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RESEARCH ARTICLE

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Genetic and environmental influences on infant anthropometry at birth and four months of life: evidence from singleton and twin data in the HEALS and earlyFOOD projects

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ABSTRACT

Prenatal and postnatal developmental outcomes are associated with newborn survival and respiratory health and are determined by complex interactions between genes and the environment. However, the contribution of genetic dominance has been scarcely investigated. We aimed to investigate the genetic and environmental influences on infant weight, length, and head circumference in singleton and twin infants at birth and four months of life, using both traditional and behavioral genetics approaches accounting for genetic dominance.
A total of 173 newborns (65 singletons and 54 twin pairs) were consecutively recruited within the HEALS and earlyFOOD projects. At birth and four months of life, developmental outcomes were expressed as standard deviation scores (z-scores), and information about maternal and family factors was collected using questionnaires. We first considered singletons and a randomly selected twin for each pair and run linear regression models at birth and four months of life for each outcome. Then, we considered the twin pairs and estimated behavioral genetic models to disentangle the contribution of additive genetic effects (A), genetic dominance (D), shared (C) and unique (E) environmental influences.
In regression analyses, twin births were significantly associated with lower outcomes at birth ($p < 0.05$) and fertility treatment was significantly associated with higher birth length ($\beta = 0.58$, $p = 0.026$). ACDE models highlighted significant percentages of variance explained by additive genetic factors (23 to 29%). Significant percentages of variance explained by shared environmental factors were observed at four months of life for weight (43%, $p = 0.029$) and head circumference (50%, $p = 0.004$). A significant percentage of variance explained by dominance genetic factors was observed for length at birth (37%, $p = 0.037$).

KEY WORDS
Respiratory-related developmental outcomes; exposome; genome; infants; twins.

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The joint assessment of additive and non-additive genetic effects, together with shared and unique environmental influences, provides new insights into the study of the determinants of respiratory-related developmental outcomes such as infant weight, length, and head circumference.

HIGHLIGHTS BOX

What is already known about this topic? Prenatal and postnatal developmental outcomes are associated with newborn survival and respiratory health and are determined by complex interactions between genes and the environment. In this regard, the contribution of genetic dominance has been scarcely investigated. **What does this article add to our knowledge?** We investigated the genetic and environmental influences on infant weight, length, and head circumference, considering singleton and twin data, and using both traditional models and behavioral genetics approaches also accounting for genetic dominance. **How does this study impact current management guidelines?** The joint assessment of additive/non-additive genetic effects, together with shared/unique environmental influences, represents an added value to the study of the determinants of respiratory-related developmental outcomes such as infant weight, length, and head circumference.

INTRODUCTION

Prenatal and postnatal developmental outcomes are important predictors of newborn survival and respiratory health and are determined by complex interactions between maternal and fetal genomes (1), along with intra-uterine and extra-uterine environments (2).

Using traditional approaches (correlation and regression), singleton studies identified potentially modifiable factors associated with birth weight such as maternal age and body mass index (BMI), parity, economic condition, education, and smoking (3, 4). Moreover, genome-wide association studies (GWAS) identified SNPs at several loci of the fetal genotype that were associated with offspring birth weight (5). Also, GWAS detected substantial correlations among birth weight, length, and head circumference that were ascribed to a substantial contribution of shared genetic effects (1).

Twins share several genes, as well as the prenatal and postnatal environment, and provide a unique opportunity to disentangle the relative contributions of the genome and the exposome (*i.e.*, the totality of the exposures experienced by an individual throughout life) (6) in explaining inter-individual differences in developmental outcomes (7). Indeed, previous studies have reported considerable geographical differences in the relative contribution of environmental factors, mainly due to marked geographical differences in the inter-individual variation of maternal dietary habits and other family factors (8). Moreover, due to identifiability concerns, comprehensive behavioral genetics approaches accounting for non-additive genetic effects (*i.e.*, dominance) have been scarcely adopted in previous twin studies (9).

In the framework of the HEALS ("Health and Environment-wide Associations based on Large population Surveys") (10) and the earlyFOOD ("Long-term impact of gestational and early-life dietary habits on infant gut immunity and disease risk") (11) projects, we aimed to investigate the genetic and environmental influences on infant weight, length, and head circumference in singleton and twin infants at birth and four months of life, using both traditional and behavioral genetics approaches accounting for genetic dominance.

