exposure

analysis. Two experienced raters (one a certified industrial hygienist and one an occupational epidemiologist, each with 10 + years in retrospective exposure assessment) independently rated each job for exposure to a list of *a priori* agents: disinfectants and cleaners, solvents, pesticides, ionizing agents, anesthetics, pharmaceuticals, paints, varnishes and lacquers, infectious agents, metals, automotive fluids, machine fluids, and polycyclic aromatic hydrocarbons (PAHs). In a mid-rating review, the raters added two additional exposure categories (oil mists and antimicrobials) to the exposure assessment. Any disagreements between the two raters were resolved by a consensus conference. Exposure was assigned as a single categorical variable for: none/below population background level; low; medium; or high exposure. These categories were relative to jobs in the population-based sample, not to all possible jobs. Raters were blinded to case or control status throughout exposure assessment.

2.5. Statistical analyses

Maternal occupation classes were defined by the first 2 digits of the assigned SOC job code in order to yield maximum sample sizes for comparison (e.g., an SOC of 51–3099 was grouped together with all other SOCs starting with 51 to make up the Production Occupation class).

Maternal age (< 35 years [referent group] vs. ≥ 35 years); maternal parity (≤3 [referent group] vs. > 3 pregnancies); maternal race/ethnicity (White non-Hispanic [referent group], Black non-Hispanic, Hispanic, or Other race/ethnicity); proband sex (male [referent group] vs. female); maternal smoking status, defined as smoking 1 or more cigarettes per day during the first three months of pregnancy (no [referent group] vs. yes); maternal alcohol consumption, defined as any alcohol consumption during the first three months of pregnancy (no [referent group] vs. yes); and household income (≤$25,000 vs. ≥ $25,000 [referent group]) were considered as potential covariates based on *a priori* criteria as well as prior analyses in this population (Hunter et al., 2013). Chi-square tests (X^2) for these categorical variables were performed to assess the difference in cases vs. control, MI cases vs. controls, MII cases vs. controls, and MI cases (referent group) vs. MII cases. Comparisons for each of these outcomes were assessed separately. Maternal age, smoking, parity, language, and maternal race/ethnicity were significantly different in at least two of the four outcomes ($p < 0.05$). Although income was not observed to be significantly different, it was included in the model due to strong prior evidence of its association with MII nondisjunction (Hunter et al., 2013; Torfs and Christianson, 2003; Christianson et al., 2004; Ghosh et al., 2014).

Primary analyses were focused on the association between maternal occupation class and nondisjunction. Multivariate logistic regression models were utilized to make comparisons among four different outcomes: case vs. control, MI case vs. control, MII case vs. control, and MI case (referent group) vs. MII case. Each outcome was analyzed in separate models containing the same covariates. For each occupation class, the main predictor was working in that occupation vs. not working in that occupation (i.e., 1 = part of occupation class, 0 = not part of occupation class). Maternal age, parity, language, smoking status, maternal race/ethnicity, and income were included in the full model and tested for multicollinearity. There was no evidence of multicollinearity. Backwards eliminations were performed on each model to determine which covariates were included in the final models. All final models had the same covariates: maternal age, parity, language, income, and smoking.

Secondary analyses were focused on specific exposures and were guided by the results of the multivariate logistic regression described above. An exposure assessment was conducted on study subjects who worked in occupation classes that were significantly associated with nondisjunction. If at least 10 subjects within an occupation class were occupationally exposed to an agent at any level (low, medium, or high) this exposure was statistically analyzed. Multivariate logistic regression models were used to evaluate the association between occupational exposure and nondisjunction for the same four outcomes of interest among the subset of study subjects included in the exposure analysis (i.e., worked in an occupation class associated with nondisjunction). These models were adjusted for maternal age (the strongest predictor of nondisjunction) and stratified by occupation class. Additional covariates were not included in these models due to small sample size.

Odds ratios and 95% confidence intervals are reported. Analyses were not adjusted for multiple testing. All statistical analyses were performed in SAS, Version 9.3 (SAS Institute Inc., Cary, NC, USA) using a significance level of $p \leq 0.05$.

