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Association of twins' sex discordance and age at menarche

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Abstract

Introduction Age at menarche (AAM) is the point in development when the female starts her first menstrual period and is one of the first milestones in female reproductive life. A combination of genetic and environmental factors plays a role in the timing of female's age at menarche.

Material and methods This study's purpose was to investigate the association between the biological sex of the co-twin and the age at menarche experienced by the female twin. Females from pairs of female–female twins ($n = 12{,}176$) and female–male twins ($n = 2286$) were collected through the Washington State Twin Registry.

Results Environmental and genetic analyses were conducted. There was no significant difference between females with female twins and females with male twins regarding early, late or normal age at menarche ($P = 0.87$). However, the adjusted odds of early menarche among females with female twins were 35% lower than females with male co-twins (0.65, 95% CI 0.50–0.83). When using Falconer's formula, an estimated heritability of 0.81 was found with shared (21.8%) and non-shared (40.8%) environmental factors contributing to the age at menarche.

Conclusion Having a male twin during fetal life as a co-twin does not change the age of menarche in future life, although female–female twins have lower age of menarche compared to females from female–male pair. Both genetic and environmental factors determine the age of menarche.

Keywords Age of menarche · Twin · Sex discordance

Introduction

Age at menarche is defined as the age at which a female begins her first menstrual period [1]. Age at menarche has been found in previous studies to occur, on average, around 12–13 years of age among females in the United States [2, 3]. Early age at menarche has previously been associated with a variety of health outcomes including cardiovascular disease, type 2 diabetes [4], depression, eating disorders, and breast cancer [5, 6]. Previous studies have defined early menarche as before the age of 12 and late menarche as after the age of 14.3 years of age [3]. Because of the role that age at menarche plays in overall health, many studies have investigated the genetic and environmental factors that impact age at menarche in females. This study is investigating the impact that sex of a co-twin has on a female twin's age at menarche.

Among the various environmental and genetic factors considered to impact period age, one factor that has come into question is the impact of sex discordance (female–female co-twins in comparison to femalemale co-twins). Prenatal hormone levels have been commonly studied in many litter-bearing mammals due to the ethical concerns with studying and manipulating human fetuses in utetro [15]. With such animal-based twin studies being so readily available they are commonly used for evaluating the transfer of prenatal hormones among opposite sex twin pairs [7]. While one previous study among Malaysian and Iranian twins had found no significant differences between sex of co-twin and age at menarche [1], another study had found a significant difference among Finnish twin populations [10].

The current study investigates the impact of co-twin's sex on the age at menarche of female twins among participants in the Washington State Twin Registry. In this study we hope to get a better understanding of some of the environmental

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and genetic factors that come into play with influencing age at menarche.

Methods

Samples

The Washington State Twin Registry was established in 2002 at the University of Washington. The collected data from several cohorts till 2009. Twin pairs born in the state of Washington are identified through the Department of Licensing to avoid the use of duplicate license numbers [8]. Through these records, those over the age of 18 were recruited to join the state's twin registry.

The sample relevant to female reproductive history consisted of 14,462 female twins in the state of Washington. Included in this set were 12,176 females from same-sex twin sets (84.2%) and 2286 females from opposite-sex twin sets (15.8%).

Definitions

Monozygotic twins are originated from one egg and can only have the same gender (either malemale or female–female) while dizygotic twins can either be female–female or femalemale. A femalemale twin, therefore, cannot be monozygotic.

Measures

The Health and Wellbeing Survey that was utilized included questions on a variety of lifestyle factors. Background information on socio-demographic factors relevant to this study includes the following variables: marital status, level of education, employment status, and household income.

Inclusion of the following questions assessed reproductive health histy of female participants: age at menarche, polycystic ovarian syndrome, histy of pregnancies, number of living children, number and type of miscarriages, and histy of infertility.

Statistical analyses

Descriptive analysis was executed using SPSS software. Age at menarche was categorized into three groups including early menarche (under 9–12), regular menarche (13–14), and late menarche (15–16 and older). Descriptive analysis and computation of variance and covariance of variables w done using SPSS version 24.

