Title

Intracranial Volume Is Driven by Both Genetics and Early Life Exposures: The SOL-INCA-MRI Study.

Journal

Ethnicity & Disease, 34(2)

ISSN

1049-510X

Authors

Sofer, Tamar

Granot-Hershkovitz, Einat

Tarraf, Wassim

et al.

Publication Date

2024-02-01

DOI

10.18865/ed.34.2.103

Peer reviewed

Original Report

Intracranial Volume Is Driven by Both Genetics and Early Life Exposures: The SOL-INCA-MRI Study

Tamar Sofer, PhD[1,2,3]; Einat Granot-Hershkovitz, PhD[1]; Wassim Tarraf, PhD[4]; Paola Filigrana, PhD[5]; Carmen R. Isasi, MD, PhD[6]; Shakira F. Suglia, ScD[7]; Robert Kaplan, PhD[6,8]; Kent Taylor, PhD[9]; Martha L. Daviglus, MD, PhD[10]; Fernando D. Testai, MD, PhD[11]; Donglin Zeng, PhD[12]; Jianwen Cai, PhD[12]; Myriam Fornage, PhD[13]; Hector M. González, PhD[14]; Charles DeCarli, MD[15]

Intracranial volume (ICV) reflects maximal brain development and is associated with later-life cognitive abilities. We quantified ICV among first- and second-generation Hispanic and Latino adults from the Study of Latinos-Investigation of Cognitive Aging – MRI (SOL-INCA-MRI), estimated ICV heritability, and tested its associations with previously reported genetic variants, both individually and as a genetic risk score (GRS). We also estimated the association of ICV with early life environmental measures: nativity or age of immigration and parental education. The estimated heritability of ICV was 19% (95% CI, 0.1%-56%) in n=1781 unrelated SOL-INCA-MRI individuals. Four of 10 tested genetic variants were associated with ICV and an increase of 1 SD of the ICV-GRS was associated with an increase of 10.37 cm^3 in the ICV (95% CI, 5.29-15.45). Compared to being born in the continental United States, immigrating to the United States at age 11 years or older was associated with 24 cm^3 smaller ICV (95% CI, −39.97 to −8.06). Compared to both parents having less than high-school education, at least 1 parent completing high-school education was associated with 15.4 cm^3 greater ICV (95% CI, 4.46-26.39). These data confirm the importance of early life health on brain development. *Ethn Dis.* 2024;34(2):103–112; doi:10.18865/ed.34.2.103

Keywords: Hispanic or Latino; Genetic Associations; Heritability; Early Life Development

[1] Division of Sleep and Circadian Disorders, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA
[2] CardioVascular Institute, Beth Israel Deaconess Medical Center, Boston, MA
[3] Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, MA
[4] Institute of Gerontology, Wayne State University, Detroit, MI
[5] Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, NY
[6] Department of Epidemiology & Population Health, Department of Pediatrics, Albert Einstein College of Medicine, Bronx, NY
[7] Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, GA
[8] Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle WA
[9] The Institute for Translational Genomics and Population Sciences, Department of Pediatrics, The Lundquist Institute for Biomedical Innovation at Harbor-UCLA Medical Center, Torrance, CA
[10] Department of Medicine, Institute for Minority Health Research, University of Illinois at Chicago, IL
[11] Department of Neurology, University of Illinois at Chicago College of Medicine, Chicago, IL
[12] Department of Biostatistics, Gillings School of Global Public Health, University of North Carolina, Chapel Hill, NC
[13] Brown Foundation Institute of Molecular Medicine, McGovern Medical School, The University of Texas Health Science Center at Houston, Houston, TX
[14] Department of Neurosciences and Shiley-Marcos Alzheimer's Disease Center, University of California, San Diego, La Jolla, CA
[15] Alzheimer's Disease Research Center, Department of Neurology, University of California, Davis, Sacramento, CA

Address correspondence to Tamar Sofer, PhD; CardioVascular Institute, Beth Israel Deaconess Medical Center, Center for Life Sciences, Boston, MA. tsofer@bidmc.harvard.edu

Introduction

Brain and intracranial volume (ICV) growth begin in utero, increase throughout childhood, and reach a maximum size in early adulthood[1] after which ICV remains fixed in size and is considered a stable and valid measure for maximally attained brain size.[2–4] ICV is also a highly heritable trait, estimated to be h^2=0.91 in the NHBLI (National Heart, Lung, and Blood Institute) Twins Study[5], h^2=0.78 in the Queensland Twin Imaging Study, and h^2=0.84 in the Genetics of Brain Structure and Function Study.[6] While heritability quantifies the overall genetic contribution to a trait, it is, fundamentally, a measure of proportion of variance.[7] Thus, it is possible that differences in environmental exposure during brain development could lead to greater ICV variability and lower heritability across populations. For example, prior work found that older Hispanic/Latino adults (age>60 years) in the United States had smaller ICV than African Americans and White older adults.[8] This difference may reflect heterogeneity of early life exposures in Hispanic/Latino individuals in the United States, many of whom immigrated to the United States at an older age or had adverse childhood exposures potentially

