Twin Research and Human Genetics (2023), **26**, 199–208
doi:10.1017/thg.2023.23

CAMBRIDGE UNIVERSITY PRESS

Article

Handedness and 23 Early Life Characteristics in 37,495 Dutch Twins

Veronika V. Odintsova[1,2], Jenny van Dongen[1,2], Catharina E. M. van Beijsterveldt[1], Lannie Ligthart[1], Gonneke Willemsen[1], Eco J. C. de Geus[1], Conor V. Dolan[1] and Dorret I. Boomsma[1,2]

[1]Department of Biological Psychology, Vrije University Amsterdam, Amsterdam, The Netherlands and [2]Amsterdam Reproduction and Development (AR&D) Research institute, Amsterdam, The Netherlands

Abstract

In studies of singletons, a range of early-life characteristics have been reported to be associated with handedness, but some of these associations have failed to replicate. We examined associations between 23 early life characteristics with handedness in a large sample of 37,495 5-year-old twins. We considered three definitions of handedness: left-handedness (LH), mixed-handedness (MH), and non-right-handedness (NRH). Our main aim was to test whether the associations with sex, birth weight, gestational age, and season of birth — as reported in singletons — replicate in twins, and to examine twin-specific variables, including zygosity, chorionicity, birth order, and intertwin delivery time. Compared to previously published data from adults born as singletons (7.23%), the prevalence of NRH was higher in both twins (16.19%) and their parents (15.09%). In the twins, LH and NRH were associated with parents' LH. Male sex and lower gestational age were associated with NRH, and LH was associated with not being breastfed. MH was related to neurodevelopmental delays and higher externalizing problems later in childhood. Other previously reported associations were not replicated, and no twin-specific characteristics were related to handedness. These results emphasize the importance of considering multiple definitions of handedness and indicate a small number of replicated associations across studies.

Keywords: handedness; early life factors; prenatal factors; neurodevelopmental delay; externalizing problems; twins

(Received 17 May 2023; accepted 22 May 2023; First Published online 14 July 2023)

Handedness refers to the preference for, or the use of, one hand over the other hand, and can already be observed on ultrasound scans early in prenatal life (Hepper, 2013; Hepper et al., 1991; Parma et al., 2017). The most common form of handedness is right-handedness (RH), with a prevalence of around 90% in nearly all human populations, and the remaining is non-right-handed, which subsumes left- and mixed-handedness (LH and MH). Comparing twins with singletons in large meta-analysis, the prevalence of non-right-handedness (NRH) is higher in twins (11.11%) than in singletons (7.23%) (Pfeifer et al., 2022), and it has been hypothesized that this NRH is related to a higher rate of complications during multiple pregnancies and births (Davis & Annett, 1994; de Kovel et al., 2019; Ellis et al., 1988; Heikkilä et al., 2018; Heikkilä et al., 2015; Pfeifer et al., 2022; Sicotte et al., 1999; Vuoksimaa et al., 2009). Twins are generally born preterm and have a lower birth weight than singletons. They are also at a greater risk of congenital disorders and perinatal morbidity (Willemsen et al., 2021). The increased risk of complications in twins may be related to increased NRH, but a within-family analysis of twins and their siblings showed that the prevalence of LH among twins was comparable to that among their non-twin siblings (Medland et al., 2009; Medland et al., 2003).

Hypotheses concerning the etiology of handedness include polygenic (Armour et al., 2014) and epigenetic factors (Odintsova et al., 2022), environmental influences, and random or stochastic events (Annett, 1985; I. McManus, 1985). Medland et al. (2009) studied 54,270 twins and their non-twin siblings. Correcting for year of birth, birth weight and sex, the heritability of LH was estimated to be around 24%, with the remainder accounted for by nonshared environment. The heritability estimate based on measured genetic variants was 3.45% in a meta-analysis of genetic association studies (Cuellar-Partida et al., 2021) that found 41 loci associated with LH. A recent meta-analysis of DNA methylation in two cohorts ($N_{\text{bloodDNA}} = 3914$, $N_{\text{buccal}} = 1737$) detected a few cohort-specific differentially methylated regions associated with LH, but no robustly associated DNA methylation loci (Odintsova et al., 2022).

Identification of environmental factors is likely to be difficult (C. McManus, 2021), and the associations with pre- and perinatal factors were a focus for several decades. Bakan et al. (1973) related NRH to the 'birth stress' index, which incorporated multiple births, premature birth, prolonged labor, cesarean section, breech position and breathing difficulty at birth; that is, risk factors that may cause perinatal hypoxia and brain damage.

A meta-analysis of 23 studies comprising ~47,000 individuals reported that prenatal stress, fetal presentation (breech position in males), gestational age and mode of delivery (cesarean section)

Corresponding author: Veronika V. Odintsova; Email v.v.odintsova@vu.nl; Dorret Boomsma; Email: di.boomsma@vu.nl

Cite this article: Odintsova VV, van Dongen J, van Beijsterveldt CEM, Ligthart L, Willemsen G, de Geus EJC, Dolan CV, Boomsma DI. (2023) Handedness and 23 Early Life Characteristics in 37,495 Dutch Twins. *Twin Research and Human Genetics* **26**: 199–208, https://doi.org/10.1017/thg.2023.23

were associated with NRH (Searleman et al., 1989). A Danish study of ∼35,000 singletons found associations between MH and mother's and father's handedness, preterm birth and mode of conception with children conceived after intrauterine insemination having twice the risk of being mixed-handed compared to naturally conceived children (Zhu et al., 2009). Associations with parental age were inconsistent (Bailey & McKeever, 2004; Dragović et al., 2013; Johnston et al., 2013; Karev, 2008; Searleman et al., 1989). Stressful events in the third period of pregnancy were related to a higher prevalence of MH in offspring (Gutteling et al., 2007; Obel et al., 2003). Preterm born children were more often NRH than children born after 37 weeks of gestation (Domellöf et al., 2011; van Heerwaarde et al., 2020). NRH was also related to low Apgar scores (Dragović et al., 2013) and adverse later outcomes, including neurodevelopment and neuropathology (Darvik et al., 2018), and externalizing problems (Dinsdale et al., 2011; Logue et al., 2015; van der Feen et al., 2020). A large study of ∼500,000 adult participants from the UK Biobank reported higher rates of LH in males, increased prevalence of LH with more recent year of birth up to 1970, a higher prevalence of LH if born in the UK, if born during summer, if of lower birth weight, and not being breastfed (de Kovel et al., 2019).

Some studies reported that first-born twins are more likely to be left-handed than second-born twins (James & Orlebeke, 2002), but this finding has not been replicated (Derom et al., 1996; Medland et al., 2003, 2009; Vuoksimaa et al., 2010). One hypothesis is that the monozygotic twinning split could be related to NRH (Sicotte et al., 1999). However, monozygotic (MZ) and dizygotic (DZ) twins showed no difference in their prevalence of LH (Derom et al., 1996; Medland et al., 2003; Sicotte et al., 1999), and among MZ twins, no effect of chorionicity was found (Derom et al., 1996; van Beijsterveldt et al., 2016).

Our overview of 32 studies on the role of early life characteristics in handedness is presented in Supplementary Table 1. Clearly, many effects do not replicate. This may be due to differences in the definitions of handedness, the study populations, differences in assessment methods, or in the definition of predictor variables and limited sample size. Pfeifer et al. (2022) carried out a systematic review of handedness in twins that identified 59 studies of 63,295 twins, and performed meta-analyses that revealed sources of heterogeneity related to year of publication (pre- and post-1975), availability of information on pre- and perinatal conditions that could have a moderating effect on relationship between handedness and multiple birth in different studies, differences in definition of handedness (particularly MH), and determination of zygosity.

Here we present the results of analyses in a large sample of twins. We considered three definitions of handedness: (1) right-handed versus left-handed, (2) right-handed versus mixed-handed, and (3) right-handed versus non-right-handed, aiming (a) to determine whether the risk factors for handedness, as previously identified in singleton and population-based cohorts, replicate in twins; and (b) to test the associations between handedness and twin-specific characteristics. To these ends, we analyzed data on handedness from 5-year-old twins from the Netherlands Twin Register (NTR) who were born in the Netherlands after 1986 and followed longitudinally since birth (Ligthart et al., 2019).