MATERIALS AND METHODS

Study design

Within the HEALS and earlyFOOD projects, a cohort of singleton and twin infants' mothers was consecutively recruited between May 2018 and September 2021, at the Obstetrics and Gynecology unit of the Buccheri La Ferla Hospital, Palermo, Italy. Mothers and related infants were excluded in the case of heterologous fertilization and lack of written informed consent.

The study was approved by the local Institutional Ethics Committee (Palermo 1, Italy, No. 07/2017). All the participant mothers were informed about all aspects of the research and provided their written consent before study entry.

Procedures

Pregnant mothers were invited to participate in the study upon arrival to the hospital. After birth, a neonatologist recorded weight, length, and head circumference of the infants. Before discharge, a structured questionnaire interview was administered to the enrolled mothers by a trained obstetrician, aiming to collect information about dietary habits, environmental exposures, and characteristics of the pregnancy. Mother-child pairs were also invited to participate in a follow-up visit four months after birth including children's anthropometric measurements and questionnaire evaluation.

Anthropometric measurements

Infant's weight, length, and head circumference were measured within 1 hour from delivery in a supine position by a trained neonatologist. Weight was measured using an electronic baby scale (Seca, Hamburg, Germany), length and head circumferences were measured with an inelastic tape.

The three anthropometric measurements at birth were expressed as standard deviation (SD) scores (z-scores) in relation to gestational age, gender, and primiparous status, using the Italian Neonatal Study (INeS) growth charts (12). Z-scores of the measurements at four months of life were calculated using the sex- and age-specific reference values of the World Health Organization (WHO) (13).

Questionnaire data

The questionnaire at birth included questions about the socio-demographic characteristics of the infants and their mothers, characteristics of the pregnancy, family context, health, lifestyle, and dietary habits of the mother in the four months before delivery. Variables included in the current analysis were gestational age (<37 weeks: preterm birth; ≥37 weeks: full-term birth), zygosity (monozygotic, MZ, and dizygotic DZ: only for twins), delivery mode (C-section or vaginal), primiparous status, maternal age (<35 years or ≥35 years), maternal body mass index (BMI, kg/m^2) before pregnancy (BMI < 25 or BMI ≥ 25), maternal education (graduated or not), maternal smoking during pregnancy, fertility treatment (*in vitro* fertilization (IVF), sperm fertilization), maternal health problems during pregnancy (vomiting, abortion threats, hypertension, gestational diabetes), and 40 maternal dietary habits in the four months before delivery (intake of alcohol, intake of coffee, consumption of 5 portions/day of fruits and vegetables, and consumption of other 37 food categories at least once a week). Included follow-up variables were breastfeeding duration (months) and maternal/paternal smoking.

Statistical analysis

Statistical analyses were carried out using R version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria). Characteristics of the study participants were summarized through means and SD for quantitative variables and numbers (n) and percentages (%) for categorical variables. Group comparisons were carried out using the Kruskal-Wallis test (continuous variables) and Fisher's exact test (categorical variables). Statistical significance was set at $p < 0.05$.

To summarize the dietary patterns of the mothers during pregnancy, the answers to the 40 questions about the dietary habits were used as input for a clustering algorithm. Gower's general dissimilarity coefficient was used to compute a distance matrix (14), and the partitioning around medoids algorithm was applied (15). The optimal number of clusters, from one to five, was determined using the Silhouette statistic (the larger, the better) (16).

Genetic and environmental determinants of weight, length, and head circumference at birth and four months of life were investigated using two approaches: a conventional regression approach and a behavioral genetics approach (ACDE models).

In the first approach, singletons and only one randomly selected twin for each pair were included in order to address the issue of non-independence between paired observations (using mixed-models may not be advisable since mother-level random effects would overlap with model residuals in singletons). Then, for each outcome, we run linear regression models at birth and four months of life. Factors included in models at both visits were twin birth, maternal age ≥35 years, mother's graduation, and fertility treatment. Factors included only in models at birth (*i.e.*, the factors that were more temporally related with the contextual outcomes) were maternal dietary patterns during pregnancy (identified through the aforementioned cluster analysis), maternal smoking during pregnancy, maternal health problems during pregnancy, and maternal BMI ≥ 25 kg/m² before pregnancy. Factors included only in models at four months of life were breastfeeding duration, maternal/paternal smoking, C-Section, and preterm birth.