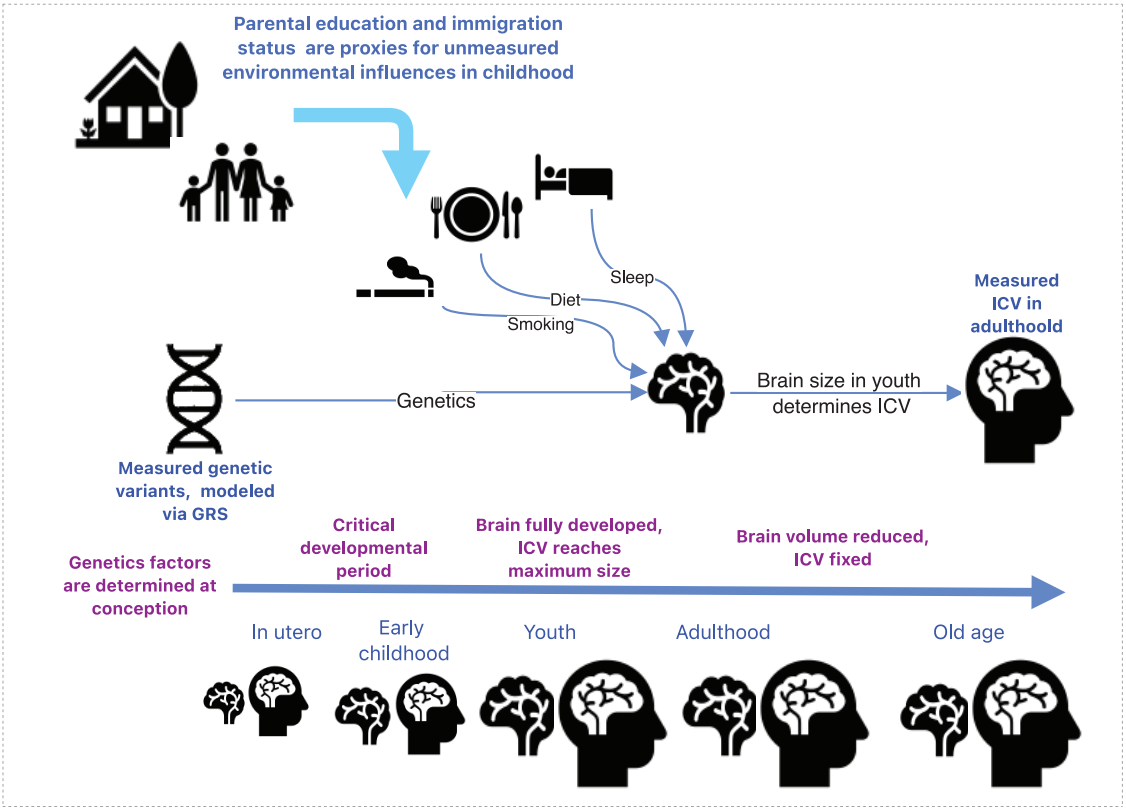

Figure. Both genetic determinants and environmental influences at the critical developmental period (in utero and early childhood) affect brain development, which in turn determines the attained ICV. ICV remains fixed after reaching full size, while brain size decreases in old age. Abbreviations: GRS, genetic risk score; ICV, intracranial volume

affecting brain development.[9,10] Indeed, as Tierney and Nelson[11] noted, prenatal development is driven by the interaction between the mother's physiology and genetics, whereas postnatal development is driven by the interaction between genetics and the environment during development and throughout life. Given that much of postnatal growth in brain and ICV occurs during the first 5 years of life,[1,4,12] this would be an expected period whereby environmental influences might be greatest. Our study relies on the current understanding that both genetic and early life influences affect brain development that drives ICV, which remains stable in adulthood (Figure). Early life influences, therefore, likely affect population-based differences such as between race/ethnicity groups, which often share environmental exposures.

Here, we estimated the heritability of ICV in Hispanic and Latino adults in the United States from the Study of Latinos, Investigation of Neurocognitive Aging – MRI (SOL-INCA-MRI) study. We tested generalization of previously identified genetic associations with ICV to Hispanic/Latino older adults from SOL-INCA-MRI via single single nucleotide polymorphism (SNP) analysis and an analysis of a genetic risk score (GRS) combining genetic alleles based on all previously reported single-SNP associations. Given previous results from the Hispanic Community Health Study/Study of Latinos (HCHS/SOL),[13] we expected that significant genetic influences on ICV will also be present in this cohort. We, however, also hypothesized that ICV heritability will be lower in Hispanic/Latino individuals compared with previously reported heritability estimates from studies of White individuals as SOL-INCA-MRI, participants have a more diverse early life environment.[14]

Methods

SOL-INCA-MRI Study Population

The HCHS/SOL is a population-based longitudinal multisite cohort study of Hispanic/Latino adults in the United States. The study enrolled participants via multistage sampling design from primarily 6 self-identified backgrounds: Cuban, Central American, Dominican, Mexican, Puerto Rican, and South American.[14,15] A total of 16,415 adults, 18 to 74 years of age,

were enrolled at baseline at 4 field centers (Bronx, NY; Chicago, IL; Miami, FL; and San Diego, CA) in the United States during 2008 to 2011. Gender was ascribed by the interviewer, and when genetic data were available, biological sex was verified for match with the reported gender. SOL-INCA-MRI took place during 2017-2022, recruiting 260 individuals younger than 50 years, and 2008, with individuals 55 years or older at the time of magnetic resonance imaging (MRI) examination. The older group included 301 individuals with mild cognitive impairment (MCI), where MCI was evaluated in the SOL-INCA study.[16] The remaining were selected at random among sex- and center-matched individuals with no evidence of MCI.[17,18] SOL-INCA study had majority female participants (~60%), and MCI was more common among females, leading to a higher proportion of female participants. MRI measures of ICV were available for 2289 individuals.

Ethics Statement

The HCHS/SOL was approved by the institutional review boards at each field center, where all participants gave written informed consent in their preferred language (Spanish/English), and at the University of North Carolina at Chapel Hill, Coordinating Center to the HCHS/SOL data. This study was also approved by the Mass General Brigham Institutional Review Board under protocol No. 2018P001797, and by the Beth Israel Deaconess Medical Center Committee on Clinical Investigations under protocol No. 2023P000277.