Materials and Methods

Overview

We studied the association between handedness at 5 years and early life characteristics and outcomes in 37,495 Dutch twins. We considered three handedness definitions and investigated 23 variables related to prenatal and early life (see Supplementary Table 2). Six variables have been studied by de Kovel et al. (2019), and 13 have featured in previous studies of early life characteristics in association with handedness, including twin-specific characteristics such as zygosity and chorionicity. In addition, we included amnionicity and the time interval between the birth of the first and second twin, characteristics that have not been considered previously, although increased time interval has been associated with adverse neonatal outcomes for the second twin (Lindroos et al., 2018) and can be considered an indicator of birth-stress. As handedness is related to neurodevelopmental delays (Darvik et al., 2018) and externalizing problems (Dinsdale et al., 2011; Logue et al., 2015; van der Feen et al., 2020), we included neurodevelopmental delay at 5 years, and externalizing problems at 7 years.

Subjects

Initially, we obtained data on 38,496 5-year-old twins who were born between 1989 and 2014 and were registered with the NTR by their parents at birth. Informed consent was obtained from parents prior to recruitment. Surveys, including questions on pregnancy, birth details and the 23 variables of interest were sent to mothers after registration of their newborn twins. After excluding the twins without data on handedness, the resulting sample size was 37,495 twins in 18,630 complete and 235 incomplete twin pairs, and 31,813 parents of twins. The zygosity of the same-sex twins was determined by blood/DNA polymorphisms (18%), or by parental reports based on questionnaires addressing several aspects of physical resemblance and the degree to which the twins are confused by their parents or by other relatives and strangers (Ligthart et al., 2019). In 174 twins (0.46%), the information on zygosity was missing, and those were excluded from analysis testing zygosity differences.

Handedness

Handedness in twins was assessed at age 5 by the question: 'Which hand do the children use to draw on paper?', which was answered for both twins. We found that this item captured the relevant information on which hand was used by the child when drinking from a cup, eating, throwing a ball, picking up a coin, and combing their hair (see Supplementary Table 3). Response options were 'left hand', 'right hand', 'both hands' and 'I don't know'. Twins with missing data ($n = 949$) or the response 'I don't know' ($n = 52$) were excluded from the study. Parents' handedness was obtained from the survey collected when the twins were 2 years (Orlebeke et al., 1996), which included a question about mother's and father's hand preference with three response categories: left-handed, right-handed and both hands. For current analysis, LH was coded as right-handed (0) and left-handed (1). MH was coded as right-handed (0) and mixed-handed (1). NRH was coded as right-handed (0) and non-right-handed (left-handed and mixed-handed combined) (1).

Early Life Characteristics

We investigated the following five sets of early life characteristics (see Supplementary Table 2):

(1) *General:* demographic (sex, year of birth), familial (mother's and father's handedness).

(2) *Prenatal:* mother's and father's age at birth, mode of conception (natural vs. assisted), prenatal maternal smoking (no/yes), and maternal stress during pregnancy (no/yes).

(3) *Perinatal:* season of birth (being born in summer or not), gestational age (continuous), fetal presentation at birth (cephalic presentation and noncephalic presentation: breech and horizontal), mode of delivery (vaginal and intervention with vacuum extraction, forceps, or cesarean section), birth weight (continuous), and Apgar score at 1st minute (continuous score).

(4) *Postnatal:* breastfeeding (no/yes), neurodevelopmental delay (no/yes), and externalizing problems (continuous score). Neurodevelopmental delay was assessed based on bowel and bladder toilet skill delay at age five by the questions 'How often do the children defecate in their pants?' and 'How often do the children pee in their pants during the day?' (see Supplementary Appendix 1). Normal development in bowel and bladder toilet skills is indicated by having fewer than four wetting accidents per week by the age of 4 (Francis et al., 2017; Schum et al., 2002). Externalizing problems were assessed using the subscale of the Aggressive Behavior of the Child Behavior Checklist (CBCL), which mothers completed when their children were 7 years old (Achenbach & Rescorla, 2001).

(5) *Twin-specific:* zygosity (dizygotic or monozygotic), chorionicity (dichorionic or monochorionic), amnionicity (diamniotic or monoamniotic), birth order (first or second born), and the time interval between the birth of the first- and second-born twin.

Pre- and perinatal characteristics were obtained from the survey that was sent to mothers in the first year after the birth of the twins. Parents' handedness and information on breastfeeding were obtained from the survey collected when the twins were 2 years (Orlebeke et al., 1996), which included a question about mother's and father's hand preference with three response categories: left-, right-handed, and both hands, and the question: 'Was your twin breastfed?' (responses categorized into yes/no responses). Information on toilet skills was obtained from the survey at 5 years. Information on chorion status was obtained by linking to the records from the database of the Dutch pathological anatomy national automated archive (PALGA; van Beijsterveldt et al., 2016). The distributions of the data, broken down by the definition of handedness, are presented in Supplementary Figures 1 and 2. Several variables were characterized by missingness due to the absence of questions in earlier surveys, nonresponse, or absence in the record linkage: chorionicity and amnionicity (70% missing), fetal presentation at birth (81%), maternal stress during pregnancy (81%), Apgar scores at 1 minute (86%), and aggression at age 7 (45%).

Continuous variables were dichotomized to report odd ratios. To dichotomize year of birth the mean (born in 2000) was used. To dichotomize parental age the value of 40 years was chosen. For gestational age, the sample was divided in full-term birth (>37 weeks) and preterm birth (<37 weeks), and the additional sensitivity analysis was performed with this categorical variable. Birth weight was categorized at 2500 g. The time interval between the twin births included six cases with extreme values (i.e., more than 33 hours between birth of first- and second-born twins). These extreme values were recoded as missing. The time between birth of first and second twins was divided into two groups <30 minutes and >30 minutes for dichotomous variable. Apgar score was divided into two groups below and above 7 points that corresponds to lower threshold of intermediate values of the scale (Odintsova, Dolan et al., 2019). For aggression, a sum score defined high-scoring children based on mother rating ≥5 points, the same as detailed in Hagenbeek et al. (2020).

Statistical Analysis

All statistical analyses were performed in R version 4.1.0. Due to missingness in early life characteristics, the number of subjects in the regression analyses varied between 4515 and 37,495.

Descriptive Statistics

The frequencies of categorical variables, means and standard deviations (*SD*) of the continuous variables were obtained in the total sample, and within the RH, LH and MH groups. As descriptive measures of association between early life characteristics, we report Pearson correlations for the continuous variables (R package 'stats'), polychoric correlations for the categorical variables (R package 'polychor') and point polyserial correlations between the continuous and categorical variables (R package 'stats'). The differences in proportion of LH/MH/NRH versus right-handed twins in a previously published meta-analysis (Pfeifer et al., 2022) and the current study sample, between males and females, in NRH parents, in twins from the same-sex and opposite-sex pairs, in preterm and full-term born were tested with the two-sample test for equality of proportions (R package 'stats').The same test was applied to test differences in proportion of LH/MH/NRH fathers and mothers.

Association Analysis

Given dichotomous predictors and dichotomized continuous predictors, we reported the odds ratios (*OR*s) and the 95% confidence intervals (CI) (R package 'epitools'). An *OR* of 1 indicates no group differences, *OR*s > 1 suggest a higher prevalence of LH, MH or NRH in categories of early life characteristics, and ORs < 1 suggest a higher prevalence of RH. For testing associations between handedness and the characteristics of interest, we used generalized estimating equation (GEE) regression analyses to account for the relatedness of the twins. We conducted three GEE analyses in which we related the 23 predictors to the three definitions of handedness. The coding of the predictors is presented in Supplementary Table 2.

Explained Variance

To determine the amount of variance in handedness explained by early life factors, the model was fitted with logistic regression, including seven characteristics that were significant in the association analysis. The model was applied to all three definitions of handedness. The explained variance explained by the seven characteristics was obtained on the liability scaled underlying binary responses as proposed by Lee et al. (2012).