Genetic analysis

Genetic analysis was done using Falconer's formula to estimate heritability. Heritability (h^2) was calculated using $h^2 = 2(r_{MZ} - r_{DZ})$. Shared environment, or common environment (C), is estimated by deducting heritability value from MZ correlation: $C = (r_{MZ} - h^2)$. Non-shared environment (E)is an estimation of the degree to which identical twins that are raised together are dissimilar. Non-shared environment is calculated using $E = (1 - r_{MZ})$.Genetic analysis was limited to these basic estimations of heritability.

Results

Descriptive analysis

Descriptive analysis of socio-demographic characteristics of female twins ($n = 14{,}462$) is shown in Table 1 The average age of the survey participants was 41.18 ± 17.66 years with all participants falling between the ages of 18.02 and 97 years of age. The average BMI of the survey participants was 25.69 ± 6.03 kg/m^2. More than 47% of females surveyed reported early menarche, 28.5% of females reported normal menarche, and 23.9% of females reported late menarche. Most of the females were white (93.1%), attended some college (26.8%), worked full time (41.1%), had a household income of over $80,000 (34.1%) and were married (47.1%). The majority of the subjects were monozygotic (57.7%), from female–female twin pairs (84.2%), and had a co-twin that weighed more at birth (52.4%). Only 5.5% of twins still lived in the same room as their co-twin and 8.4% of twins were not separated from their co-twin at the time of taking the study. Over 24% of twins lived in separate rooms between ages 11 and 14 and 64.4% of twins were separated between ages 18 and 21.

Descriptive analysis of reproductive health characteristics is shown in Table 2. Over 17% of subjects reported having a miscarriage, 9.8% reported fertility issues, and 4.2% reported polycystic ovarian syndrome (PCOS). At the time of the survey 97.2% of females were not currently pregnant. Over 45% of subjects did not have any living children and 24.2% of subjects had two living children.

Bivariate analysis

Table 3 focuses on bivariate analysis of socio-demographic and reproductive health characteristics when comparing female–female ($n = 12{,}176$) and femalemale ($n = 2286$) twins. There was no significant difference between females with female twins and females with male twins in regard to age at menarche ($P = 0.87$). There was a significant

Table 1 Sociodemographic of female Washington State twin registry participants

Quantitative variable	Mean (SD)	Min–max
Age	41.18 ± 17.66	18.02–97
BMI	25.69 ± 6.03	13–72
Qualitative variable	Frequency	Percentage
Age at menarche		
Early menarche	6038	47.5
Nmal menarche	3626	28.5
Late menarche	3039	23.9
Sex discdance		
FF	12,176	84.2
MF	2286	15.8
Zygosity		
MZ	8342	57.7
DZ	6120	42.3
Birth weight discdance		
You	2122	47.6
Your twin	2334	52.4
Birthder		
You	4059	49.5
Your twin	4056	49.5
Unknown	82	1
Age of separate rooms		
Never	292	5.5
Befe age 6	692	13
Age 6–10	961	18
Age 11–14	1314	24.7
Age 15–17	859	16.1
Age 18–21	1082	20.3
Age 22–24	104	2
Age 25older	25	0.5
Age apart from twin		
Still together	534	8.4
Befe age 6	16	0.3
Age 6–10	21	0.3
Age 11–14	73	1.2
Age 15–17	718	11.3
Age 18–21	4074	64.4
Age 22–24	700	11.1
Age 25older	194	3.1
Race		
White	13,467	93.1
Asian	545	3.8
Black	338	2.3
Hispanic	543	3.8
Native	229	1.6
Pacific islander	110	0.8
Other	2.5	1.4
Education		
Grade 1–8	34	0.2
Grade 9–11	371	2.6
Grade 12/High School/GED	2195	15.2
Some college	3870	26.8
Associate's degree	1232	8.5
Technicalvocational degree	183	1.30
Bachel's degree	3584	24.8
Graduateprofessional degree	2532	17.5
Employment status		
Wking full time	397	41.1
Wking part time	157	16.3
Unemployed	100	10.4
Temparily laid off, sick leave, other	7	0.7
Disabled	31	3.2
Homemaker	70	7.2
Retired, no longer wking	179	18.5
Retired, wking fullpart time	25	2.6
Household income		
Less than $20,000	2092	15.6
$20,000–29,999	1159	8.6
$30,000–39,999	1271	9.5
$40,000–49,999	1196	8.9
$50,000–59,999	1139	8.5
$60,000–69,999	1042	7.8
$70,000–79,999	946	7
$80,000+	4584	34.1
Marital status		
Single	4203	29.1
Married	6808	47.1
Widowed	490	3.4
Divced	1325	9.2
Separated	155	1.1
Living with partner	920	6.4