Genotyping and Imputation

Genotyping was performed by using Illumina custom array, and quality control has been previously described.[19] All individuals with genetic data who passed quality control had biological sex matching their reported gender. Principal components (PCs) and kinship matrix appropriate for admixed individuals were computed with PC-AiR and PC-Relate, implemented in the GENESIS R package.[20,21] "Genetic analysis groups" were constructed from a combination of self-identified Hispanic/Latino backgrounds and genetic similarity.[19] These groupings are used for genetic analyses, as it allows for better control of population stratification while including individuals who do not self-identify with a specific Hispanic/Latino background.[19,22] Genome-wide imputation via the Michigan server was conducted with the TOPMed Freeze 5b as a reference panel.[23] Ancestry-specific allele frequencies of genetic variants were computed by using the global-ancestry-specific allele frequency estimation in admixed populations (GAFA) procedure, based on continental-ancestry proportions.[24]

Brain MRI Measure of ICV

MRI measures were made at the Imaging of Dementia and Aging (IDeA) laboratory on high-resolution 3DT1 MR sequences, using a recently developed and robustly validated Convolutional Neural Network method for estimation of ICV.[25] See supplemental material for more details regarding method and stability of measure.

Heritability Estimation

ICV heritability was estimated via the Haseman-Elston method-of-moment estimator,[26] using the variance explained by the kinship matrix, representing the additive effects of common genetic variants. Heritability was estimated from 1862 individuals with ICV and genetic data, of whom 1781 were unrelated after excluding >third-degree relatives estimated by the kinship coefficients. We also estimated the heritability of height, using the same individuals. It is useful to compare ICV and height because heritability estimates of height from family studies are similar to heritability estimates of ICV[27]; height is largely determined pre adulthood (then declines somewhat in old age), and height is highly correlated with ICV. Further, we previously showed that height variance is largely explained by both genetics and household environment.[26]

Association Analyses of ICV with Previously Reported Genetic Variants

We used generalized linear mixed models implemented in the GENESIS R package[21] to test for genetic associations with ICV. Correlations between individuals were modeled via kinship, household, and census block unit sharing matrices. Analyses were adjusted for age and sex, and to account for population stratification, for genetic analysis group, and for the first 5 PCs of genetic data. Population stratification is the phenomenon whereby differences in allele frequencies align with differences in phenotype distribution, but both are due to confounding factors. For example, demographic history may lead to differences in variant frequencies (because ancestral populations are somewhat isolated from one another and are subject to different population genetic effects such as drift, or selection to increase fitness in the local environment) and to differences in environmental and lifestyle exposures, which associate with adult ICV distribution, thus leading to biased effect estimates. We used this model to estimate the associations of 10 previously reported variants with ICV.[6,28,29] We report standard 2-sided P values from the score test, and 1-sided P values to account for the direction of association in the discovery study. When using 1-sided P value, an association cannot be declared as replicated when the directions of associations do not match between the discovery and replication analyses.[13] Next, we used the 10 variants to construct an unweighted GRS in which the number of ICV-increasing alleles was summed across the

variants, and estimated the GRS association with ICV.

Assessment of the Association of Early Life Socioeconomic Status with ICV

For this study, early life exposures were defined by (1) participant immigration status, including place of birth (continental United States, or not) and age at immigration for those born outside the continental United States; and (2) their parents' education level. Immigration status was coded as a 4-level variable: born in the continental United States (reference), immigrated to the United States between ages 0 and 5 years, immigrated to the United States between ages 6 and 10, and immigrated to the United States at age 11 or older. Parents' education was coded as a 3-level variable: both parents having less than high-school education (reference), at least 1 parent having high-school or vocation-school education, and at least 1 parent having college education. We assessed the potential association of early life exposures with ICV by using both these variables. Environmental associations were first assessed in linear mixed models that did not include genetic data. The minimally adjusted model included random effects for household, for block unit sharing based on baseline data, and for sampling stratum, because sampling strata in HCHS/SOL were defined according to socioeconomic status[15] and fixed effects for age at SOL-INCA-MRI, gender, and study center. A second model adjusted for self-reported Hispanic/Latino background. These analyses were performed with the "lmer" R package and standard errors and P values were computed with the "lmerTest" R package. Next, we estimated the association of these nativity and early immigration measures in a model that also included the ICV GRS. For this analysis we used the genetic analysis framework and fitted linear mixed models using the GENESIS R package with kinship, household, and block unit sharing matrices, 5 PCs of genetic data, and genetic analysis groups as fixed effects. We further adjusted for age at SOL-INCA-MRI, and for gender. We report the estimated association of the genetic and early life socioeconomic variables in the model in which all were used as exposure variables. In addition, we also compared the variance explained by both sets of measures. To do this, we computed the total variance (sum of kinship, household, block unit, and residual variance component estimates) from a baseline model with none of the GRS, immigration, and parents' education measures; from models with only the GRS added; and from a model with immigration and parents' education variables added (but without the GRS). The percent variance explained by the 2 categories of measures was the percent reduction in total variance from the baseline model to the model with the respective set of measures.

Results

Table 1 summarizes the demographic and lifestyle characteristics of the SOL-INCA-MRI datasets with ICV measures, and those who have both ICV and genetic data, both as total and as a subset of unrelated individuals (after excluding ≤third-degree relatives). Overall, there were 2289 individuals with ICV, 1872 individuals with both ICV and genetic data, and 1781 genetically unrelated individuals with genetic data and ICV. The proportion of males was ∼33% in all these dataset subsets, and the mean age was ∼62 years at the MRI examination. Mean ICV was similar across these subsets.

Estimated Heritability of ICV and Comparison with Height

The estimated heritability for ICV is provided in Table 2. Heritability was estimated at 34% (95% CI, 3%-70%) when using all individuals (n=1862), and lower when excluding related individuals: 19% (95% CI, 0.1%-56%), with n=1781. By comparison, heritability of height on the same samples was 76% using the unrelated set and 81% using all individuals.

Association Analysis of Previously Reported ICV Loci and GRS with ICV

Table 3 summarizes the results from replication testing of genetic variants previously associated with ICV. Eight of 10 associations had a consistent direction of estimated effects with prior literature. Four of 10 variants also had nominally significant association in the HCHS/SOL analytic sample (1-sided P value<.05): rs4273712 (chr6q22.32), rs10784502, rs138074335 (chr12q14.3), and rs199525 (chr17q21.31). Eight of these associations were also reported in a Hispanic population, and the direction of associations between HCHS/SOL and the previous study population[29] matched for 7 of the 8 variants. Ancestry-specific allele frequencies of all variants, using GAFA,[16] showed that allele frequencies differed across the 3 HCHS/SOL ancestral populations, but with no clear pattern (Supplementary Table 1).