Table 1
Distribution of maternal factors by percent among women participating in the National Down Syndrome Project stratified by case/control status.

			Maternal Nondisjunction Cases		
Variable	Values	Controls	All Cases	MI Cases	MII Cases
		N = 973	N = 714	N = 532	N = 182
		%	%	%	%
Maternal Age[a,b]	< 35 years	82.3	49.3	51.9	41.8
	≥35 years	17.7	50.7	48.1	58.2
Maternal Race/Ethnicity[a]					
	White, non-Hispanic	50.2	51.7	51.7	51.7
	Black, non-Hispanic	15.7	9.9	9.6	11
	Hispanic	27.9	34.3	34	35.2
	Other	6.2	3.9	4.7	1.7
	Missing	0.1	0.14	0	0.55
Alcohol Consumption During First 3 Months of Pregnancy					
	No	82.5	82.7	83	82
	Yes	17.6	17.3	17	18
	Missing	10	13	9	4
Smoked Cigarettes During First 3 Months of Pregnancy					
	No	88.4	91.6	92	90.6
	Yes	11.6	8.4	8	9.4
	Missing	14	11	9	2
Maternal Language Preference[a]					
	English	80	73.4	73.7	72.5
	Spanish	19	25.2	25.2	25.3
	Missing	1	1.4	1.1	2.2
Proband Sex					
	Male	50.6	52.1	53	49.5
	Female	49.4	47.9	47	50.5
Maternal Parity[a]					
	Median(range)	2 (10)	2 (13)	2 (11)	2 (13)
	Missing (n)	1	1	1	0
Household Income					
	> $25,000	62	62	63	59.3
	≤$25,000	27.8	29.3	27.3	35.2
	Missing	10.2	8.7	9.8	5.5

[a] Significant difference between cases and controls.
[b] Significant difference between MI Cases and MII Cases.

3. Results

Characteristics of the study population are presented in Table 1 stratified by control vs. case and type of maternal nondisjunction. Maternal age was statistically different between cases and controls with controls more likely to be younger than cases ($X^2 = 207.6$, $p < 0.0001$). There was also a statistical difference in maternal age between MI and MII nondisjunction ($X^2 = 5.6$, $p = 0.02$) with MII nondisjunction being more common in women aged 35 and older. Cases and controls differed significantly by maternal race/ethnicity ($X^2 = 20.2$, $p = 0.0002$); a difference was not observed between MI cases and MII cases ($X^2 = 3.54$, $p = 0.32$). Cases and controls also

Table 2
Distribution of Study Population within each Work Category. Percentages are defined as the percentage by respective control or case status for that work category.