In the second approach, twin pairs were included (singletons were excluded) and ACDE models were run (A: additive genes; C: common environment; D: genetic dominance; E: erratic effects). ACDE models are structural equation models for twin data aiming to disentangle the contribution of the human genome and exposome in explaining the variance of a given outcome (7) and can be presented as:

$$\begin{cases} Y_1=\mu_z+aA_1+cC_1+dD_1+E_1 \\ Y_2=\mu_z+aA_2+cC_2+dD_2+E_2 \end{cases}$$

In the above equations, Y_1 and Y_2 are the outcomes in twins 1 and 2, respectively, and parameter μ_z is an intercept dependent on the zygosity status (z = DZ, MZ). A_1 and A_2 are latent random variables accounting for additive genetic influences, C_1 and C_2 are latent random variables accounting for common (or shared) environmental influences (*e.g.*, the intra-uterine environment), D_1 and D_2 are latent random variables accounting for dominance genetic influences. These random variables are assumed mutually uncorrelated within the same twin, and to follow a standard normal distribution. E_1 and E_2 are model residuals accounting for erratic (or unique) environmental factors (*e.g.*, the fetal intra-uterine position); they are assumed uncorrelated with latent variables, and to follow a normal distribution with variance equal to e^2. Consequently, a^2 is the outcome variance explained by additive genetic factors, c^2 is the variance explained by shared environmental factors, d^2 is the variance explained by dominance genetic factors, and e^2 is the variance explained by unique environmental factors (including measurement error).

The correlation between A_1 and A_2 is assumed 1 in MZ twins and 0.5 in DZ twins. The correlation between C_1 and C_2 is assumed 1 both in MZ and in DZ twins. The correlation between D_1 and D_2 is assumed 1 in MZ twins and 0.25 in DZ twins. All other pairs of latent variables (among which E_1 and E_2) are assumed uncorrelated with each other (**Figure 1**) (7). Identifiability concerns were addressed using a previously proposed estimation method (9), and the results were expressed as percentages of the total variance ($a^2 + c^2 + d^2 + e^2$) explained by each factor.

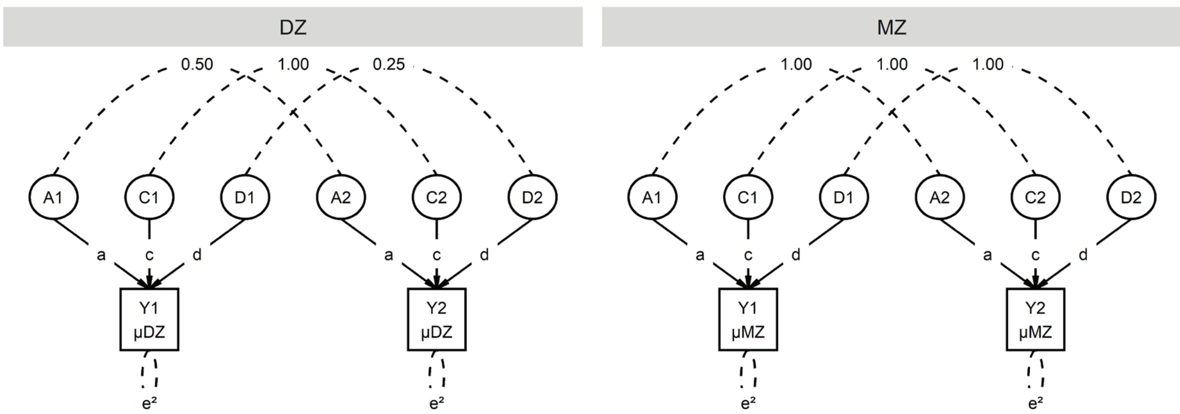

Figure 1. *Path diagram of the ACDE structural equation model for twin data. DZ: dizygotic. MZ: monozygotic. Squares represent observed variables (Y) with their intercepts (μ_{DZ} and μ_{MZ}). Circles represent random variables (A: additive genetic factors, C: shared environmental factors, D: dominance genetic factor), and solid lines refer to their effects (a, c, d). Dashed lines represent non-zero correlations among the random variables, and the variance of unique environmental factors (e²).*