We also tested the association of an ICV GRS summing all 10 ICV-increasing alleles (where the direction was determined by the previous studies). The ICV GRS was positively associated with ICV with effect size of 3.94-cm^3 increase in ICV per 1 allele increase in the GRS (standard error=0.92, P value=1.9×10^{-5}).

Association of Nativity and Early Life Immigration with ICV

Table 4 summarizes the associations of ICV volume to nativity (born in continental United States) as the reference and early life immigration at ages 0-5 years, ages 6-10, and ages 11 and older, and the association between ICV and maximal parental education (high

Table 1. Demographics and ICV Characteristics of the SOL-INCA-MRI ICV Study Sample Datasets

	SOL-INCA-MRI	SOL-INCA-MRI, Genetic Consent	SOL-INCA-MRI, Genetic Consent, Unrelated Individuals
n	2289	1872	1781
Sex, M (%)	742 (32.4)	628 (33.5)	607 (34.1)
Age, mean (SD), y	61.98 (9.42)	61.99 (9.48)	62.01 (9.43)
Education (%)			
<12	859 (37.6)	680 (36.4)	647 (36.4)
12	507 (22.2)	422 (22.6)	405 (22.8)
>12	920 (40.2)	767 (41.0)	727 (40.9)
Background (%)			
Dominican	189 (8.3)	165 (8.8)	153 (8.6)
Central America	293 (12.8)	232 (12.4)	216 (12.1)
Cuban	350 (15.3)	305 (16.3)	293 (16.5)
Mexican	840 (36.7)	651 (34.8)	620 (34.9)
Puerto Rican	373 (16.3)	311 (16.6)	301 (16.9)
South American	193 (8.4)	165 (8.8)	159 (8.9)
More than 1/other heritage	48 (2.1)	40 (2.1)	37 (2.1)
Center (%)			
Bronx	518 (22.6)	442 (23.6)	415 (23.3)
Chicago	676 (29.5)	530 (28.3)	504 (28.3)
Miami	646 (28.2)	554 (29.6)	531 (29.8)
San Diego	449 (19.6)	346 (18.5)	331 (18.6)
Age at immigration, mean (SD), y	31.35 (13.30)	31.55 (13.52)	31.39 (13.55)
Age at immigration level (%)			
US born	241 (10.6)	208 (11.1)	196 (11.0)
Immigration age 0 to 5 y	55 (2.4)	51 (2.7)	51 (2.9)
Immigration age 6 to 10 y	57 (2.5)	44 (2.4)	44 (2.5)
Immigration age 11 y and older	1931 (84.5)	1565 (83.8)	1488 (83.6)
Parents' education level (%)			
Less than high school	1151 (65.0)	919 (63.9)	867 (63.4)
High school or trade school	414 (23.4)	342 (23.8)	329 (24.0)
College	206 (11.6)	178 (12.4)	172 (12.6)
ICV, mean (SD), cm^3	1154.64 (116.78)	1157.56 (119.14)	1158.42 (119.77)

Abbreviations: ICV, intracranial volume; SOL-INCA-MRI, Study of Latinos-Investigation of Cognitive Aging – MRI

US born refers to birth in the continental United States

Parents' education level refers to the highest education level of the 2 parents

Age at immigration is reported only for individuals who were born outside the continental United States

Unrelated individuals refer to a sample in which no 2 individuals are related of the third degree or closer

school and college), compared to less than high school (reference). There were 241 individuals born in mainland United States; 55 individuals who immigrated to the United States between ages 0 and 5 years; 57 individuals who immigrated between ages 6 and 10; and 1939 individuals who immigrated at ages 11 or older. The associations were similar in minimally adjusted models (only age, gender, and study center), and models further adjusted for self-reported Hispanic/Latino background. Birth in the continental United States was associated with a 24 cm^3 greater ICV volume (95% CI, 8.1-40; minimally adjusted model), compared to immigrating to the United States at age 11 or older (P=.003). Differences in ICV volume between those born in the United States and individuals immigrating to the United States at ages below 11 years were not statistically significant.

When examining parental education, there were 206 individuals whose parents had college or greater levels of education, 414 with high school or equivalent, and 1151 individuals with less than high-school education. Compared to those individuals whose parents had less than high-school education, individuals of parents achieving high-school education had greater ICV volumes of 15.4 cm^3 (95% CI, 5.6-27.5; P=.006). Individuals whose parents had a college education also had larger ICV volumes, but this difference was not statistically significant.

In models including ICV GRS, the previous associations between early life environmental measures and ICV were reduced somewhat but remained

Table 2. Estimated Heritability of ICV and of Height in the Same Analytic Samples

Trait	Analysis Set	n	Estimated Heritability	95% CI
ICV	SOL-INCA-MRI, with genetic data	1862	0.34	0.03-0.70
ICV	SOL-INCA-MRI, with genetic data, unrelated set	1781	0.19	0.001-0.56
Height	SOL-INCA-MRI, with genetic data	1859	0.76	0.44-1.00
Height	SOL-INCA-MRI, with genetic data, unrelated set	1779	0.81	0.44-1.00

Abbreviations: ICV, intracranial volume; MRI, magnetic resonance imaging; SOL-INCA-MRI, Study of Latinos-Investigation of Cognitive Aging – MRI

Heritability was estimated as the proportion variance explained by genetic data, using a mixed model with random effects corresponding to genetic relatedness, household, and block-sharing matrices fitted via the GENESIS R package

Fixed effects included age at MRI (for ICV) or age at baseline (for height), sex, study center, 5 principal components of genetic data, and genetic analysis group

Unrelated set of individuals is a set of people such that no 2 individuals are related of the third degree or closer

Three individuals from the ICV analytic sample had missing height data (2 when considering the unrelated set)

statistically significant for those immigrating to the United States after age 10 years (P=.01), and the pattern of associations was essentially unchanged (Table 5). The estimated effect per 1 SD increase in GRS was equal to a volume of 10.4 cm^3 (95% CI, 5.3-15.5). Variance in ICV explained by the GRS was 1.02% compared to 0.66% by the early environmental variables of age at immigration and maximal parental education (Table 5).