Standard Occupation Classification (SOC) Grouping	Total in SOC N = 1687 N(%)	Controls N = 973 N (%)	Maternal nondisjunction Cases		
			All Cases N = 714 N (%)	MI Cases N = 532 N (%)	MII Cases N = 182 N (%)
Management	118(7.0)	72(7.4)	46(6.4)	33(6.2)	13(7.1)
Business and Financial Operations	85(5.0)	48(4.9)	37(5.2)	26(4.9)	11(6.0)
Computer and Mathematical	34(2.0)	23(2.4)	11(1.5)	8(1.5)	3(1.6)
Architecture and Engineering	10(0.6)	6(0.6)	4(0.6)	2(0.4)	2(1.1)
Life, Physical, and Social Science	23(1.4)	7(0.7)	16(2.2)	15(2.8)	1(0.5)
Community and Social Service	31(1.8)	20(2.1)	11(1.5)	9(1.7)	2(1.1)
Legal	16(0.9)	10(1.0)	6(0.8)	5(0.9)	1(0.5)
Education, Training, and Library	134(7.9)	78(8.0)	56(7.8)	39(7.3)	17(9.3)
Arts, Design, Entertainment, Sports, and Media	39(2.3)	21(2.2)	18(2.5)	13(2.4)	5(2.7)
Healthcare Practitioners and Technical	106(6.3)	54(5.5)	52(7.3)	40(7.5)	12(6.6)
Healthcare Support	50(3.0)	26(2.7)	24(3.4)	18(3.4)	6(3.3)
Protective Service[a]	9(0.5)	6(0.6)	3(0.4)	3(0.6)	0(0.0)
Food Preparation and Serving Related	80(4.7)	48(4.9)	32(4.5)	26(4.9)	6(3.3)
Building and Grounds Cleaning and Maintenance	46(2.7)	21(2.2)	25(3.5)	17(3.2)	8(4.4)
Personal Care and Service	74(4.4)	42(4.3)	32(4.5)	26(4.9)	6(3.3)
Sales and Related	177(10.5)	114(11.7)	63(8.8)	49(9.2)	14(7.7)
Office and Administrative Support	269(15.9)	159(16.3)	110(15.4)	88(16.5)	22(12.1)
Farming, Fishing, and Forestry[a]	5(0.3)	2(0.2)	3(0.4)	1(0.2)	2(1.1)
Construction and Extraction[a]	3(0.2)	2(0.2)	1(0.1)	0(0.0)	1(0.5)
Installation, Maintenance, and Repair[a]	4(0.2)	3(0.3)	1(0.1)	0(0.0)	1(0.5)
Production	77(4.6)	29(3.0)	48(6.7)	28(5.3)	20(11.1)
Transportation and Material Moving	31(1.8)	19(2.0)	12(1.7)	8(1.5)	4(2.2)
Military-Specific[a]	1(0.1)	0(0.0)	1(0.1)	1(0.2)	0(0.0)
Unemployed	263(15.6)	161(16.5)	102(14.3)	77(14.5)	25(13.7)
Refused	2(0.1)	2(0.2)	0(0.0)	0(0.0)	0(0.0)

[a] These occupations were not included in the analysis due to insufficient sample size (N < 10).

differed by smoking status ($X^2 = 4.47$, p = 0.03), language ($X^2 = 9.88$, p = 0.002), and parity ($X^2 = 60.24$, p < 0.0001). MI cases and MII cases did not differ by smoking status, language or parity.

Of the 1689 participants who completed the occupational section of the questionnaire, 1424 (84.3%) identified as having a job for 6 months or longer prior to 3 months before conception, 263 (15.6%) identified as unemployed and 2 (0.1%) indicated they were employed but did not provide information necessary for an SOC assignment (Table 2). SOCs were assigned to all participants who provided occupation information, which resulted in 1687 participants available for the statistical analyses. Due to insufficient sample size, SOC assignments with < 10 participants were not statistically evaluated. These included: Protective Service; Farming, Fishing and Forestry; Construction and Extraction; Installation, Maintenance, and Repair; and Military-Specific Occupations.

Odds ratios for associations between maternal occupational groups and case and meiotic error status are shown in Table 3. Women who worked in Life, Physical, and Social Science Occupations were observed to have 4.57 greater odds of nondisjunction when compared to women working in other occupations (95% CI = 1.34, 14.55). Specifically, MI nondisjunction was 5.72 times more likely for these women than normal chromosome segregation (95% CI = 1.80, 18.20). The likelihood of MII nondisjunction was not increased among women in this work category (OR = 1.34; 95% CI = 0.13, 14.18). Mothers who worked Production jobs were observed to have increased odds of MII nondisjunction (OR = 3.15; 95% CI = 1.52, 6.55). Women in Production Occupations appear to have increased likelihood of MII errors compared to MI errors that approached statistical significance (OR = 1.96; 95% CI = 0.97, 3.95). Food Preparation and Serving Related Occupations was another maternal occupational class that was found to be significantly associated with nondisjunction. Mothers in this work category were observed to experience 1.87 greater odds of MI nondisjunction than normal chromosome segregation when compared to mothers who worked in different industries (95% CI = 1.08, 3.24). Occupations that fall into each SOC category significantly associated with chromosome nondisjunction are listed in Supplementary Table 1. Our reference group for analyzing the effect of occupational class was comprised of women who were not part of the occupation class, which included unemployed women. A sub-analysis was performed restricting the reference group to employed women only, which did not substantially change results (Supplementary Table II).