difference between the two groups in terms of zygosity, birth weight discordance, race, and employment status in regard to age at menarche ($P < 0.01$). All the reproductive health characteristics had no significant difference between female–female and femalemale twins in regard to age at menarche.

Unadjusted and adjusted regression

Unadjusted and adjusted regressions are shown in Table 4. Before adjusting for other characteristics, none of the socio-demographic or reproductive health characteristics were found to be significant when obtaining the association between early age at menarche and normal age at menarche.

We found a significant association between early age of menarche and sex discordance after adjusting for zygosity, birth weight discordance, birth order, race, fertility issues,

Table 2 Reproductive health characteristics of female Washington State twin registry participants

Qualitative variable	Frequency	Percentage
Miscarriage		
Yes	2116	17.2
No	10,202	82.8
First trimester miscarriage		
Yes	193	23.6
No	626	76.4
Late-term miscarriage		
Yes	45	5.5
No	770	94.5
Fertility issues		
Yes	1418	9.8
No	12,439	86
Polycystic ovarian syndrome		
Yes		4.2
No	12,930	95.8
Currently pregnant		
Yes	179	2.8
No	6298	97.2
Previous pregnancy		
Yes	3805	26.3
No	2664	41.2
Living children		
Zero	5588	45.1
One	1688	13.6
Two	2998	24.2
Three	1361	11
Four	486	3.9
Five	155	1.3
Six	59	0.5
Seven or me	49	0.4

and PCOS. The odds of early menarche among females with female twins were 35% lower than females with male co-twins (0.65, 95% CI 0.50–0.83).

The odds of early menarche among dizygotic (DZ) twins were 25% lower than monozygotic (MZ) twins (0.75, 95% CI 0.61–0.93). The odds of early menarche among subjects who are born first were 25% higher than subjects who were born second (1.25, 95% CI 1.04–1.49). The odds of early menarche among subjects who experienced fertility issues were 29% lower than those who did not experience fertility issues (0.71, 95% CI 0.52–0.96).

Basic genetic analysis

Data related to genetic analysis found in Table 5. When using Falconer's formula it was found that shared (21.8%) and non-shared (40.8%) environmental factors contributed to determining the age at menarche. Pearson correlation for dizygotic twins was calculated to be 0.19 ($P < 0.01$). Pearson correlation for monozygotic twins was calculated to be 0.59 ($P < 0.01$). Based off of these calculated values, heritability was estimated to be 0.81.

Discussion

The purpose of this study was to find the association between age at menarche and sex discordance among twins. We had hypothesized that sex discordance in twins would be associated with female twin's age at menarche. This hypothesis was supported when other variables were adjusted for. Jahanfar et al.[1] had found no significant differences between female–female twins and femalemale twins in regard to age at menarche among Malaysian and Iranian twins [1]. Previous studies using the Finnish twin registry had found a significant difference between female–female twins and femalemale twins in regard to age at menarche [10].

As hypothesized, genetics were found to play an important role in determining age at menarche among females in the Northwest United States. These results agree with previous studies that found heritability estimated at 0.71 among Australian subjects [9], 0.66 among Malaysian and Iranian subjects [1], and 0.675 among Finnish subjects [10].