Discussion

Our study found lower ICV, but similar height heritability, when compared to studies of non-Hispanic White populations. Despite lower ICV heritability, GRS associations with ICV were consistent with prior reports from primarily non-Hispanic White cohorts,[6,28] confirming genetic influence on ICV in this cohort. Additionally, we found that immigration status and maximal parental education were also associated with greater ICV volume. Moreover, both the genetic traits and early life environmental variables were significant, independent predictors of ICV. We conclude that genetic and environmental factors are both influencing ICV in this cohort of Hispanic/Latino individuals. We further hypothesize that the diverse early life environmental conditions likely have a stronger influence on this cohort than the more homogeneous early life environments of non-Hispanic White populations previously studied.

Genetic Influences

Why were the heritability estimates for ICV of this cohort different from prior non-Hispanic White cohorts, while heritability of height was more similar?

Heritability, or more specifically, "narrow sense heritability," is defined as the proportion of variance explained by additive genetic effects.[30] We estimated heritability as the ratio between the variance component corresponding to the kinship matrix to the total variance of the model, that is, the sum of

Table 3. Genetic Associations with ICV in HCHS/SOL MRI Analytic Sample

								Estimated Association			
Previous Publication	rsID	Chr	Position (hg38)	EA	NEA	EAF	MAC	Beta	SE	P Value	One-Sided P Value
Adams et al, 2016	rs2022464	6	108624167	A	C	0.41	1569	−4.12	3.13	.188	.094
Adams et al, 2016	rs11759026	6	126470949	A	G	0.61	1511	−3.24	3.38	.336	.168
Ikram et al, 2012	rs4273712	6	126643364	A	G	0.60	1511	−5.66	3.30	.086	.043
Adams et al, 2016	rs11191683	10	103410892	G	T	0.72	1091	−3.84	3.43	.264	.132
Adams et al, 2016	rs9811910	3	190953113	G	C	0.97	91	16.06	10.02	.109	.945
Stein et al, 2012	rs10784502	12	65950030	C	T	0.38	1374	9.44	3.27	.004	.002
Adams et al, 2016	rs138074335	12	65980467	A	G	0.36	1308	9.51	3.27	.004	.002
Adams et al, 2016	rs2195243	12	102529208	G	C	0.88	432	6.13	4.81	.203	.101
Adams et al, 2016	rs9915547	17	46135416	T	C	0.80	797	5.79	3.88	.136	.932
Adams et al, 2016	rs199525	17	46770468	T	G	0.86	532	9.97	4.50	.027	.013

Abbreviations: Chr, chromosome; EA, effect allele; EAF, effect allele frequency (estimated in all of HCHS/SOL); HCHS/SOL, Hispanic Community Health Study/Study of Latinos; ICV, intracranial volume; MAC, minor allele count; MRI, magnetic resonance imaging; NEA, non–effect allele; PCs, principal components; SE, standard error

The association model was adjusted for age at the MRI examination, center, genetic analysis group, and first 5 genetic PCs

One-sided P values were computed to account for the direction of association reported in the discovery study

There were n=1862 individuals in the analysis

Ancestry-specific allele frequencies were estimated by using GAFA, as reported in Granot-Hershkovitz et al (2022) and are provided in Supplementary Table 1

Table 4. Estimated Associations of Early Life Socioeconomic Status with ICV

Nativity/Immigration Measure	Beta	SE	P Value	95% CI
	Minimally Adjusted Model			
Immigration age, y				
US born	(ref)			
≤5	6.46	17.72	.715	−28.27 to 41.19
6-10	−13.77	17.13	.422	−47.34 to 19.8
≥11	−24.01	8.14	.003	−39.97 to −8.06
Parents' education				
Less than high school	(ref)			
High school or trade school	16.54	5.58	.003	5.6 to 27.47
College	13.06	7.28	.073	−1.2 to 27.32
	Model Adjusted for Hispanic/Latino Background			
Immigration age, y				
US born	(ref)			
≤5	2.54	17.62	.885	−32 to 37.08
6-10	−15.31	17.07	.370	−48.76 to 18.14
≥11	−27.49	8.74	.002	−44.62 to −10.37
Parents' education				
Less than high school	(ref)			
High school or trade school	15.43	5.59	.006	4.46 to 26.39
College	10.88	7.34	.138	−3.5 to 25.26

Abbreviations: ICV, intracranial volume; SE, standard error; SOL-INCA-MRI, Study of Latinos-Investigation of Cognitive Aging – MRI

Models were fitted as mixed models with the lmer R package, with random effects corresponding to household, block unit, and sampling strata (the latter is related to socioeconomic status)

Standard errors and P values were computed by using the lmerTest R package

All models adjusted for age at SOL-INCA-MRI, gender, and study center

Other model adjustments included Hispanic/Latino background, as described by table titles

There were n=1767 participants in these analyses

Table 5. Evaluation of the Contribution of Genetic Risk Score and Early Life Socioeconomic Status on ICV

Exposure	Beta	SE	P Value	95% CI	Variance Explained
GRS	10.37	2.59	6.3E-05	5.29 to 15.45	1.02%
Immigration age, y					
US born	(ref)				0.66% (combined early childhood
≤5	1.59	18.39	.93	−34.46 to 37.65	socioeconomic status variables)
6-10	−13.12	19.03	.49	−50.43 to 24.18	
≥11	−24.58	9.64	.01	−43.47 to −5.69	
Parents' education					
Less than high school	(ref)				
High school or trade school	10.18	6.22	.10	−2.01 to 22.36	
College	7.57	8.00	.34	−8.1 to 23.25	

Abbreviations: GRS, genetic risk score; ICV, intracranial volume; SE, standard error