An *a priori* list of occupational exposures was created based on agents (or groups) that are 1) suspected reproductive hazards and/or mutagens, or that might be associated with the three occupational classes in which an association was found (Life, Physical, and Social Science; Food Preparation and Serving Related; and Production Occupations); 2) were estimated, based on employment statistics and exposure prevalence in prior studies to possibly be common enough in a population-based sample to allow analysis; and 3) were defined in groups that raters believed were sufficiently distinguishable (e.g., while it might be possible to determine if a person was using chemical sterilizers, raters did not attempt to estimate use of a specific sterilizing chemical). Raters were blinded to nondisjunction/control status and demographic characteristics.

Eight exposure agents met the criterion of at least 10 occupationally-exposed subjects within one or more of the three occupational classes: disinfectants and cleaners, solvents, infectious agents, metals, oil mists, antibiotics, pesticides, and PAHs (Table 4). The prevalence of exposures among Food Preparation and Serving Related workers was largely homogenous (i.e., all workers exposed or all workers unexposed), therefore statistical analyses could not be performed for this occupation class.

Among Life, Physical, and Social Science workers there was no association between the evaluated occupational exposures and nondisjunction (Table 5), although sample sizes were limited (Table 4). Solvent exposure was a significant predictor of nondisjunction (OR = 5.50; 95% CI = 1.30, 23.31) among mothers working in Production Occupations. Specifically, within this occupation class the odds of MI nondisjunction were 8.23 times higher when women were exposed to solvents (95% CI = 1.68, 40.35). The solvents group included

Table 3
Results from logistic regression models examining the effect of maternal occupation on case outcome adjusted for maternal age, parity, language, smoking, and occupation.

SOC Grouping	Case (N = 714) vs. Control (N = 973)		MI Case (N = 532) vs. Control (N = 973)		MII Case (N = 182) vs. Control (N = 973)		MII (N = 182) vs. MI Case[a] (N = 532)	
	OR	95% CI	OR	95%CI	OR	95% CI	OR	95% CI
Management	0.72	(0.46, 1.12)	0.66	(0.40, 1.06)	0.78	(0.39, 1.57)	1.28	(0.63, 2.62)
Business and Financial Operations	0.84	(0.52, 1.38)	0.78	(0.45, 1.34)	1.09	(0.52, 2.30)	1.42	(0.66, 3.03)
Computer and Mathematical	0.44	(0.18, 1.07)	0.38	(0.13, 1.07)	0.72	(0.19, 2.71)	1.67	(0.38, 7.17)
Architecture and Engineering	1.05	(0.26, 4.32)	0.81	(0.14, 4.54)	2.11	(0.35, 12.66)	3.08	(0.42, 22.50)
Life, Physical, and Social Science	**4.57**	**(1.34, 14.55)**[b]	**5.72**	**(1.80, 18.20)**[b]	1.34	(0.13, 14.18)	0.16	(0.02, 1.25)
Community and Social Service	0.85	(0.39, 1.89)	0.9	(0.39, 2.05)	0.81	(0.18, 3.74)	0.65	(0.14, 3.06)
Legal Occupations	0.67	(0.21, 2.16)	0.73	(0.21, 2.52)	0.63	(0.07, 5.50)	0.73	(0.08, 6.64)
Education, Training, and Library	1.15	(0.77, 1.71)	1.03	(0.67, 1.59)	1.49	(0.80, 2.78)	1.41	(0.75, 2.66)
Arts, Design, Entertainment, Sports and Media	0.68	(0.34, 1.35)	0.62	(0.29, 1.32)	0.72	(0.25, 2.06)	1.22	(0.41, 3.57)
Healthcare Practitioners and Technical	1.22	(0.78, 1.90)	1.23	(0.77, 1.98)	1.13	(0.55, 2.34)	1.07	(0.53, 2.15)
Healthcare Support	1.62	(0.88, 2.98)	1.68	(0.88, 3.22)	1.36	(0.50, 3.73)	0.88	(0.34, 2.34)
Food Preparation and Serving Related	1.55	(0.92, 2.61)	**1.87**	**(1.08, 3.24)**[b]	0.81	(0.30, 2.17)	0.58	(0.23, 1.49)
Building and Grounds Cleaning and Maintenance	0.97	(0.48, 1.95)	1.04	(0.49, 2.19)	0.69	(0.23, 2.03)	0.96	(0.35, 2.60)
Personal Care and Service	0.84	(0.48, 1.47)	0.98	(0.54, 1.75)	0.61	(0.22, 1.72)	0.6	(0.22, 1.65)
Sales and Related Occupations	0.73	(0.51, 1.06)	0.75	(0.51, 1.12)	0.7	(0.37, 1.32)	0.86	(0.45, 1.65)
Office and Administrative Support	1.15	(0.85, 1.55)	1.21	(0.88, 1.67)	1.01	(0.60, 1.71)	0.79	(0.47, 1.33)
Production Occupations	1.61	(0.94, 2.76)	1.26	(0.69, 2.31)	**3.15**	**(1.52, 6.55)**[b]	1.96	(0.97, 3.95)
Transportation and Material Moving	0.94	(0.41, 2.17)	0.82	(0.62, 1.13)	1.14	(0.33, 3.88)	1.58	(0.44, 5.63)
Unemployed	0.92	(0.65, 1.32)	0.93	(.63, 1.37)	0.93	(0.52, 1.70)	0.88	(0.50, 1.57)