Multiple Testing Corrections

As a Bonferroni correction for multiple testing tends to be conservative, we considered the correction suggested by Nyholt (2004), which involves calculating the effective number of tests given the correlations among the predictors. Correlations among the 23 early life characteristics are presented in Supplementary Figure 3. The mean correlation was .14, and the effective number of tests was 22.5 (see Supplementary Appendix 2). Given the two definitions (LH and MH; note that NRH represents the combination of these two), we set the alpha-per-test to equal $\alpha = 0.05/(22.5*2) = 0.001$.

https://doi.org/10.1017/thg.2023.23 Published online by Cambridge University Press

Ethics Statement

The study protocols were approved by the Central Ethics Committee on Research Involving Human Subjects of the VU University Medical Center, Amsterdam). A written informed consent was given by parents of participants for the children and themselves.

Data Availability

Data were provided by the Netherlands Twin Register (reference NTR-DSR-2552) and can be requested for replication or alternative analyses through the NTR data access procedure (https://tweelingenregister.vu.nl/information_for_researchers/working-with-ntr-data).

Results

Descriptives: Prevalence of Handedness in Twin Families

Twins. The study cohort included 37,495 twins with measurements of handedness at 5 years old from 18,865 twin pairs born between 1986 and 2014. Of these, 49.7% were males and 35% were MZ twins. Characteristics of the participants are given in Table 1. The prevalence of RH was 83.81% and NRH was 16.19% (14.86% LH and 1.33% MH). The prevalence of LH in twins was higher than the prevalence in adult singletons, as reported in a recent meta-analysis (14.86% in our study vs. 6.97% in singletons; Pfeifer et al., 2022), $\chi^2(1) = 2326.5$, p <0.001). The prevalence of MH in twins was lower than the prevalence in adult singletons (1.33% in our study vs. 2.67% in singletons; Pfeifer et al., 2022), $\chi^2[1] = 102.68$, $p < .001$). The prevalence of LH and MH was higher in boys than in girls (15.9% of left-handed boys vs. 13.8% of left-handed girls, $\chi^2[1] = 32.74$, $p < .001$; and 1.8% of mixed-handed boys vs. 0.8% of mixed-handed girls, $\chi^2[1] = 66.3$, $p < .001$).

Parents of twins. In the NTR, 84.91% of the parental generation with known handedness ($n = 31{,}813$, 49.9% males) were right-handed and 15.09% were non-right-handed, of whom 11.45% were left-handed, and 3.64% were mixed-handed. Thus, the prevalence of NRH was higher in parents of twins than in adult singletons (15.09% vs. 7.23%; Pfeifer et al., 2022), $\chi^2[1] = 2010.3$, $p < .001$). The prevalence of LH was higher in fathers than in mothers (12.4% of left-handed fathers vs. 10.5% of left-handed mothers, $\chi^2[1] = 26.79$, $p < .001$), but no difference was seen for MH (3.7% of mixed-handed fathers vs. 3.6% of mixed-handed mothers, $\chi^2[1] = 0.52$, $p = .47$). In comparison with right-handed, non-right-handed mothers and fathers more often had left-handed twins (non-right-handed mothers 31.2% vs. right-handed mothers 26.9% of left-handed offspring, $\chi^2[1] = 19.45$, $p < .001$; non-right-handed fathers 35.5% vs. right-handed fathers 26.2% of left-handed offspring; χ^2 $(1) = 80.95$, $p< .001$). No differences were observed for having mixed-handed offspring (non-right-handed mothers 4% vs. right-handed mothers 3.1% of mixed offspring, $\chi^2[1] = 3.45$, $p = .063$; non-right-handed fathers 3.4% vs. right-handed fathers 3.2% of mixed-handed offspring; $\chi^2[1] = 0.14$, $p = .71$). When one parent or both parents were non-right-handed, the risk of having left-handed offspring increased on 4.2% and 10.2% respectively, and the risk of having mixed-handed offspring by only 0.2%. The prevalence of offspring handedness as a function of parental handedness is presented in Supplementary Table 4.

Associations of Handedness With Early Life Characteristics

The odds ratios of left- versus right-handed, mixed- versus right-handed, and non-right- versus right-handed twins for 23 early life characteristics are presented in Figure 1. To correct for relatedness between twins in tests of the significance of the associations between 23 characteristics and handedness, univariate analyses were done with GEE logistic regression (see Table 2 and Supplementary Table 5). A higher probability of being left-handed, mixed-handed or non-right-handed was observed ($p < .0011$) in boys (LH OR =1.2, 95% CI [1.14, 1.26]; MH $OR = 2.27$, 95% CI [1.93, 2.67]; NRH OR =1.26, 95% CI [1.2, 1.32]), and children born with shorter gestational age (LH $OR = 0.91$, 95% CI [0.86, 0.95]; MH $OR = 0.78$, 95% CI [0.67, 0.92]; NRH $OR = 0.90$, 95% CI [0.85, 0.94]). In twins who were born preterm, the prevalence of LH (15.58%) and MH (1.5%) was higher than in term-born twins (14.39% left-handed, $p < .001$, and 1.21% mixed-handed, $p = .019$) (see Supplementary Table 6).

Parental LH increased the risk of being left-handed in offspring (mother: $OR = 1.60$, 95% CI [1.48, 1.73]; father: $OR = 1.27$, 95% CI [1.18, 1.37]). Parental NRH also increased the risk of being non-right-handed in offspring (mother: $OR = 1.47$, 95% CI [1.38, 1.58]; father: $OR = 1.23$, 95% CI [1.15, 1.31]), whereas the association between parental and offspring' MH was not significant.

We observed a decrease of LH in twins who were breastfed in childhood (OR =0.90, 95% CI [0.85, 0.95]). Notably, mixed-handed twins had a 2.5-fold higher risk of neurodevelopmental delays at age 5 ($OR = 2.51$, 95% CI [1.75, 3.59]), and almost twofold higher risk of externalizing problems measured as aggression at age 7 ($OR = 1.96$, 95% CI [1.53, 2.51]).

Next, the seven significantly associated characteristics (sex, gestational age, mother's and father's handedness in the same definition as child's handedness, breastfeeding, aggression at age 7, and neurodevelopmental delay at 5 years) were included in a multivariate general linear model with each definition of handedness as its own dependent variable. All characteristics together explained 1.25% of the variation in LH, 7.82% in MH, and 1.3% in NRH on the liability scale.

Association of Handedness With Twin-Specific Characteristics

Both LH and MH were equally common in MZ and DZ twins (15.52% of left-handed MZ vs. 14.8% of left-handed DZ twins, $\chi^2[1] = 3.36$, $p = .067$; and 1.44% mixed-handed MZ vs. 1.62% mixed-handed DZ twins, $\chi^2[1] = 1.37$, $p = .242$), and in first- and second-born twins (15.44% left-handed first-born vs. 14.69% second-born, $\chi^2[1] = 3.97$, $p = .046$; and 1.44% mixed-handed first-born vs. 1.68 % second-born $\chi^2[1] = 2.78$, $p = .095$).