RESULTS

A total of 173 newborns (65 singletons and 54 twin pairs, 20 MZ, 34 DZ) were included in this study (Table 1). Compared to singletons, in twins (one twin selected at random from each pair) we observed significantly higher percentages of preterm births, C-sections, fertility treatments, maternal problems during pregnancy, and lower outcome z-scores at birth. A total of 93 newborns (29 singletons and 32 twin pairs, 12 MZ, 20 DZ) underwent the follow-up visit after 4 months. Compared to singletons, in twins a significantly lower duration of breastfeeding, higher frequency of maternal/paternal smoking, and lower outcome z-scores were observed (**Table 1**).

Two maternal dietary patterns (9 distinctive dietary habits) were identified by the clustering algorithm (**Figure 2**). Dietary pattern 1 (hypocaloric diet, 65/119 mothers) was characterized by significantly higher frequency of coffee (83% *vs.* 59%) and fruit/vegetables consumption (91% *vs.* 76%) with respect to dietary pattern 2. Dietary pattern 2 (hypercaloric diet, 54/119 mothers) was characterized by significantly higher frequency of alcohol (17% *vs.* 3%), pasta (78% *vs.* 28%), appetizers (30% *vs.* 5%), sweet pastries (96% *vs.* 14%), cakes (93% *vs.* 22%), chocolate bars (44% *vs.* 20%), and beef consumption (48% *vs.* 28%) with respect to dietary pattern 1.

Conventional linear regression models showed that twin births were significantly associated with lower z-scores for all the outcomes at birth: weight ($\beta = -0.74$, $p < 0.001$), length ($\beta = -0.6$, $p = 0.001$), and head circumference ($\beta = -0.62$, $p = 0.005$) (**Table 2**). Fertility treatment was significantly associated with higher

Table 1. *Characteristics of the study participants at birth and four months of life, by birth type. Data are reported as n (column %) for categorical variables and mean (SD) for quantitative variables. Significant p-values are in bold.*

	Overall	Twins	Randomly selected twins	Singletons	P-value+
Birth	n = 173	n = 108	n = 54	n = 65	
Female gender	74 (43)	51 (47)	23 (43)	23 (35)	0.454
Preterm birth (<37 weeks)	73 (42)	72 (67)	36 (67)	1 (2)	**<0.001**
C-Section	119 (69)	94 (87)	47 (87)	25 (38)	**<0.001**
Primiparous	93 (54)	62 (57)	31 (57)	31 (48)	0.357
Maternal age ≥35 years	73 (42)	52 (48)	26 (48)	21 (32)	0.092
Maternal BMI ≥25 kg/m² before pregnancy	47 (27)	34 (31)	17 (31)	13 (20)	0.203
Graduated mother	70 (40)	38 (35)	19 (35)	32 (49)	0.140
Maternal smoking during pregnancy	16 (9)	14 (13)	7 (13)	2 (3)	0.077
Maternal hypercaloric diet during pregnancy	77 (45)	46 (43)	23 (43)	31 (48)	0.586
Fertility treatment	28 (16)	24 (22)	12 (22)	4 (6)	**0.014**
Maternal health problems during pregnancy	56 (32)	46 (43)	23 (43)	10 (15)	**0.002**
Weight z-score	-0.43 (0.98)	-0.69 (0.84)	-0.66 (0.87)	0.00 (1.04)	**<0.001**
Length z-score	-0.54 (0.97)	-0.76 (0.99)	-0.69 (1.00)	-0.16 (0.82)	**0.002**
Head circumference z-score	-0.10 (1.05)	-0.27 (0.92)	-0.27 (0.95)	0.18 (1.19)	**0.024**
Four months of life	n = 93	n = 64	n = 32	n = 29	
Breastfeeding duration, months	2.4 (1.6)	1.9 (1.6)	1.9 (1.6)	3.6 (0.9)	**<0.001**
Maternal/paternal smoking	20 (22)	18 (28)	9 (28)	2 (7)	**0.046**
Weight z-score	-0.49 (1.02)	-0.67 (1.01)	-0.62 (1.05)	-0.09 (0.96)	**0.024**
Length z-score	-0.66 (1.34)	-1.05 (1.12)	-0.86 (1.06)	0.18 (1.39)	**0.002**
Head circumference z-score	-0.55 (1.23)	-0.85 (1.20)	-0.74 (1.07)	0.10 (1.04)	**0.004**

+ Randomly selected twins vs. singletons.