In a previous study using primates, age at menarche was delayed among those exposed to prenatal androgens [11]. Previous findings are conflicting with the current study, which suggest that females with male co-twins are more likely to experience early age at menarche than females with female co-twins. Due to the inability to monitor prenatal androgen levels in research utilizing twin studies, there is difficulty in finding associations between the two study types.

The biggest strength of this study is the size of the subject pool in the Washington State Twin Registry. Previous studies on the topic of sex discordance did not exceed 1500 subjects, while the Washington State Twin Registry have over 14,000 subjects that were relevant to female reproductive health research. The twin registry used in this study also represented the largest age range of subjects in comparison to previous research on the topic [10], [1].

There were a few potential limitations to this study. The twin registry used in this study only includes twins living

Table 3 Bivariate analysis of females with male co-twins and females with female co-twins

	FF ($n=12,176$)	MF ($n=2286$)	p value
Age at menarche			
Early menarche	4296 (79.7%)	1097 (20.3%)	0.87
Nmal menarche	2605 (80.1%)	648 (19.9%)	
Late menarche	2157 (79.6%)	553 (20.4%)	
Zygosity			
MZ	8330 (99.9%)	12 (0.1%)	0.01
DZ	3846 (62.8%)	2274 (37.2%)	
Birth weight discdance			
You	1910 (90.0%)	212 (10.0%)	0.01
Your twin	1919 (82.2%)	415 (17.8%)	
Same	234 (84.2%)	44 (15.8%)	
Don't know	523 (87.5%)	75 (12.5%)	
Birthder			
You	2283 (86.2%)	365 (13.8%)	0.90
Your twin	2272 (86.0%)	377 (14.2%)	
Don't know	43 (86.0%)	7 (14.0%)	
Race			
White	11,281 (72.1%)	4372 (27.9%)	0.01
Asian	500 (84.7%)	90 (15.3%)	0.01
Black	286 (73.3%)	104 (26.7%)	0.78
Hispanic	488 (81.6%)	110 (18.4%)	0.01
Native	203 (79.0%)	54 (21.0%)	0.02
Pacific islander	100 (83.3%)	20 (16.7%)	0.01
Other	192 (88.1%)	26 (11.9%)	0.01
Education			
Grade 1–8	34 (75.6%)	11 (24.4%)	0.16
Grade 9–11	329 (67.7%)	157 (32.3%)	
Grade 12/high school/GED	1904 (71.9%)	744 (28.1%)	
Some college	3253 (73.0%)	1202 (27.0%)	
Associate's degree	1008 (73.4%)	366 (26.6%)	
Technicalvocational degree	152 (77.9%)	43 (22.1%)	
Bachel's degree	3018 (72.3%)	1155 (27.7%)	
GraduateProfessional degree	2052 (72.1%)	793 (27.9%)	
Employment status			
Wking full time	334 (70.3%)	141 (29.7%)	0.01
Wking part time	134 (77.0%)	40 (23.0%)	
Unemployed	88 (78.6%)	24 (21.4%)	
Temparily laid off, sick leave, other	7 (77.8%)	2 (22.2%)	
Disabled	25 (65.8%)	13 (34.2%)	
Homemaker	61 (87.1%)	9 (12.9%)	
Retired, no longer wking	137 (63.7%)	78 (36.3%)	
Retired, wking fullpart time	23 (65.7%)	12 (34.3%)	
Household income			
Less than $20,000	1725 (73.4%)	624 (26.6%)	0.21
$20,000–29,999	982 (73.3%)	358 (26.7%)	
$30,000–39,999	1037 (73.0%)	383 (27.0%)	
$40,000–49,999	983 (73.2%)	360 (26.8%)	
$50,000–59,999	970 (73.1%)	357 (26.9%)	
$60,000–69,999	830 (69.4%)	366 (30.6%)	
$70,000–79,999	784 (71.7%)	310 (28.3%)	
$80,000 +	3978 (71.8%)	1566 (28.2%)	