We tested the difference in the prevalence of LH and MH in girls from the opposite-sex and same-sex twin pairs and in boys from the opposite-sex and same-sex twin pairs, but did not observe significant differences in LH and MH related to sex of co-twin (left-handed girls from the same-sex and opposite-sex pairs $\chi^2[1] = 5.72$, $p = .017$, and left-handed boys from the same-sex and opposite-sex pairs $\chi^2[1] = 1.3$, $p = .255$; mixed-handed girls $\chi^2[1] = 0.73$, p=.393, and mixed-handed boys $\chi^2[1] = 1.7$, $p = .197$; see Supplementary Table 7). None of the twin-specific characteristics were associated with handedness.

https://doi.org/10.1017/thg.2023.23 Published online by Cambridge University Press

Table 1. Characteristics of twin participants

	N total	Total *N* = 37,495	RH *n* = 31,425	LH *n* = 5572	MH *n* = 498
General characteristics					
Year of birth, range		1986–2014	1986–2014	1986–2014	1987–2014
Sex	37,495				
Males, *n* (%)		18616 (49.6%)	15,314 (48.7%)	2964 (53.2%)	338 (67.9%)
Females, *n* (%)		18879 (50.4%)	16,111 (51.3%)	2608 (46.8)	160 (32.1%)
Mother's handedness	31,883				
LH, *n* (%)		3357 (10.5%)	2622 (9.8%)	699 (14.7%)	36 (8.8%)
RH, *n* (%)		27379 (85.9%)	23,170 (86.7%)	3858 (81.3%)	351 (85.4%)
MH, *n* (%)		1133 (3.6%)	920 (3.4%)	189 (4%)	24 (5.8%)
Father's handedness	31,777				
LH, *n* (%)		3931 (12.4%)	3185 (12%)	695 (14.7%)	51 (12.5%)
RH, *n* (%)		26536 (83.5%)	22,358 (84%)	3850 (81.2%)	328 (80.2%)
MH, *n* (%)		1176 (3.7%)	971 (3.6%)	177 (3.7%)	28 (6.8%)
Prenatal characteristics					
Mother's age at birth, mean (*SD*)	36,364	31.4 (4)	31.4 (4)	31.4 (3.9)	31.4 (4.3)
Father's age at birth, mean (*SD*)	35,990	33.9 (4.7)	33.9 (4.7)	33.8 (4.7)	34.1 (5.2)
Mode of conception					
Natural, *n* (%)	34,526	25675 (74.4%)	21,457 (74.2%)	3873 (75.3%)	345 (73.7%)
Assisted, *n* (%)		8851 (25.6%)	7455 (25.8%)	1273 (24.7%)	123 (26.3%)
Prenatal maternal smoking					
No, *n* (%)		30000 (82.5%)	25,206 (82.7%)	4416 (81.6%)	378 (78.4%)
Yes, *n* (%)		6360 (17.5%)	5257 (17.3%)	999 (18.4%)	104 (21.6%)
Maternal stress during pregnancy					
No, *n* (%)	7202	4540 (63%)	3837 (63.4%)	651 (61%)	52 (61.2%)
Yes, *n* (%)		2662 (37%)	2212 (36.6%)	417 (39%)	33 (38.8%)
Perinatal characteristics					
Season of birth	37,491				
Not summer, *n* (%)		8896 (23.7%)	7497 (23.9%)	1270 (22.8%)	129 (25.9%)
Summer, *n* (%)		9707 (25.9%)	8082 (25.7%)	1490 (26.7%)	135 (27.1%)
Fetal presentation	7,268				
Head, *n* (%)		4769 (65.6%)	4003 (65.6%)	718 (66.5%)	48 (55.8%)
Breech, *n* (%)		1923 (26.5%)	1617 (26.5%)	283 (26. %2)	23 (26.7%)
Horizontal, *n* (%)		576 (7.9%)	483 (7.9%)	78 (7.2%)	15 (17.4%)
Mode of delivery	31,818				
Vaginal, *n* (%)		18594 (58.4%)	15549 (58.4%)	2789 (59.0%)	256 (57.5%)
Cesarean section planned, *n* (%)		3861 (12.1%)	3259 (12.2%)	555 (11.7%)	47 (10.6%)
Vacuum/forceps *n* (%)		2942 (9.2%)	2432 (9.1%)	470 (9.9%)	40 (9.0%)
Cesarean section urgent, *n* (%)		6421 (20.2%)	5405 (20.3%)	914 (19.3%)	102 (22.9%)
Gestational age, mean (*SD*)	36,277	36.5 (2.5)	36.6 (2.5)	36.4 (2.6)	36.1 (2.8)
Birth weight, mean (*SD*)	36,045	2490.3 (549.8)	2493.5 (546)	2480.2 (566.1)	2404.9 (596)
Apgar score at 1 minute, mean (*SD*)	5,281	8.3 (1.8)	8.3 (1.7)	8.3 (1.7)	7.7 (2.5)
Postnatal characteristics					
Breastfeeding	32,038				
No, *n* (%)		13,057 (40.8%)	10,835 (40.4%)	2053 (43%)	169 (40.8%)
Yes, *n* (%)		18,981 (59.2%)	16,012 (59.6%)	2724 (57%)	245 (59.2%)

(*Continued*)

https://doi.org/10.1017/thg.2023.23 Published online by Cambridge University Press

Table 1. (*Continued*)

	N total	Total *N* = 37,495	RH *n* = 31,425	LH *n* = 5572	MH *n* = 498
Neurodevelopmental delay at 5 years	37,106				
No, *n* (%)		36,252 (97.7%)	30,408 (97.8%)	5381 (97.7%)	463 (94.3%)
Yes, *n* (%)		854 (2.3%)	700 (2.25%)	126 (2.3%)	28 (5.7%)
Aggression score at 7 years, mean(*SD*)	20,595	5.1 (4.9)	5.1 (4.9)	5.2 (4.8)	7.1 (5.6)
Low <*5 points, n* (%)		11,389 (55.3%)	9620 (55.8%)	1664 (54%	105 (39.2%)
High ≥*5 points, n* (%)		9206(44.7%)	7628(44.2%)	1415 (46%)	163 (60.8%)
Twin-specific characteristics					
Birth order	37,465				
First born, *n* (%)		18,776 (50.1%)	15,684 (49.9%)	2863 (51.4%)	229 (46%)
Second born, *n* (%)		18,689 (49.8%)	15,715 (50%)	2706 (48.6%)	268 (53.8%)
Zygosity	37,321				
Monozygotic, *n* (%)		13,129 (35.2%)	10,956 (35%)	2013 (36.3%)	160 (32.4%)
Dizygotic, *n* (%)		24,192 (64.8%)	20,327 (65%)	3531 (63.7%)	334 (67.6%)
Chorionicity	11,201				
Monochorionic, *n* (%)		3483 (31.1%)	2908 (31%)	533 (32.2%)	42 (26.6%)
Dichorionic, *n* (%)		7718 (68.9%)	6478 (69%)	1124 (67.8%)	116 (73.4%)
Amnionicity	11,155				
Monoamniotic, *n* (%)		281 (2.5%)	231 (2.5%)	49 (3%)	1 (0.6%)
Diamniotic, *n* (%)		10,874 (97.5%)	9120 (97.5%)	1600 (97%)	154 (99.4%)
Time interval between birth of the first and second twin, mean (*SD*)	30,746	13 (22.2)	19.5 (736.7)	21 (361.7)	11.9 (17.3)

Note: LH, left-handed; RH, right-handed; MH, mixed-handed. Values are presented as mean and standard deviation (*SD*) or number (*n*) and frequency in the group (%).

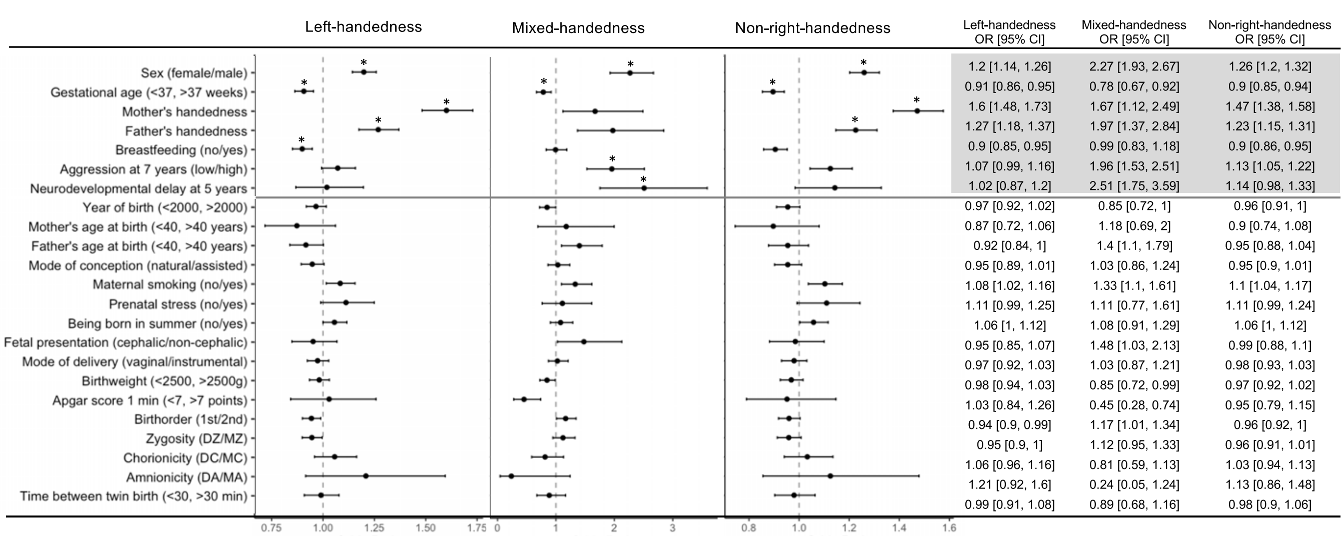

Figure 1. Odds ratio of early life characteristics in left-handed, mixed-handed, or non-right-handed twins. The plot shows the odds ratio (*OR*) with the 95% confidence interval (CI). Note: *Indicates the early life characteristics that resulted in significance in the GEE regression model (see Table 2)