Table 2. *Regression models for developmental outcomes at birth and four months of life. Significant effects are in bold.*

	Weight z-score		Length z-score		Head circumference z-score	
Birth (n = 119)	β (p-value)	95% CI	β (p-value)	95% CI	β (p-value)	95% CI
Intercept	-0.19 (0.318)	(-0.56, 0.18)	-0.37 (0.036)	(-0.71, -0.02)	0.08 (0.701)	(-0.33, 0.49)
Twin	**-0.74 (<0.001)**	**(-1.13, -0.34)**	**-0.60 (0.001)**	**(-0.97, -0.24)**	**-0.62 (0.005)**	**(-1.05, -0.19)**
Maternal age ≥35 years	0.14 (0.464)	(-0.24, 0.52)	0.27 (0.131)	(-0.08, 0.62)	0.50 (0.018)	(0.09, 0.92)
Graduated mother	-0.14 (0.465)	(-0.51, 0.23)	-0.01 (0.946)	(-0.36, 0.33)	-0.30 (0.148)	(-0.71, 0.11)
Fertility treatment	0.36 (0.192)	(-0.19, 0.91)	**0.58 (0.026)**	**(0.07, 1.09)**	0.58 (0.060)	(-0.02, 1.19)
Maternal hypercaloric diet during pregnancy	0.32 (0.081)	(-0.04, 0.67)	0.22 (0.185)	(-0.11, 0.55)	0.13 (0.503)	(-0.26, 0.53)
Maternal smoking during pregnancy	-0.01 (0.983)	(-0.69, 0.68)	-0.04 (0.890)	(-0.68, 0.59)	0.12 (0.751)	(-0.63, 0.88)
Maternal health problems during pregnancy	-0.16 (0.452)	(-0.57, 0.26)	-0.23 (0.235)	(-0.61, 0.15)	-0.22 (0.337)	(-0.68, 0.23)
Maternal BMI ≥25 kg/m^2 before pregnancy	0.30 (0.177)	(-0.14, 0.73)	0.11 (0.584)	(-0.29, 0.51)	0.08 (0.749)	(-0.40, 0.56)
Four months of life (n = 61)	β (p-value)	95% CI	β (p-value)	95% CI	β (p-value)	95% CI
Intercept	-0.49 (0.311)	(-1.46, 0.47)	-0.11 (0.850)	(-1.26, 1.04)	-0.41 (0.420)	(-1.41, 0.60)
Twin	-0.46 (0.253)	(-1.25, 0.34)	-0.66 (0.165)	(-1.61, 0.28)	-0.55 (0.192)	(-1.37, 0.28)
Maternal age ≥35 years	0.26 (0.352)	(-0.3, 0.81)	0.36 (0.282)	(-0.30, 1.02)	0.29 (0.318)	(-0.29, 0.87)
Graduated mother	0.34 (0.278)	(-0.28, 0.97)	0.22 (0.551)	(-0.52, 0.97)	0.35 (0.287)	(-0.30, 1.00)
Fertility treatment	0.37 (0.331)	(-0.39, 1.14)	0.51 (0.263)	(-0.40, 1.42)	0.13 (0.742)	(-0.66, 0.93)
Breastfeeding duration (1 month increase)	0.03 (0.788)	(-0.2, 0.26)	0.03 (0.832)	(-0.24, 0.30)	0.06 (0.602)	(-0.17, 0.30)
Maternal/paternal smoking	0.08 (0.843)	(-0.72, 0.88)	0.10 (0.829)	(-0.85, 1.06)	0.06 (0.884)	(-0.77, 0.90)
C-Section	-0.19 (0.594)	(-0.89, 0.52)	-0.42 (0.316)	(-1.26, 0.42)	-0.19 (0.605)	(-0.92, 0.54)
Preterm birth (<37 weeks)	0.01 (0.984)	(-0.85, 0.87)	-0.47 (0.361)	(-1.50, 0.56)	-0.16 (0.725)	(-1.06, 0.74)