Associations were estimated in a mixed linear model by using the GENESIS R package in a joint model of the GRS and early immigration measures. The GRS was scaled so that the estimated GRS association effect (beta) is per 1 SD increase in the GRS

Random effects accounted for genetic relatedness, household, and block unit sharing

Fixed effects included age, sex, 5 principal components of genetic data, and genetic analysis group

Variance explained was computed as the percent reduction in total variance from a model with only baseline covariates (not including the GRS or the early socioeconomic status measures) to a model with also the GRS, or a model with also early life socioeconomic status measures (age at immigration and parents' education, in the same model). Reference level for age at immigration variable is "US born" (ie, born in the continental United States). Reference level of parents' education is both parents having less than high-school education

P values were computed from the score test

The sample size was n=1429

variance components corresponding to the kinship matrix, household, block unit matrices, and error variance.[26] For this study, the kinship matrix was computed from all common genotyped variants, thus likely capturing most causal variants, including those with small effects. Thus, this estimated heritability is often also called "SNP-based heritability."[31] Notably, the HCHS/SOL genotyping chip was designed to capture the genetic diversity of the Hispanic/Latino population, and therefore highly suitable for heritability estimation, and did not suffer from inappropriate variant selection[7] (as could happen when genetic variants used upstream in the analysis are not highly correlated with causal variants in the specific population used). We postulate that the heritability observed in our study is lower than in previous studies because the overall variance is higher, rather than because the estimate of the genetic variance is biased. A potential reason for an overall higher variance is that environmental influences may act more strongly owing to less homogeneous early life environmental influences. Further, it is important to note that the 95% CIs of the estimated heritability were wide, and future testing of a much larger Hispanic/Latino population might lead to a more accurate measure as discussed below.

It was previously shown that the proportion of variance explained by the kinship matrix is asymptotically equivalent to the proportion of variance explained by the set of causal variants of a trait, if they are individually modelled in a regression.[32] Comparing the variance explained by the GRS, which combines multiple, previously reported ICV loci to the estimated heritability, we see that the GRS only accounts for a fraction of the estimated heritability. This is because the known genetic variants, used in the GRS, are likely only a small fraction of genes underlying ICV. This is consistent with studies of other phenotypes: usually genetic, or polygenic, scores explain a substantially lower proportion of variance than the estimated heritability.[33,34] Recently, a genome-wide association study of height, using about 5.4 million individuals, constructed a genetic scores using roughly 12,000 variants, explaining about 40% of the variance of height in individuals of European genetic ancestries,[35] yet it explained lower proportion of variance in other populations. It is likely that similarly large sample sizes would be needed to identify more genetic variants underlying ICV in Hispanic/Latino populations. Alternatively, innovative statistical and bioinformatics methods that leverage information from other sources (other traits, other types of genetic data) to increase detected associations would be beneficial.

Environmental Influences

Associations between ICV and location of birth or immigration status within the first 5 years of life and parental education are likely only summary indicators of early life environmental influence. For example, degree of parental education is considered a measure of childhood environment, particularly low social economic status. Low social economic status in childhood can lead to poor nutrition, an inadequately stimulating home environment, and psychological stress.[36] Parental education is also associated with later-life cognitive ability in this cohort[10] and is known to influence brain development[37] and therefore is a salient measurement of early life environment.

ICV is also considered as a proxy for brain reserve[2,3] and a significant independent predictor of cognition in old age.[3,38] Understanding the impact of modifiable environmental influences on brain development, therefore, could prove meaningful to both maximally attained and maintained cognitive abilities.

It is important to emphasize the difference between ICV and brain size in adulthood. While ICV represents the maximum attained brain size, brain size changes in adulthood and is typically reduced with normal aging,[39] while ICV remains stable.[2,3] Accordingly, ICV is not affected by social determinants of health in adulthood, but rather in utero and early childhood, while brain size, which is reduced in adulthood, is likely subject to various life course influences. Thus, our analysis did not use measures such as participant education or current socioeconomic status, as these may be the consequence of early life brain development.

The study has a few limitations. First, our measures of early life environment were limited to age of immigration and maximally attained parental education. We modeled the association of immigration to the continental United States in groups defined by ages 5 and 10 years. While age groups reflecting narrower age ranges at early age would ideally have been used, we were limited by the number of individuals who immigrated to the continental United States at infancy and early childhood. Second, many of the individuals who immigrated to the United States between ages 0 and 5 years were of Puerto Rican background. However, it is unlikely that such effects are driven by a specific background. Measures of maximally attained parental education were similarly restricted with 65% of participants having less than high-school education and only 12% having obtained a college degree. Consequently, our power to detect continuous or threshold effects of education was limited. Finally, this dataset is limited to a subset of Hispanic/Latino individuals of HCHS/SOL who consented to MRI, and was enriched for individuals with MCI, and therefore, may not generalize to all US Hispanic/Latino adults.

Reviews on the impact of immigration as a social determinant of health often focus on adverse health effects such as obesity, insulin resistance, and poor access to health care.[9,40] To the degree that increased brain development is represented by larger ICV, our

data suggest a beneficial effect of early life environmental effects, despite the limited measures available. We should, however, interpret these results cautiously, particularly regarding the effect of age at immigration status on ICV volume. We did not assess reasons for immigration or social conditions upon arrival beyond the estimates provided by parental education. Thus, we cannot infer from these data that early immigration to the United States is causally related to better brain development. Additionally, this is an observational study where the population studied represents both first- and second-generation immigrants, further influencing the impact of immigration status. Still, these data confirm the importance of early life health on brain development, which should be emphasized in public health initiatives.

Future directions based on this work would be to perform a more nuanced study of childhood environment and brain development, that is, with prospective data collection of both home and outdoor environmental factors. From the genetic perspective, it would be useful to assess potential gene-environment interactions, where exposures such as nutrition and activity may modulate genetic influences.