Discussion

We investigated the associations between handedness at 5 years of age and a large set of early life characteristics in a population-based sample of twins from the Netherlands Twin Register. Some of the twin-specific characteristics have not been analyzed before, including amnionicity, time interval between the birth of the first and second twin, the neurodevelopmental indices of bowel and bladder toilet skill delays at age 5, and externalizing problems measured as aggression at age 7. Taken together, seven early life characteristics that had independent effects on handedness (namely sex, gestational age, mother's and father's handedness in the same definition as child's handedness, breastfeeding,

https://doi.org/10.1017/thg.2023.23 Published online by Cambridge University Press

Table 2. Results (regression coefficients) from univariate analysis of handedness and early life characteristics in twins with correction for relatedness

	Left-handedness		Mixed-handedness		Non-right-handedness	
	β	*p*	β	*p*	β	*p*
Sex (female/male)	0.182	6.7×10^{-10}	0.819	1.4×10^{-16}	0.231	4.7×10^{-16}
Gestational age	−0.097	0.00016	−0.244	4.9×10^{-05}	−0.110	2.6×10^{-06}
Mother's handedness*	0.470	1.1×10^{-23}	0.513	.034	0.387	6.7×10^{-21}
Father's handedness*	0.238	3.1×10^{-7}	0.680	.002	0.204	4.8×10^{-07}
Breastfeeding (no/yes)	−0.107	0.00099	−0.006	.953	−0.100	.0014
Aggression score at 7 years	−0.001	.244	1.032	1.5×10^{-12}	0.130	.004
Neurodevelopmental delay at 5 years	0.019	.844	0.920	2.4×10^{-05}	0.134	.143
Year of birth	−0.035	.526	−0.165	.621	−0.046	.628
Mother's age at birth	−0.136	.199	0.162	.912	−0.109	.204
Father's age at birth	−0.087	.454	0.338	.453	−0.046	.626
Mode of conception (natural/assisted)	−0.053	.133	0.033	.764	−0.047	.173
Maternal smoking (no/yes)	0.081	.039	0.285	.015	0.098	.009
Prenatal stress (no/yes)	0.106	.135	0.105	.642	0.105	.126
Being born in summer (no/yes)	0.055	.102	0.077	.473	0.056	.083
Fetal presentation (cephalic/noncephalic)	−0.049	.479	0.391	.077	−0.015	.826
Mode of delivery (vaginal/instrumental)	−0.026	.426	0.025	.799	−0.021	.51
Birth weight	−0.018	.125	−0.166	.002	−0.031	.019
Apgar score at 1 minute	0.030	.506	−0.790	.025	−0.050	.971
Twin-specific characteristics						
Birth order (first/second)	−0.058	.042	0.153	.077	−0.041	.138
Zygosity (DZ/MZ)	−0.055	.076	0.114	.261	−0.041	.169
Chorionicity (DC/MC)	0.055	.347	−0.206	.304	0.033	.567
Amnionicity (DA/MA)	0.190	.26	−1.434	.153	0.118	.479
Time between birth of first and second twin	0.022	.113	−0.059	.368	0.017	.213

Note: β, regression coefficient; *p* value in regression with correction for relatedness (GEE); MZ, monozygotic; DZ, dizygotic; MC, monochorionic; DC, dichorionic; MA, monoamniotic; DA, diamniotic. Greg highlighted section, early life characteristics significant for one of three definitions of handedness (α = .001). See Supplementary Table 5 for standard errors and *z* statistics.
*Mother's and father's handedness are included in the regression analysis in the same definition as the twin handedness.

aggression at age 7, and neurodevelopmental delay at 5 years) in our study explain 1.3% of the variance in NRH, 1.25% in LH, and 7.4% in MH.

Our results show a higher prevalence of LH in twins (14.86%) compared to the adult singleton population (6.97%; Pfeifer et al., 2022)), consistent with the results of a recent meta-analysis of 59 twin studies (Pfeifer et al., 2022) that reported higher prevalence of LH in twins compared to singletons. However, Pfeifer et al. note that the conclusion on the association of twinning with handedness is unsafe because the meta-analysed studies are unadjusted to other characteristics (such as gestational age and birth weight). We note that no evidence for prevalence differences was found in the within-family comparison of twins and their non-twin siblings (Medland et al., 2009) and that our within-family analysis on parental and offspring's handedness also indicates small differences. Parental LH was strongly predictive of LH in their twin offspring, which was not the case for MH. These results also are consistent with earlier reports (Fagard et al., 2021; Johnston et al., 2013; Zhu et al., 2009). Consistent with the meta-analysis of handedness in twins, we observed comparable prevalence of MH in twins, that is, 1.33% versus 2.67% in singletons (Pfeifer et al., 2022).

We confirmed a higher prevalence of LH and MH in males as has been demonstrated previously (Papadatou-Pastou et al., 2008; Peters et al., 2006), and in preterm-born individuals (<37 weeks) compared to twins born after 37 weeks of gestation. This higher prevalence of NRH in preterm born children was also seen in studies of singleton children at age 5–6 years (Gutteling et al., 2007; Marlow et al., 2007; van Heerwaarde et al., 2020). It is thought that preterm birth interrupts the lateralization process (van Heerwaarde et al., 2020) and is a cause of brain injury (Domellöf et al., 2011).

We found that MH and LH have different correlates. The most notable finding in our study was the relationship between MH and two later life outcomes, neurodevelopmental delay measured by toilet skills problem at 5 years and externalizing problems measured as aggression at age 7. Our study indicates that one phenotypic marker of increased risk for adverse neurodevelopment could be MH. Mixed-handed twins, but not left-handed twins, had a higher risk of toilet skill problems at 5 years, a factor that is relevant to neurodevelopment, and a higher risk of externalizing problems at 7 years. Mental health problems tend to be more severe in non-right-handed adolescents (van der Hoorn et al., 2010).

https://doi.org/10.1017/thg.2023.23 Published online by Cambridge University Press

We found that a lack of breastfeeding is associated with LH (de Kovel et al., 2019; Hujoel, 2019). Several factors could underlie this association. For example, insufficient lactation in mothers who have had multiple births can cause early breastfeeding cessation (Damato et al., 2005). There may be common genetic factors that lead to insufficient lactation in mothers and LH in offspring. Infant breastfeeding can be adversely affected by cesarean sections (Hobbs et al., 2016), and cesarean sections are more prevalent in twin births. Finally, in comparison to breastfeeding, bottle-feeding can decrease myelination and neurodevelopment (Deoni et al., 2013; Hujoel, 2019). The epigenetic factors may explain the link between breastfeeding and handedness, as epigenetic signals were detected for both breastfeeding and handedness in the Netherlands Twin Register. However, no overlap was observed in the differentially methylated positions associated with breastfeeding (Odintsova, Hagenbeek et al., 2019) and differentially methylated regions associated with LH (Odintsova et al., 2022).