Table 3. *ACDE models: percentage contributions of genetic/environmental factors to the inter-individual variation in developmental outcomes. Significant effects are in bold.*

	A		C		D		E	
Birth (54 twin pairs, 20 MZ, 34 DZ)	% (p-value)	95% CI	% (p-value)	95% CI	% (p-value)	95% CI	% (p-value)	95% CI
Weight z-score	**27 (<0.001)**	**(13, 40)**	0 (1.000)	(0, 46)	40 (0.055)	(0, 81)	**33 (0.002)**	**(12, 55)**
Length z-score	**29 (<0.001)**	**(18, 39)**	11 (0.594)	(0, 53)	**37 (0.037)**	**(2, 72)**	**23 (0.003)**	**(8, 38)**
Head circumference z-score	**23 (<0.001)**	**(11, 35)**	24 (0.239)	(0, 63)	23 (0.199)	(0, 58)	**30 (0.003)**	**(10, 50)**
Four months of life (32 twin pairs, 12 MZ, 20 DZ)	% (p-value)	95% CI	% (p-value)	95% CI	% (p-value)	95% CI	% (p-value)	95% CI
Weight z-score	**25 (<0.001)**	**(15, 34)**	**43 (0.029)**	**(4, 81)**	15 (0.349)	(0, 48)	**17 (0.026)**	**(2, 33)**
Length z-score	**26 (<0.001)**	**(15, 37)**	33 (0.135)	(0, 77)	22 (0.235)	(0, 59)	**19 (0.025)**	**(2, 35)**
Head circumference z-score	**23 (<0.001)**	**(14, 32)**	**50 (0.004)**	**(16, 85)**	9 (0.533)	(0, 38)	**17 (0.026)**	**(2, 33)**

A: additive genetic factors; C: shared environmental factors; D: dominance genetic factors; E: unique environmental factors.

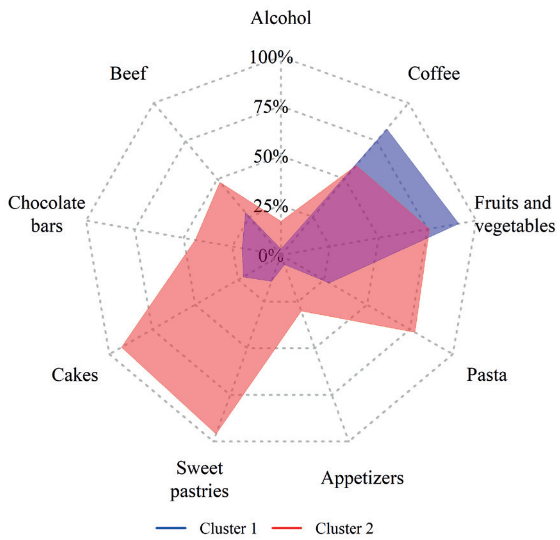

Figure 2. *Percentage distribution of distinctive dietary habits across the two dietary patterns.*

z-scores of length at birth (β = 0.58, p = 0.026). No significant associations were found at four months of life.

For all the outcomes, at both visits, ACDE models (**Table 3**) highlighted significant percentages of variance explained by additive genetic factors (23 to 29%). Significant percentages of variance explained by shared environmental factors were observed at four months of life for weight (43%, p = 0.029) and head circumference (50%, p = 0.004). A significant percentage of variance explained by dominance genetic factors was observed for length at birth (37%, p = 0.037). All the percentages of variance explained by unique environmental factors were significant (23 to 33% at birth, 17 to 19% at four months of life). No significant differences were observed between mean outcomes (model intercepts) in MZ and DZ (data not shown).

DISCUSSION

This study provides new insights into the genetic and environmental influences on infant anthropometric characteristics at birth and four months of life, combining singleton and twin data, and using a comprehensive behavioral genetics approach also accounting for dominance genetic influences. Through the application of conventional regression models, we found lower z-scores in twins and higher birth length following fertilization treatment of the parents. Through the application of ACDE models, we found persistent additive genetic effects through the study follow-up window, dominance genetic effects for length at birth, and significant influences of the shared environment at four months of life.