[a] Comparisons were made with MI as the referent group.
[b] Bolding denotes statistically significant results.

aliphatic, aromatic (e.g. gasoline, benzene, xylene, toluene) and halogenated solvents (e.g. methylene chloride, perchloroethylene).

4. Discussion

We observed several occupation classes with greater odds of chromosome 21 nondisjunction. A hypothesis-generating evaluation of exposure agents did not identify a specific agent that increased the likelihood of MII nondisjunction within selected occupational classes. However, MI errors were associated with solvent exposure among production workers. It is important to point out that the Production Occupations category represents a heterogeneous group of occupations in regard to exposures (Supplementary Table I). Furthermore, the sample size of mothers with MII errors was relatively small. Thus, a larger sample size would provide the ability to examine more detailed SOC codes and tease out underlying associations between occupation and nondisjunction as they pertain to MII type errors. With a larger sample size, it would also be possible to categorize exposure by estimated dose/frequency and confidence rather than as a simple dichotomous variable.

Solvent exposure demonstrated an increased likelihood of MI nondisjunction among Production Workers, an occupation class that was not associated with increased likelihood of MI errors from the primary analyses. Experimental research in animal models has demonstrated that some organic solvents cross the placental barrier and can be embryotoxic, genotoxic, and teratogenic (Desrosiers et al., 2015; Klaassen et al., 2013). There have been systematic reviews of environmental and occupational risk factors for adverse reproductive outcomes due to solvent exposure. However, results are limited by a variety of inconsistencies across studies including differences in study design, exposure assessment strategies and nationally acceptable levels of exposure, making synthesis of such results difficult to interpret (Nieuwenhuijsen et al., 2013a,b; Snijder et al., 2012; Stillerman et al., 2008; Windham and Fenster, 2008; Burdorf et al., 2006). Nonetheless, such work is valuable as it adds to what is currently understood in this ever-evolving field. Solvent exposure during the mother's lifetime up until conception may influence oocyte quality, and this could account for the observed increase in MI errors. Further research is warranted to confirm our findings and to understand the biological mechanism by which this could occur.

Table 4
Prevalence of exposure among statistically significant work categories stratified by occupation.