There was no effect on handedness of season of birth, and of the sharing the womb with a male twin of opposite-sex twin. Both effects have been hypothesized based on a potentially higher prenatal testosterone exposure (Nicholls, 1998; Vuoksimaa et al., 2010). The effect of the season of birth on hand preferences was reported, but its explanation remained unclear in the literature (de Kovel et al., 2019). The exposure to higher testosterone level during pregnancy on females from opposite-sex twin pairs was also discussed in association with handedness (Vuoksimaa et al., 2010), but is inconsistent with the results of studies that actually measured androgen concentrations in girls of opposite-sex twin pairs. For example, Kuijper et al. (2015) did not find higher androgen concentrations in girls from DZ opposite-sex twin pairs.

We found no evidence that twins' birth weight is associated with handedness. Birth weight in twins is likely to be affected by different factors than in singletons, as intrauterine growth restrictions play an important role in twin pregnancies (Muhlhausler et al., 2011). We found no association of handedness with any of the other characteristics such as year of birth, parental age at birth, mode of conception, prenatal smoking, stress during pregnancy, fetal presentation, mode of delivery and Apgar scores in the present study.

With respect to twin-specific characteristics, we did not find differences between handedness in MZ and DZ twins, consistent with other studies in twins (Derom et al., 1996; Medland et al., 2003; Pfeifer et al., 2022). As reported by others, we found that the handedness in twins was not associated with chorion or amnion type (Derom et al., 1996; Medland et al., 2003). In contrast with these previous studies (Medland et al., 2003), we found no effect of birth order on handedness. We studied association of handedness with the time between the birth of the first and second twin, which could be an indicator of longer perinatal hypoxia for a second-born twin. As previously suggested, hypoxia is a risk factor for adverse outcomes in the second twin (Bakan, 1977). But we found no effect of intertwin delivery time on handedness.

One limitation of the current study may be that the measurement of handedness was based on parental reports from a single question, but we showed that this item captures nearly all information from other handedness items. Another limitation is the definition of the mixed-handed group. We labeled MH based on the parental responses, but could not ascertain the extent to which children may prefer one hand over the other. Thus, we could not define the ambidexterity group, as suggested by other authors (Papadatou-Pastou et al., 2020). The mixed-handed group in our analysis could include both mixed-handed and ambidextrous individuals, as in the recent meta-analysis of Pfeifer et al. (2022).

The missing data problem tends to be a general limitation of many association studies on handedness and early life characteristics, including the present study. For some participants, data on early life characteristics were missing due to the absence of the relevant questions in earlier surveys (e.g., fetal presentation at birth, mode of conception, maternal stress during pregnancy, Apgar scores). The data on chorionicity and amnionicity, obtained from the Dutch national pathology database, are highly reliable. Unfortunately, these data were available only in a subsample of twins after linking to the NTR data.

In conclusion, associations with handedness (based on three definitions) and a wide range of early life characteristics in a national twin cohort depend on the definition of handedness. Sex and gestational age are associated with all definitions of handedness, but there is some variation in associations with other early life characteristics and LH or MH. LH was associated with parental LH and breastfeeding, and MH was associated with a higher risk of neurodevelopmental delays at 5 years of age, and externalizing problems measured as aggression at 7 years of age. Twin-specific characteristics were not related to handedness.

Supplementary material. To view supplementary material for this article, please visit https://doi.org/10.1017/thg.2023.23

Acknowledgments. We warmly thank all the twins and their families for their lifelong cooperation with the NTR.

Authors' contributions. Veronika Odintsova: Formal analysis, Software, Methodology, writing — original draft preparation, visualisation. Conor Dolan: Conceptualization, Methodology, Supervision, Writing — Original draft preparation. Catharina E.M. van Beijsterveld: Data curation; writing — review and editing. Lannie Ligthart: Data curation. Gonneke Willemsen: Data curation; Writing — review and editing. Eco J. C. de Geus: Writing — review and editing. Jenny van Dongen: Writing — review and editing. Dorret Boomsma: Conceptualization; supervision; funding acquisition; writing — review and editing.

Funding. The authors would like to acknowledge the Netherlands Organization for Scientific Research (NWO) and The Netherlands Organisation for Health Research and Development (ZonMW) grants: Twin family database for behavior genomics studies (NWO 480-04-004); Twin research focusing on behavior (NWO 400-05-717); Genotype/phenotype database for behavior genetic and genetic epidemiological studies (ZonMw Middelgroot 911-09-032); 'Why some children thrive' (OCW Gravity program – NWO-024.001.003); Netherlands Twin Registry Repository: researching the interplay between genome and environment (NWO-Groot 480-15-001/674); Spinozapremie (NWO- 56-464-14192) and KNAW Academy Professor Award (PAH/6635) to DIB; Amsterdam Public Health (APH) and Amsterdam Reproduction & Development (AR&D). We thank professor Chris McManus for his feedback on the manuscript.

Competing interests. none.

References

Achenbach, T. M., & Rescorla, L. (2001). *Manual for the ASEBA school-age forms & profiles: An integrated system of multi-informant assessment*. Achenbach System of Empirically Based *Assessment* (ASEBA).

Annett, M. (1985). *Left, right, hand, and brain: The right shift theory*. Lawrence Erlbaum Associates.

Armour, J. A. L., Davison, A., & McManus, I. C. (2014). Genome-wide association study of handedness excludes simple genetic models. *Heredity*, *112*, 221–225. https://doi.org/10.1038/hdy.2013.93

Bailey, L. M., & McKeever, W. F. (2004). A large-scale study of handedness and pregnancy/birth risk events: implications for genetic theories of handedness. *Laterality*, *9*, 175–188. https://doi.org/10.1080/13576500342000013

Bakan, P. (1977). Left handedness and birth order revisited. *Neuropsychologia*, *15*, 837–839. https://doi.org/10.1016/0028-3932(77)90018-5

Bakan, P., Dibb, G., & Reed, P. (1973). Handedness and birth stress. *Neuropsychologia*, *11*, 363–366. https://doi.org/10.1016/0028-3932(73)90050-x

Cuellar-Partida, G., Tung, J. Y., Eriksson, N., Albrecht, E., Aliev, F., Andreassen, O. A., Barroso, I., Beckmann, J. S., Boks, M. P., Boomsma, D. I., Boyd, H. A., Breteler, M. M. B., Campbell, H., Chasman, D. I., Cherkas, L. F., Davies, G., de Geus, E. J. C., Deary, I. J., Deloukas, P., . . . Medland, S. E. (2021). Genome-wide association study identifies 48 common genetic variants associated with handedness. *Nature Human Behaviour*, *5*, 59–70. https://doi.org/10.1038/s41562-020-00956-y

Damato, E. G., Dowling, D. A., Standing, T. S. & Schuster, S. D. (2005). Explanation for cessation of breastfeeding in mothers of twins. *Journal of Human Lactation*, *21*, 296–304. https://doi.org/10.1177/0890334405277501

Darvik, M., Lorås, H., & Pedersen, A. V. (2018). The prevalence of left-handedness is higher among individuals with developmental coordination disorder than in the general population. *Frontiers in Psychology*, *9*, 1948. https://doi.org/10.3389/fpsyg.2018.01948

Davis, A., & Annett, M. (1994). Handedness as a function of twinning, age and sex. *Cortex*, *30*, 105–111. https://doi.org/10.1016/s0010-9452(13)80326-7

de Kovel, C. G. F., Carrión-Castillo, A., & Francks, C. (2019). A large-scale population study of early life factors influencing left-handedness. *Scientific Reports*, *9*, 584. https://doi.org/10.1038/s41598-018-37423-8

Deoni, S. C. L., Dean, D. C. 3rd, Piryatinsky, I., O'Muircheartaigh, J., Waskiewicz, N., Lehman, K., Han, M., & Dirks, H. (2013). Breastfeeding and early white matter development: A cross-sectional study. *NeuroImage*, *82*, 77–86. https://doi.org/10.1016/j.neuroimage.2013.05.090

Derom, C., Thiery, E., Vlietinck, R., Loos, R., & Derom, R. (1996). Handedness in twins according to zygosity and chorion type: A preliminary report. *Behavior Genetics*, *26*, 407–408. https://link.springer.com/content/pdf/10.1007/BF02359484.pdf