Table 3 (continued)

	FF ($n=12,176$)	MF ($n=2286$)	p value
Marital status			
Single	3712 (72.1%)	1439 (27.9%)	0.50
Married	5679 (72.2%)	2185 (27.8%)	
Widowed	367 (74.6%)	125 (25.4%)	
Divced	1031 (71.8%)	405 (28.2%)	
Separated	141 (76.6%)	43 (23.4%)	
Living with partner	733 (73.7%)	261 (26.3%)	
Miscarriage			
Yes	1493 (82.5%)	317 (17.5%)	0.29
No	7338 (83.5%)	1149 (16.5%)	
First trimester miscarriage			
Yes	107 (83.6%)	21 (16.4%)	0.55
No	349 (85.7%)	58 (14.3%)	
Late-term miscarriage			
Yes	25 (83.3%)	5 (16.7%)	0.78
No	426 (85.2%)	74 (14.8%)	
Fertility issues			
Yes	1114 (73.5%)	401 (26.5%)	0.28
No	10,456 (72.2%)	4019 (27.8%)	
Polycystic ovarian syndrome			
Yes	415 (82.2%)	90 (17.8%)	0.11
No	9090 (79.3%)	2380 (20.7%)	
Currently pregnant			
Yes	92 (80.7%)	22 (19.3%)	0.12
No	3548 (85.9%)	584 (14.1%)	
Previous pregnancy			
Yes	2129 (85.8%)	351 (14.2%)	0.87
No	1506 (85.7%)	252 (14.3%)	
Living children			
Zero	4792 (72.0%)	1860 (28.0%)	0.32
One	1397 (72.4%)	532 (27.6%)	
Two	2455 (72.4%)	935 (27.6%)	
Three	1091 (70.9%)	447 (29.1%)	
Four	392 (67.4%)	190 (32.6%)	
Five	137 (72.5%)	52 (27.5%)	
Six	49 (71.0%	20 (29.0%)	
Seven or me	36 (66.7%)	18 (33.3%)	

in the state of Washington, making this study representative of only a small portion of females racially and geographically. Another potential limitation of this study was the use of self-reported data. Due to the large age range of subjects in this study, the possibility of recall bias is higher than in studies that utilized twins under the age of 20 [10]. Even though this study dealt with potential of recall bias, previous studies into recalling age at menarche found mean errors to be lower than 0.5 years [12, 13]. Another limitation to this study was temporality, or the order in which information regarding the exposure and outcome are collected [14]. Due to the cross-sectional nature of this study, the time sequence between data collection does not allow for causal links between any of the variables tested. There is also no report of BMI available at the time of menarche which could be an important confounder in the relationship between sex discordance and age of menarche.

Results of this study have important clinical implications in obstetrics and gynecological practices. Age at menarche has been found in previous studies to be associated with many reproductive and other health outcomes including breast cancer, disordered eating, and breast cancer [5], [6]. Early menarche was found in this study to be lower among those who experienced fertility issues. Age at menarche is an

Table 4 Unadjusted and adjusted regression when comparing early menarche and normal menarche