	Food Preparation & Serving Related Occupations N = 80				Life, Physical, and Social Science Occupations N = 23				Production Occupations N = 77			
	Controls N = 48 N(%)	All Cases N = 32 N(%)	MI Cases N = 26 N(%)	MII Cases N = 6 N(%)	Controls N = 7 N(%)	All Cases N = 16 N(%)	MI Cases N = 15 N(%)	MII Cases N = 1 N(%)	Controls N = 29 N(%)	All Cases N = 48 N(%)	MI Cases N = 28 N(%)	MII Cases N = 20 N(%)
Disinfectant & Cleaners	48(100)	32(100)	26(100)	6(100)	5(71.4)	9(56.3)	9(60.0)	0(0.0)	6(20.7)	11(22.9)	5(17.9)	6(30.0)
Solvents	0(0)	0(0)	0(0)	0(0)	4(57.1)	7(43.8)	7(46.7)	0(0.0)	3(10.3)	18(37.5)	15(53.6)	3(15.0)
Infectious Agents	2(4.2)	0(0)	0(0)	0(0)	3(42.9)	7(43.8)	7(46.7)	0(0.0)	4(13.8)	7(14.6)	3(10.7)	4(20.0)
Metals	0(0)	0(0)	0(0)	0(0)	0(0.0)	1(6.3)	1(6.7)	0(0.0)	8(27.6)	19(39.6)	14(50.0)	5(25.0)
Oil Mists	0(0)	0(0)	0(0)	0(0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	16(55.2)	20(41.7)	17(60.7)	3(15.0)
Antibiotics	0(0)	0(0)	0(0)	0(0)	1(14.3)	2(12.5)	2(13.3)	0(0.0)	4(13.8)	5(10.4)	3(10.7)	2(20.0)
Pesticides	48(100)	32(100)	26(100)	6(100)	0(0.0)	4(25.0)	4(26.7)	0(0.0)	9(31.0)	11(22.9)	5(17.9)	6(30.0)
PAHs	45(93.8)	31(96.9)	25(96.2)	6(100)	2(28.6)	3(18.8)	3(20.0)	0(0.0)	6(20.7)	14(29.2)	8(28.6)	6(30.0)

Table 5
Results from logistic regression models determining the effect of exposure to environmental agent on nondisjunction case outcome and stage of origin adjusting for maternal age and stratifying by occupational class.

	Life, Physical, and Social Science[c]			Production Workers		
	OR	95% CI	N Cases (Ca)[d] N Controls (Co)[d]	OR	95% CI	N Cases (Ca)[d] N Controls (Co)[d]
Maternal Case vs. Control						
Disinfectants and Cleaners	0.91	(0.12, 7.91)	Ca = 9, Co = 5	1.56	(0.44, 5.48)	Ca = 11, Co = 6
Solvents	1.14	(0.14, 9.31)	Ca = 7, Co = 4	**5.50**[e]	**(1.30, 23.31)**	Ca = 18, Co = 3
Infectious agents	1.96	(0.24, 16.13)	Ca = 7, Co = 3	1.48	(0.34, 6.41)	Ca = 7, Co = 4
Metals[a]	–	–	–	1.53	(0.49, 4.78)	Ca = 19, Co = 8
Oil Mist[b]	–	–	–	0.61	(0.21, 1.78)	Ca = 20, Co = 16
Antibiotics	0.66	(0.04, 11.18)	Ca = 2, Co = 1	0.75	(0.15, 3.83)	Ca = 5, Co = 4
Pesticides[a]	–	–	–	0.93	(0.29, 2.98)	Ca = 11, Co = 9
Polycyclic Aromatic Hydrocarbons (PAHs)	1.24	(0.12, 12.85)	Ca = 3, Co = 2	1.66	(0.49, 5.72)	Ca = 14, Co = 6
MI Case vs. Control						
Disinfectants and Cleaners	1.00	(0.11, 8.75)	Ca = 9, Co = 5	1.00	(0.21, 4.86)	Ca = 5, Co = 6
Solvents	1.21	(0.15, 9.79)	Ca = 7, Co = 4	**8.23**[e]	**(1.68, 40.35)**	Ca = 15, Co = 3
Infectious agents	2.05	(0.25, 16.76)	Ca = 7, Co = 3	0.80	(0.11, 5.55)	Ca = 1, Co = 1
Metals[a]	–	–		2.06	(0.55, 7.69)	Ca = 14, Co = 8
Oil Mist[b]	–	–		1.41	(0.39, 5.14)	Ca = 17, Co = 16
Antibiotics	0.70	(0.04, 11.69)	Ca = 2, Co = 1	0.80	(0.11, 5.55)	Ca = 3, Co = 4
Pesticides[a]	–	–		0.62	(0.14, 2.73)	Ca = 5, Co = 9
Polycyclic Aromatic Hydrocarbons (PAHs)	1.26	(0.12, 12.94)	Ca = 3, Co = 2	1.20	(0.27, 5.37)	Ca = 8, Co = 6
MII Case vs. Control						
Disinfectants and Cleaners	–	–	–	2.58	(0.58, 11.50)	Ca = 6, Co = 6
Solvents	–	–	–	3.43	(0.56, 20.91)	Ca = 3, Co = 3
Infectious agents	–	–	–	2.61	(0.49, 13.94)	Ca = 4, Co = 4
Metals	–	–	–	1.23	(0.28, 5.31)	Ca = 5, Co = 8
Oil Mist	–	–	–	0.23	(0.05, 1.08)	Ca = 3, Co = 16
Antibiotics	–	–	–	0.83	(0.11, 6.25)	Ca = 2, Co = 4
Pesticides	–	–	–	1.54	(0.37, 6.33)	Ca = 6, Co = 9
Polycyclic Aromatic Hydrocarbons (PAHs)	–	–	–	2.58	(0.58, 11.50)	Ca = 6, Co = 6