Dinsdale, N. L., Reddon, A. R., & Hurd, P. L. (2011). Sex differences in the relationship between aggressiveness and the strength of handedness in humans. *Laterality*, *16*(4), 385–400. https://doi.org/10.1080/13576501003683087

Domellöf, E., Johansson, A.-M., & Rönnqvist, L. (2011). Handedness in preterm born children: A systematic review and a meta-analysis. *Neuropsychologia*, *49*, 2299–2310. https://doi.org/10.1016/j.neuropsychologia.2011.04.033

Dragović, M., Milenković, S., Kocijancić, D., & Zlatko, S. (2013). Etiological aspect of left-handedness in adolescents. *Srpski Arhiv Za Celokupno Lekarstvo*, *141*, 354–358. https://doi.org/10.2298/sarh1306354d

Ellis, S. J., Ellis, P. J., & Marshall, E. (1988). Hand preference in a normal population. *Cortex*, *24*, 157–163. https://doi.org/10.1016/s0010-9452(88)80025-x

Fagard, J., de Agostini, M., Huet, V., Granjon, L., & Heude, B. (2021). Is handedness at five associated with prenatal factors? *International Journal of Environmental Research and Public Health*, *18*, 3529. https://doi.org/10.3390/ijerph18073529

Francis, K., Mannion, A., & Leader, G. (2017). The assessment and treatment of toileting difficulties in individuals with autism spectrum disorder and other developmental disabilities. *Review Journal of Autism and Developmental Disorders*, *4*, 190–204. https://doi.org/10.1007/s40489-017-0107-3

Gutteling, B. M., de Weerth, C., & Buitelaar, J. K. (2007). Prenatal stress and mixed-handedness. *Pediatric Research*, *62*, 586–590. https://doi.org/10.1203/PDR.0b013e3181558678

Hagenbeek, F. A., Roetman, P. J., Pool, R., Kluft, C., Harms, A. C., van Dongen, J., Colins, O. F., Talens, S., van Beijsterveldt, C. E. M., Vandenbosch, M. M. L. J. Z., de Zeeuw, E. L., Déjean, S., Fanos, V., Ehli, E. A., Davies, G. E., Hottenga, J. J., Hankemeier, T., Bartels, M., Vermeiren, R. R. J. M., & Boomsma, D. I. (2020). Urinary amine and organic acid metabolites evaluated as markers for childhood aggression: The ACTION Biomarker Study. *Frontiers in Psychiatry*, *11*, 165. https://doi.org/10.3389/fpsyt.2020.00165

Heikkilä, K., van Beijsterveldt, C. E. M., Haukka, J., Iivanainen, M., Saari-Kemppainen, A., Silventoinen, K., Boomsma, D. I., Yokoyama, Y., & Vuoksimaa, E. (2018). Triplets, birthweight, and handedness. *Proceedings of the National Academy of Sciences of the United States of America*, *115*, 6076–6081. https://doi.org/10.1073/pnas.1719567115

Heikkilä, K., Vuoksimaa, E., Saari-Kemppainen, A., Kaprio, J., Rose, R. J., Haukka, J., Pitkäniemi, J., & Iivanainen, M. (2015). Higher prevalence of left-handedness in twins? Not after controlling birth time confounders. *Twin Research and Human Genetics*, *18*, 526–532. https://doi.org/10.1017/thg.2015.53

Hepper, P. G. (2013). The developmental origins of laterality: Fetal handedness. *Developmental Psychobiology*, *55*, 588–595. https://doi.org/10.1002/dev.21119

Hepper, P. G., Shahidullah, S., & White, R. (1991). Handedness in the human fetus. *Neuropsychologia*, *29*, 1107–1111. https://doi.org/10.1016/0028-3932(91)90080-r

Hobbs, A. J., Mannion, C. A., McDonald, S. W., Brockway, M., & Tough, S. C. (2016). The impact of caesarean section on breastfeeding initiation, duration and difficulties in the first four months postpartum. *BMC Pregnancy and Childbirth*, *16*(1), 90. https://doi.org/10.1186/s12884-016-0876-1

Hujoel, P. P. (2019). Breastfeeding and handedness: A systematic review and meta-analysis of individual participant data. *Laterality*, *24*, 582–599. https://doi.org/10.1080/1357650X.2018.1555254

James, W. H., & Orlebeke, J. F. (2002). Determinants of handedness in twins. *Laterality*, *7*, 301–307. https://doi.org/10.1080/13576500143000320

Johnston, D. W., Nicholls, M. E. R., Shah, M., & Shields, M. A. (2013). Handedness, health and cognitive development: Evidence from children in the National Longitudinal Survey of Youth. *Journal of the Royal Statistical Society: Series A (Statistics in Society)*, *176*, 841–860. https://doi.org/10.1111/j.1467-985X.2012.01074.x

Karev, G. B. (2008). Season of birth and parental age in right, mixed and left handers. *Cortex*, *44*, 79–81. https://doi.org/10.1016/j.cortex.2006.01.001

Kuijper, E. A. M., Twisk, J. W. R., Korsen, T., Caanen, M. R., Kushnir, M. M., Rockwood, A. L., Meikle, A. W., Hompes, P. G., Wit, J. M., & Lambalk, C. B. (2015). Mid-pregnancy, perinatal, and neonatal reproductive endocrinology: A prospective cohort study in twins and singleton control subjects. *Fertility and Sterility*, *104*, 1527–1529. https://doi.org/10.1016/j.fertnstert.2015.08.016

Lee, S. H., Goddard, M. E., Wray, N. R., & Visscher, P. M. (2012). A better coefficient of determination for genetic profile analysis. *Genetic Epidemiology*, *36*, 214–224. https://doi.org/10.1002/gepi.21614

Ligthart, L., van Beijsterveldt, C. E. M., Kevenaar, S. T., de Zeeuw, E., van Bergen, E., Bruins, S., Pool, R., Helmer, Q., van Dongen, J., Hottenga, J.-J., van't Ent, D., Dolan, C., Davies, G. E., Ehli, E. A., Bartels, M., Willemsen, G., de Geus, E. J. C., & Boomsma, D. I. (2019). The Netherlands Twin Register: Longitudinal research based on twin and twin-family designs. *Twin Research and Human Genetics*, *22*, 623–636. https://doi.org/10.1017/thg.2019.93

Lindroos, L., Elfvin, A., Ladfors, L., & Wennerholm, U.-B. (2018). The effect of twin-to-twin delivery time intervals on neonatal outcome for second twins. *BMC Pregnancy and Childbirth*, *18*, 36. https://doi.org/10.1186/s12884-018-1668-6

Logue, D. D., Logue, R. T., Kaufmann, W. E., & Belcher, H. M. E. (2015). Psychiatric disorders and left-handedness in children living in an urban environment. *Laterality*, *20*, 249–256. https://doi.org/10.1080/1357650X.2014.961927

Marlow, N., Hennessy, E. M., Bracewell, M. A., & Wolke, D. (2007). Motor and executive function at 6 years of age after extremely preterm birth. *Pediatrics*, *120*, 793–804. https://doi.org/10.1542/peds.2007-0440

McManus, C. (2021). Is any but a tiny fraction of handedness variance likely to be due to the external environment? *Laterality*, *26*, 310–314. https://doi.org/10.1080/1357650X.2021.1892126

McManus, I. (1985). Handedness, language dominance and aphasia: A genetic model. *Psychological Medicine. Monograph Supplement*, *8*, 3–40. https://doi.org/10.1017/S0264180100001879

Medland, S. E., Duffy, D. L., Wright, M. J., Geffen, G. M., Hay, D. A., Levy, F., van-Beijsterveldt, C. E. M., Willemsen, G., Townsend, G. C., White, V., Hewitt, A. W., Mackey, D. A., Bailey, J. M., Slutske, W. S., Nyholt, D. R., Treloar, S. A., Martin, N., G. & Boomsma, D. I. (2009). Genetic influences on handedness: Data from 25,732 Australian and Dutch twin families. *Neuropsychologia*, *47*, 330–337. https://doi.org/10.1016/J.NEUROPSYCHOLOGIA.2008.09.005