When considering the pool of individual data referring to singletons and a random representative for each twin pair, we found significantly lower mean z-scores at birth in twins than in singletons. This result is consistent with previous findings and may be ascribed to several aspects of the intra-uterine environment, such as uterine size and placental structure (17, 18).

Length z-scores at birth were significantly higher in infants born to parents who underwent fertilization treatment. Although some studies reported no association (19) or increased risk of adverse birth outcomes associated with IVF (20, 21), others highlighted patterns of increased length during gestation (22), preschool (23), and school age (24) associated with IVF, compared to spontaneous conception. Whether high levels of growth promoting hormones and epigenetic imprinting may play a role needs to be further explored.

For all the respiratory-related developmental outcomes, the analysis of twin data through the ACDE model highlighted a persistent effect of additive genetic factors through the study follow-up window (23 to 29%) and significant, prevalent effects of shared environmental factors only at four months of life. Whereas similar patterns were observed in several studies (25-33), opposite patterns have been observed in other studies where the shared environment was the most influential factor at birth (34-41). Such different findings may be ascribed to population differences in the inter-individual variation of maternal and family factors (8), gene-environment interaction processes (33, 41, 42), or potential confounding effects of the maternal genotype, which may jointly influence the genotype and the shared (*e.g.*, uterine) environment of the infants (43-45). Interestingly, fertility treatment (a component of the shared environment) was associated with birth length in regression models: such association may actually involve genetic mechanisms in the underlying causal pattern, consistently with higher insulin-like growth factor (IGF-I and IGF-II) levels found in IVF children (46).

We found substantial effects of dominance genetic factors at birth, even if the effect was statistically significant only for length. At four months of life, dominance effects were lower and were not statistically significant. Only a few previous studies included the evaluation of dominance effects in their analysis. Some Authors found that the heritability of BMI was about 64%, with a genetic component that was predominantly non-additive (31). Other Authors included dominance effects in their analysis, but C (shared environmental effects) and D (dominance effect) contributions were estimated separately (using ACE or ADE models) (28, 40). Although the estimated contributions of the D component were consistent with those reported in the current study, proper comparisons are not feasible in the absence of a combined evaluation of C and D.

The simultaneous estimation of A, C, D and E contributions to the inter-individual variation in developmental outcomes represents the main novelty and strength of this study. Another strength is to have considered both singleton and twin data, using traditional and modern approaches at the same time. Indeed, whereas singleton studies are suitable for studying the effects of individual environmental exposures (using conventional regression approaches) or individual genes (using GWAS) on developmental outcomes separately, twin studies allow studying the relative contributions of the whole genome and exposome (7).

The main drawback of this study is the low sample size, especially for the follow-up data, which reduced the statistical power to detect significant effects. Therefore, larger studies are warranted for confirming and strengthening the study results.

CONCLUSIONS

The combined assessment of additive and non-additive genetic effects, together with shared and unique environmental influences, provides new insights into the study of the determinants of respiratory-related developmental outcomes, such as infant weight, length, and head circumference.

A thorough knowledge about the complex interplay between genetic and environmental factors may be useful in order to suggest clinical interventions for altered fetal growth and body composition, which might lead to primary prevention of future health risks.

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COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interests

The Authors have declared no conflict of interests.

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Authorship

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Author contributions

SF contributed to the conception of the work, data analysis, and drafting the work; LM, VM, RG, MRD, and ST contributed to data acquisition and revising the work critically for intellectual content; SB, SM, IAM, GV, and SLG contributed to the conception and design of the work, data interpretation, and revising the work critically for intellectual content.

Ethical approval

Human studies and subjects

The study was approved by the local Institutional Ethics Committee (Palermo 1, Italy, No. 07/2017). All the participants were informed about all aspects of the research and provided their written consent before study entry.

Animal studies

N/A.

Data sharing and data accessibility

The data that support the findings of this study may be available from the Corresponding Author upon reasonable request.

Publication ethics

Plagiarism

Any overlaps with other articles are appropriately cited.

Data falsification and fabrication

All the data correspond to the real.

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