[a] No controls were exposed so a comparison cannot be made.
[b] No study subjects were exposed to this agent.
[c] Only 1 MII case in life, physical, and social science occupations, therefore comparisons between MII cases and controls cannot be made.
[d] Shown as the number of cases or controls exposed to the environmental agent of interest.
[e] Bolding signifies significant finding.

Our study has several strengths. To our knowledge, this is the first population-based study in the U.S. to investigate the association between maternal occupation and trisomy 21 through exposure. The multistate population-based design allowed for inclusion of a wide range of occupations, as opposed to focusing on one geographic location or industry. This gives these findings greater generalizability to the population of women in the U.S. who work prior to conception and perhaps during pregnancy. The exposure assessment strategy used for this study reduces concern for recall bias and exposure misclassification, both differential and non-differential, as it relies on more information than job title alone and is not based on self-reported occupational exposures.

Several limitations are important to discuss. By enrolling only live-born infants to this study, pregnancies with DS that were spontaneously aborted or terminated could not be included. Although the total sample size is relatively large, when broken down by occupation classes the numbers of women in certain occupations can be quite small. Similarly, for the exposure analysis the sample size was further reduced, which may affect the precision of the effect measure estimates and may not be representative of the entire study population. Information on non-occupational exposures, such as living environment and recreational hobbies, was not collected and therefore not included in the exposure classification. Therefore, the occupational exposure profiles may be a snapshot of lifetime exposures and there could be other exposures influencing the estimate of association that could not be accounted for in this analysis. Our reference group for analyzing the effect of occupational class was comprised of women who were not part of the occupation class, which included unemployed women. We conducted a sub-analysis restricting the reference group to employed women only, which did not substantially alter results (Supplementary Table II). The findings from the sub-analysis provide added reassurance that the findings from the primary analysis (Table 3) are robust and not caused by a healthy worker effect or other types of bias.

Our results provide evidence that environmental exposures through maternal occupation prior to conception may increase the risk of chromosome nondisjunction and should be a focus of future studies to determine toxigenic profiles associated with this increased risk along with the biochemical, psychosocial, and molecular sources of these exposures. The exposure assessment was only performed in three select occupation classes so that hypotheses for future research could be generated. The results from this exposure assessment did not identify agents associated with MII nondisjunction; however, with such select representation of the study population a full grasp of the situation may not be possible. There could be multiple risk factors that relate to the etiology of MII nondisjunction that were undetectable through the exploratory analysis. Currently, an exposure analysis on all study subjects is underway to determine whether these associations are a product of agent exposure, occupational bracket, or something else entirely. Understanding this relationship may lead to recognition of one or more factors which may have independent or synergistic adverse effects on maternal chromosome 21 nondisjunction events. This study is the first of its kind, and there is ample room for additional research to be done. Taking this initial step forward in characterizing occupational exposures and chromosome 21 nondisjunction could promote gathering occupation information on future registry studies.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijheh.2019.09.001.

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