Medland, S. E., Wright, M. J., Geffen, G. M., Hay, D. A., Levy, F., Martin, N. G., & Duffy, D. L. (2003). Special twin environments, genetic influences and their effects on the handedness of twins and their siblings. *Twin Research*, *6*, 119–130. https://doi.org/10.1375/136905203321536245

Muhlhausler, B. S., Hancock, S. N., Bloomfield, F. H., & Harding, R. (2011). Are twins growth restricted? *Pediatric Research*, *70*, 117–122. https://doi.org/10.1203/PDR.0b013e31821f6cfd

Nicholls, M. E. (1998). Seasonal trends in the birth of sinistrals. *Laterality*, *3*, 241–253. https://doi.org/10.1080/713754306

Nyholt, D. R. (2004). A simple correction for multiple testing for single-nucleotide polymorphisms in linkage disequilibrium with each other. *American Journal of Human Genetics*, *74*, 765–769. https://doi.org/10.1086/383251

Obel, C., Hedegaard, M., Henriksen, T. B., Secher, N. J., & Olsen, J. (2003). Psychological factors in pregnancy and mixed-handedness in the offspring. *Developmental Medicine and Child Neurology*, *45*, 557–561. https://doi.org/10.1017/s0012162203001014

Odintsova, V., Dolan, C. V., van Beijsterveldt, C. E. M., de Zeeuw, E. L., van Dongen, J., & Boomsma, D. I. (2019). Pre- and perinatal characteristics associated with Apgar scores in a review and in a new study of Dutch twins. *Twin Research and Human Genetics*, *22*, 164–176. https://doi.org/10.1017/thg.2019.24

Odintsova, V., Hagenbeek, F. A., Suderman, M., Caramaschi, D., van Beijsterveldt, C. E. M., Kallsen, N. A., Ehli, E. A., Davies, G. E., Sukhikh, G. T., Fanos, V., Relton, C., Bartels, M., Boomsma, D. I., & van Dongen, J. (2019). DNA methylation signatures of breastfeeding in buccal cells collected in mid-childhood. *Nutrients*, *11*, 2804. https://doi.org/10.3390/nu11112804

Odintsova, V., Suderman, M, Hagenbeek, F., Caramaschi, D, Hottenga, J., Pool, R., Consortium, B., Dolan, C., Ligthart, L., van Beijsterveldt, C., Willemsen, G., de Geus, E., Beck, J., Ehli, E., Cuellar-Partida, G., Evans, D., Medland, S., Relton, C., Boomsma, D., & van Dongen, J. (2022). DNA methylation in peripheral tissues and left-handedness. *Scientific Reports*, *12*, 5606. https://doi.org/10.1038/s41598-022-08998-0

Orlebeke, J. F., Knol, D. L., Koopmans, J. R., Boomsma, D. I., & Bleker, O. P. (1996). Left-handedness in twins: Genes or environment? *Cortex*, *32*, 479–490. https://doi.org/10.1016/s0010-9452(96)80005-0

Papadatou-Pastou, M., Martin, M., Munafò, M. R., & Jones, G. V. (2008). Sex differences in left-handedness: A meta-analysis of 144 studies. *Psychological Bulletin*, *134*, 677–699. https://doi.org/10.1037/a0012814

Papadatou-Pastou, M., Ntolka, E., Schmitz, J., Martin, M., Munafò, M. R., Ocklenburg, S., & Paracchini, S. (2020). Human handedness: A meta-analysis. *Psychological Bulletin*, *146*, 481–524. https://doi.org/10.1037/bul0000229

Parma, V., Brasselet, R., Zoia, S., Bulgheroni, M., & Castiello, U. (2017). The origin of human handedness and its role in pre-birth motor control. *Scientific Reports*, *7*, 16804. https://doi.org/10.1038/s41598-017-16827-y

Peters, M., Reimers, S., & Manning, J. T. (2006). Hand preference for writing and associations with selected demographic and behavioral variables in 255,100 subjects: The BBC internet study. *Brain and Cognition*, *62*, 177–189. https://doi.org/10.1016/j.bandc.2006.04.005

Pfeifer, L. S., Schmitz, J., Papadatou-Pastou, M., Peterburs, J., Paracchini, S., & Ocklenburg, S. (2022). Handedness in twins: Meta-analyses. *BMC Psychology*, *10*, 11. https://doi.org/10.1186/s40359-021-00695-3

Schum, T. R., Kolb, T. M., McAuliffe, T. L., Simms, M. D., Underhill, R. L., & Lewis, M. (2002). Sequential acquisition of toilet-training skills: A descriptive study of gender and age differences in normal children. *Pediatrics*, *109*, e48–e48. https://doi.org/10.1542/peds.109.3.e48

Searleman, A., Porac, C., & Coren, S. (1989). Relationship between birth order, birth stress, and lateral preferences: A critical review. *Psychological Bulletin*, *105*, 397–408. https://doi.org/10.1037/0033-2909.105.3.397

Sicotte, N. L., Woods, R. P., & Mazziotta, J. C. (1999). Handedness in twins: A meta-analysis. *Laterality: Asymmetries of Body, Brain and Cognition*, *4*, 265–286. https://doi.org/10.1080/713754339

van Beijsterveldt, C. E. M., Overbeek, L. I. H., Rozendaal, L., McMaster, M. T. B., Glasner, T. J., Bartels, M., Vink, J. M., Martin, N. G., Dolan, C. V., & Boomsma, D. I. (2016). Chorionicity and heritability estimates from twin studies: The prenatal environment of twins and their resemblance across a large number of traits. *Behavior Genetics*, *46*, 304–314. https://doi.org/10.1007/s10519-015-9745-3

van der Feen, F. E., Zickert, N., Groothuis, T. G. G., & Geuze, R. H. (2020). Does hand skill asymmetry relate to creativity, developmental and health issues and aggression as markers of fitness? *Laterality*, *25*, 53–86. https://doi.org/10.1080/1357650X.2019.1619750

van der Hoorn, A., Oldehinkel, A. J., Ormel, J., Bruggeman, R., Uiterwaal, C. S. P. M., & Burger, H. (2010). Non-right-handedness and mental health problems among adolescents from the general population: The Trails Study. *Laterality*, *15*, 304–316. https://doi.org/10.1080/13576500902746839

van Heerwaarde, A. A., van der Kamp, L. T., van der Aa, N. E., de Vries, L. S., Groenendaal, F., Jongmans, M. J., Eijsermans, R. J. C., Koopman-Esseboom, C., van Haastert, I.-L. C., Benders, M. J. N. L., & Dudink, J. (2020). Non-right-handedness in children born extremely preterm: Relation to early neuroimaging and long-term neurodevelopment. *PloS One*, *15*, e0235311. https://doi.org/10.1371/journal.pone.0235311

Vuoksimaa, E., Eriksson, C. J. P., Pulkkinen, L., Rose, R. J., & Kaprio, J. (2010). Decreased prevalence of left-handedness among females with male co-twins: Evidence suggesting prenatal testosterone transfer in humans? *Psychoneuroendocrinology*, *35*, 1462–1472. https://doi.org/10.1016/j.psyneuen.2010.04.013

Vuoksimaa, E., Koskenvuo, M., Rose, R. J., & Kaprio, J. (2009). Origins of handedness: a nationwide study of 30,161 adults. *Neuropsychologia*, *47*, 1294–1301. https://doi.org/10.1016/j.neuropsychologia.2009.01.007

Willemsen, G., Odintsova, V., de Geus, E., & Boomsma, D. I. (2021). Twin-singleton comparisons across multiple domains of life. In A. Khalil, L. Lewi & E. Lopriore (Eds.), *Twin and higher-order pregnancies* (pp. 51–71). Springer Nature. https://doi.org/10.1007/978-3-030-47652-6_4

Zhu, J. L., Obel, C., Basso, O., Bech, B. H., Henriksen, T. B., & Olsen, J. (2009). Infertility, infertility treatment, and mixed-handedness in children. *Early Human Development*, *85*, 745–749. https://doi.org/10.1016/j.earlhumdev.2009.10.001