	Early menarche vs. nmal menarche Unadjusted odds ratio (95% CI)	Early menarche vs. nmal menarche Adjusted odds ratio (95% CI)
Sex discdance		
MF	1.01 (0.94–1.08)	Ref.
FF	Ref.	0.65 (0.50–0.83)
Zygosity		
MZ	Ref.	Ref.
DZ	0.97 (0.89–1.05)	0.75 (0.61–0.93)
Birth weight discdance		
You	0.96 (0.83–1.11)	0.95 (0.79–1.14)
Your twin	Ref.	Ref.
Birthder		
You	1.08 (0.95–1.23)	1.25 (1.04–1.49)
Your twin	Ref.	Ref.
Race		
White	0.96 (0.82–1.14)	0.82 (0.60–1.12)
Asian	0.96 (0.77–1.20)	0.80 (0.59–1.09)
Black	0.88 (0.68–1.17)	0.75 (0.53–1.07)
Hispanic	1.16 (0.92–1.47)	1.19 (0.90–1.57)
Native	1.26 (0.89–1.79)	1.16 (0.81–1.67)
Pacific islander	1.43 (0.86–2.38)	1.26 (0.73–2.17)
Other	0.99 (0.70–1.40)	0.68 (0.41–1.15)
Education		
Grade 1–8	0.83 (0.33–2.07)	
Grade 9–11	1.10 (0.84–1.44)	
Grade 12/high school/GED	0.97 (0.84–1.12)	
Some college	1.00 (0.88–1.14)	
Associate's degree	1.07 (0.91–1.26)	
Bachel's degree	0.99 (0.87–1.12)	
Graduateprofessional degree	Ref.	
Employment status		
Wking full time	Ref.	
Wking part time	1.02 (0.67–1.56)	
Unemployed	1.49 (0.87–2.56)	
Temparily laid off, sick leave, other	3.12 (0.36–27.03)	
Disabled	2.00 (0.71–5.59)	
Homemaker	0.90 (0.49–1.67)	
Retired, no longer wking	0.97 (0.64–1.49)	
Retired, wking fullpart time	0.89 (0.33–2.41)	
Employment status (categical)		
Wking currently	0.87 (0.64–1.18)	
Not wking currently	Ref.	
Marital status		
Single	0.95 (0.79–1.13)	
Married	1.04 (0.87–1.23)	
Widowed	0.83 (0.63–1.09)	
Divced	0.93 (0.76–1.15)	
Separated	1.11 (0.71–1.73)	
Living with partner	Ref.	
Fertility issues		
Yes	Ref.	Ref.

Table 4 (continued)

	Early menarche vs. nmal menarche Unadjusted odds ratio (95% CI)	Early menarche vs. nmal menarche Adjusted odds ratio (95% CI)
No	0.87 (0.75–1.00)	0.71 (0.52–0.96)
Polycystic ovarian syndrome		
Yes	Ref.	Ref.
No	0.65 (0.52–0.81)	0.82 (0.53–1.29)
Living children		
Zero	0.97 (0.50–1.89)	
One	0.99 (0.51–1.94)	
Two	0.92 (0.47–1.78)	
Three	1.08 (0.55–2.11)	
Four	0.89 (0.45–1.79)	
Five	0.99 (0.46–2.10)	
Six	1.00 (0.39–2.54)	
Seven or me	Ref.	

Table 5 Genetic analysis of age at menarche between monozygotic and dizygotic twins

	Subject	Mean (SD)	*N*	*p* value	Pearson's *r*
Dizygotic (DZ) twin pairs	Age at menarche of twin 1	4.69 ± 1.47	2712	0.01	0.19
	Age at menarche of twin 2	4.65 ± 1.48	2630		
Monozygotic (MZ) twin pairs	Age at menarche of twin 1	4.66 ± 1.44	3670	0.01	0.59
	Age at menarche of twin 2	4.65 ± 1.38	3691		

important milestone in a female's life in the medical realm as well as socially [15, 16, 17]. Further research into the genetic and environmental factors associated with age at menarche is important in better understanding the obstetric and gynecological health outcomes.

Authors' contribution SJ has come up with the idea, drafted the proposal, cured and analyzed the data, produced outputs and critically appraised the paper, suppting and supervising HW. HW wrote the first draft, prepared tables and found the references. This was a capstone research project.

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Compliance with ethical standards

Conflict of interest The auths declare that they have no competing interests.

Ethical approval All procedures perfmed in studies involving human participants were in accdance with the ethical standards of the institutional and/national research committee and with the 1964 Helsinki Declaration and its later amendmentscomparable ethical standards. No procedure perfmed on humans. This article does not contain any studies with animals perfmed by any of the authors.

Informed consent Informed consent if the research involved Human participants: We used secondary data that collected by Washington State University Twin Registry. The consent form was filled by each participants at the time of participation.

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