Acknowledgments

The authors thank the staff and participants of HCHS/SOL and SOL-INCA for their important contributions. Investigators website—https://sites.cscc.unc.edu/hchs/. The Hispanic Community Health Study/Study of Latinos is a collaborative study supported by contracts from the National Heart, Lung, and Blood Institute (NHLBI) to the University of North Carolina (HHSN268201300001I/N01-HC-65233), University of Miami (HHSN268201300004I/N01-HC-65234), Albert Einstein College of Medicine (HHSN268201300002I/N01-HC-65235), University of Illinois at Chicago (HHSN268201300003I/N01-HC-65236 Northwestern Univ), and San Diego State University (HHSN268201300005I/N01-HC-65237). The following Institutes/Centers/Offices have contributed to the HCHS/SOL through a transfer of funds to the NHLBI: National Institute on Minority Health and Health Disparities, National Institute on Deafness and Other Communication Disorders, National Institute of Dental and Craniofacial Research, National Institute of Diabetes and Digestive and Kidney Diseases, National Institute of Neurological Disorders and Stroke, NIH Institution-Office of Dietary Supplements. This work was supported by the National Institute on Aging (R01AG048642, RF1AG054548, RF1AG061022, R21AG070644, RF1AG077639, R01AG075758, P30AG072972, RF1AG054548, R21AG056952, and R01AG080598).

Conflict of Interest

No conflict of interest reported by authors.

Author Contributions

Research concept and design: Sofer, Granot-Hershkovitz, Isasi, Kaplan, DeCarli,; Acquisition of data: Tarraf, Isasi, Kaplan, Taylor, Daviglus, Testai, Zeng, Cai, González, DeCarli; Analysis and interpretation of data: Sofer, Granot-Hershkovitz, Filigrana, Isasi, Suglia, Testai, Cai, Fornage, DeCarli; Drafting of manuscript: Sofer, Granot-Hershkovitz, Tarraf, Filigrana, Suglia, Daviglus, Testai, Fornage, González, DeCarli; Statistical expertise: Sofer, Granot-Hershkovitz, Tarraf, Zeng, Cai; Funding: Isasi, Kaplan, Daviglus, DeCarli, Cai, González; Administrative, technical or material support: Filigrana, Isasi, Suglia, Kaplan, Taylor, Testai, Cai, Fornage; Supervision: Sofer

References

1. Sgouros S, Goldin JH, Hockley AD, Wake MJ, Natarajan K. Intracranial volume change in childhood. *J Neurosurg*. 1999;91(4):610-616. doi:10.3171/jns.1999.91.4.0610
2. Farias ST, Mungas D, Reed B, et al. Maximal brain size remains an important predictor of cognition in old age, independent of current brain pathology. *Neurobiol Aging*. 2012;33(8):1758-1768. doi:10.1016/j.neurobiolaging.2011.03.017
3. Gale CR, Walton S, Martyn CN. Foetal and postnatal head growth and risk of cognitive decline in old age. *Brain*. 2003;126(pt 10):2273-2278. doi:10.1093/brain/awg225
4. Purkait R. Growth of cranial volume: an anthropometric study. *J Plast Reconstr Aesthet Surg*. 2011;64(5):e115-e117. doi:10.1016/j.bjps.2011.01.005
5. Carmelli D, DeCarli C, Swan GE, et al. Evidence for genetic variance in white matter hyperintensity volume in normal elderly male twins. *Stroke*. 1998;29(6):1177-1181.
6. Stein JL, Medland SE, Vasquez AA, et al. Identification of common variants associated with human hippocampal and intracranial volumes. *Nat Genet*. 2012;44(5):552-561. doi:10.1038/ng.2250
7. de los Campos G, Sorensen D, Gianola D. Genomic heritability: what is it? *PLOS Genet*. 2015;11(5):e1005048. doi:10.1371/journal.pgen.1005048
8. DeCarli C, Reed BR, Jagust W, Martinez O, Ortega M, Mungas D. Brain behavior relationships among African Americans, whites, and Hispanics. *Alzheimer Dis Assoc Disord*. 2008;22(4):382-391. doi:10.1097/wad.0b013e318185e7fe
9. Isasi CR, Rastogi D, Molina K. Health Issues in Hispanic/Latino Youth. *J Lat Psychol*. 2016;4(2):67-82. doi:10.1037/lat0000054
10. Filigrana P, Moon JY, Gallo LC, et al. Childhood and life-course socioeconomic position and cognitive function in adult population of the Hispanic Community Health Study/Study of Latinos (HCHS/SOL). *Am J Epidemiol*. 2023;192(12):2006-2017. doi:10.1093/aje/kwad157
11. Tierney AL, Nelson CA III. Brain development and the role of experience in the early years. *Zero Three*. 2009;30(2):9-13.
12. Bethlehem RAI, Seidlitz J, White SR, et al. Brain charts for the human lifespan. *Nature*. 2022;604(7906):525-533. doi:10.1038/s41586-022-04554-y
13. Sofer T, Heller R, Bogomolov M, et al. A powerful statistical framework for generalization testing in GWAS, with application to the HCHS/SOL. *Genet Epidemiol*. 2017;41(3):251-258. doi:10.1002/gepi.22029
14. Sorlie PD, Aviles-Santa LM, Wassertheil-Smoller S, et al. Design and implementation of the Hispanic Community Health Study/Study of Latinos. *Ann Epidemiol*. 2010;20(8):629-641. doi:10.1016/j.annepidem.2010.03.015
15. Lavange LM, Kalsbeek WD, Sorlie PD, et al. Sample design and cohort selection in the Hispanic Community Health Study/Study of Latinos. *Ann Epidemiol*. 2010;20(8):642-649. doi:10.1016/j.annepidem.2010.05.006
16. González HM, Tarraf W, Fornage M, et al. A research framework for cognitive aging and Alzheimer's disease among diverse US Latinos: design and implementation of the Hispanic Community Health Study/Study of Latinos-Investigation of Neurocognitive Aging (SOL--INCA). *Alzheimers Dement*. 2019;15(12):1624-1632. doi:10.1016/j.jalz.2019.08.192
17. Stickel AM, Tarraf W, González KA, et al. Characterizing age- and sex-related differences in brain structure among middle-aged and older Hispanic/Latino adults in the study of Latinos-investigation of neurocognitive aging magnetic resonance imaging (SOL-INCA MRI). *Neurobiol Aging*. 2023;126:58-66. doi:10.1016/j.neurobiolaging.2023.02.007
18. Gonzalez HM, Tarraf W, Gouskova N, et al. Neurocognitive function among middle-aged and older Hispanic/Latinos: results from the Hispanic Community Health Study/Study of Latinos. *Arch Clin Neuropsychol*. 2015;30(1):68-77. doi:10.1093/arclin/acu066
19. Conomos MP, Laurie CA, Stilp AM, et al. Genetic diversity and association studies in US Hispanic/Latino populations: applications in the Hispanic Community Health Study/Study of

Latinos. *Am J Hum Genet*. 2016;98(1):165-184. doi:10.1016/j.ajhg.2015.12.001
20. Conomos MP, Reiner AP, Weir BS, Thornton TA. Model-free estimation of recent genetic relatedness. *Am J Hum Genet*. 2016;98(1): 127-148. doi:10.1016/j.ajhg.2015.11.022
21. Gogarten SM, Sofer T, Chen H, et al. Genetic association testing using the GENESIS R/Bioconductor package. *Bioinformatics*. 2019;35(24): 5346-5348. doi:10.1093/bioinformatics/btz567
22. Sofer T, Zheng X, Laurie CA, et al. Variant-specific inflation factors for assessing population stratification at the phenotypic variance level. *Nat Commun*. 2021;12(1):3506. doi:10.1038/s41467-021-23655-2
23. Kowalski MH, Qian H, Hou Z, et al. Use of >100,000 NHLBI Trans-Omics for Precision Medicine (TOPMed) Consortium whole genome sequences improves imputation quality and detection of rare variant associations in admixed African and Hispanic/Latino populations. *PLoS Genet*. 2019;15(12):e1008500. doi: 10.1371/journal.pgen.1008500
24. Granot-Hershkovitz E, Sun Q, Argos M, et al. AFA: ancestry-specific allele frequency estimation in admixed populations: The Hispanic Community Health Study/Study of Latinos. *HGG Adv*. 2022;3(2):100096. doi:10.1016/j.xhgg.2022.100096
25. Fletcher E, DeCarli C, Fan AP, Knaack A. Convolutional neural net learning can achieve production-level brain segmentation in structural magnetic resonance imaging. *Front Neurosci*. 2021;15:683426. doi:10.3389/fnins.2021.683426
26. Sofer T. Confidence intervals for heritability via Haseman-Elston regression. *Stat Appl Genet Mol Biol*. 2017;16(4):259-273. doi:10.1515/sagmb-2016-0076
27. Silventoinen K, Sammalisto S, Perola M, et al. Heritability of adult body height: a comparative study of twin cohorts in eight countries. *Twin Res*. 2003;6(5):399-408. doi:10.1375/136905203770326402
28. Ikram MA, Fornage M, Smith AV, et al. Common variants at 6q22 and 17q21 are associated with intracranial volume. *Nat Genet*. 2012;44(5): 539-544. doi:10.1038/ng.2245
29. Adams HH, Hibar DP, Chouraki V, et al. Novel genetic loci underlying human intracranial volume identified through genome-wide association. *Nat Neurosci*. 2016;19(12):1569-1582. doi:10.1038/nn.4398
30. Visscher PM, Hill WG, Wray NR. Heritability in the genomics era—concepts and misconceptions. *Nat Rev Genet*. 2008;9(4):255-266. doi: 10.1038/nrg2322
31. Zhu H, Zhou X. Statistical methods for SNP heritability estimation and partition: a review. *Comput Struct Biotechnol J*. 2020;18:1557-1568. doi:10.1016/j.csbj.2020.06.011
32. Lee SH, Yang J, Goddard ME, Visscher PM, Wray NR. Estimation of pleiotropy between complex diseases using single-nucleotide polymorphism-derived genomic relationships and restricted maximum likelihood. *Bioinformatics*. 2012;28(19):2540-2542. doi:10.1093/bioinformatics/bts474
33. Jamshidi J, Williams LM, Schofield PR, et al. Diverse phenotypic measurements of wellbeing: heritability, temporal stability and the variance explained by polygenic scores. *Genes Brain Behav*. 2020;19(8):e12694. doi:10.1111/gbb.12694
34. Young AI. Solving the missing heritability problem. *PLoS Genet*. 2019;15(6):e1008222. doi:10.1371/journal.pgen.1008222
35. Yengo L, Vedantam S, Marouli E, et al. A saturated map of common genetic variants associated with human height. *Nature*. 2022;610(7933): 704-712. doi:10.1038/s41586-022-05275-y
36. Ben-Shlomo Y, Kuh D. A life course approach to chronic disease epidemiology: conceptual models, empirical challenges and interdisciplinary perspectives. *Int J Epidemiol*. 2002;31(2): 285-293.
37. Brito NH, Noble KG. Socioeconomic status and structural brain development. *Front Neurosci*. 2014;8:276. doi:10.3389/fnins.2014.00276
38. van Loenhoud AC, Groot C, Vogel JW, van der Flier WM, Ossenkoppele R. Is intracranial volume a suitable proxy for brain reserve? *Alzheimers Res Ther*. 2018;10(1):91. doi:10.1186/s13195-018-0408-5
39. Terribilli D, Schaufelberger MS, Duran FL, et al. Age-related gray matter volume changes in the brain during non-elderly adulthood. *Neurobiol Aging*. 2011;32(2):354-368. doi:10.1016/j.neurobiolaging.2009.02.008
40. Guadamuz JS, Kapoor K, Lazo M, et al. Understanding immigration as a social determinant of health: cardiovascular disease in Hispanics/Latinos and South Asians in the United States. *Curr Atheroscler Rep*. 2021;23(6):25. doi:10.1007/s11883-021-00920-9