

Supplementary Appendix for ‘Developmental origins of exceptional health and survival: a four-generation family cohort study’

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1. Methods and Materials

Figure S1. Cohort structure of Danish Longevity-Enriched Families (LEFs)

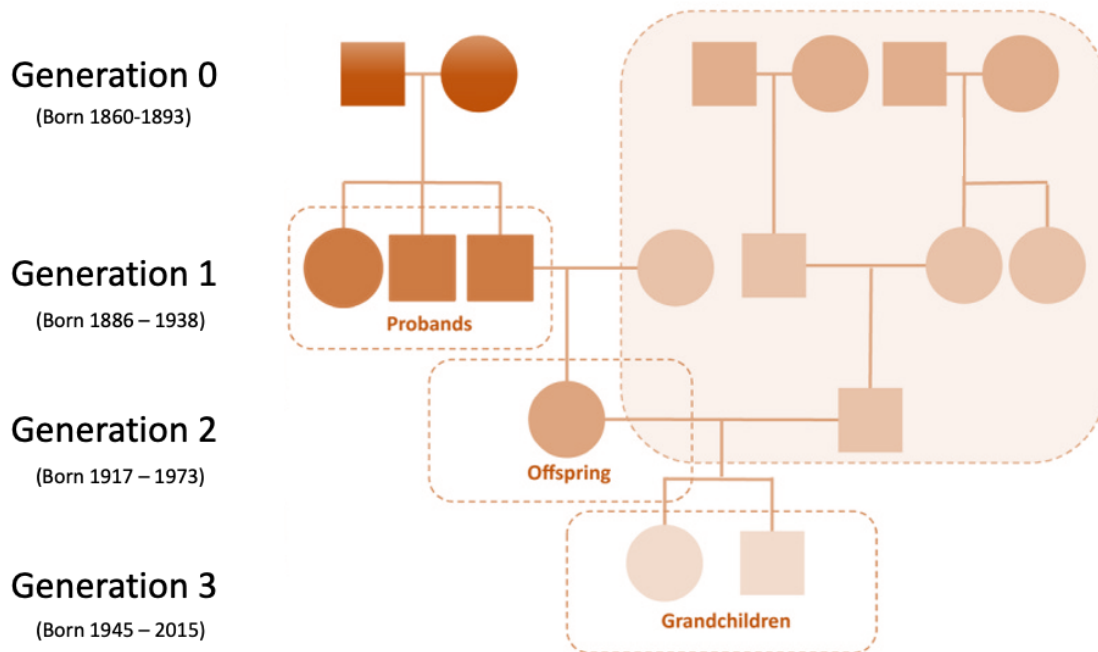


Figure S1.1 describes the structure of our cohort of longevity enriched families, including the proband generation of longevity-enriched sibships (generation 1), offspring (generation 2), and grandchildren (generation 3). The great-grandchildren (generation 4) used in the present study are not depicted, but their ascertainment is described in the main manuscript. For further details on the structure of our cohort of longevity-enriched families, please see the supplementary appendix for Aging Cell ‘Mechanisms underlying the familial aggregation of exceptional health and survival: A three-generation cohort study’ (<https://doi.org/10.1111/accel.13228>).

Table S2. ICD-8 and ICD-10 codes used to define secondary neonatal and maternal outcomes

Type	Outcome	ICD Level	ICD CODES	Notes
Neonatal	Preterm Birth	NA	NA	Calculated from gestational age variable
	Small for gestational age	NA	NA	Calculated from gestational age and birth weight variables
	Large for gestational age	NA	NA	Calculated from gestational age and birth weight variables
	Low APGAR Score	NA	NA	Calculated from gestational age and birth weight variables
	Birth Trauma	ICD-8	764-768, 772	All codes inclusive
		ICD-10	P10-P15	All codes inclusive
	Neonatal respiratory disorders	ICD-8	763-768*, 776	*With mention of hypoxia
		ICD-10	P20-P28	All codes inclusive
	Congenital malformation	ICD-8	740 - 759	All codes inclusive
		ICD-10	Q00 - Q99	All codes inclusive
	Other neonatal morbidity	ICD-8	760-779**☆	*All adverse neonatal codes not used elsewhere, ☆with exceptions
		ICD-10	P00-P96**☆	*All adverse neonatal codes not used elsewhere, ☆with exceptions

Maternal	Assisted delivery	ICD-8	650-662*	*With mention of forceps, vacuum extractor or other instrumental methods
		ICD-10	O81, O83, O84*	*With mention of forceps or vacuum extractor
	Cesarean section	ICD-8	650-662*	*With mention of cesarean section
		ICD-10	O82, O84*	*With mention of cesarean section
	Preeclampsia and eclampsia	ICD-8	637	All codes inclusive
		ICD-10	O11, O14, O15	All codes inclusive
	Placental disorders	ICD-8	632*, 634*, 651	*With mention of placenta☆
		ICD-10	O43-O45	All codes inclusive☆
	Hemorrhage	ICD-8	632, 651, 653	All codes inclusive, excluding postpartum hemorrhage☆
		ICD-10	O20, O44*, O45*, O46, O67	*With mention of hemorrhage, excluding postpartum hemorrhage☆
	Other maternal morbidity	ICD-8	630-678**☆	**All adverse maternal codes not used elsewhere, ☆with exceptions
		ICD-10	O00-O99**☆	**All adverse maternal codes not used elsewhere, ☆with exceptions

☆Please see written exceptions on next page.

★Exceptions and other explanations

See below for which codes were excluded from our measures of ‘other neonatal morbidity’ and ‘other maternal morbidity’. *Explanations* follow in italics.

Exclusion from **other neonatal morbidity**:

- ICD-8:
 - Foetal death of unknown cause (779) – *defined elsewhere*
 - Termination of pregnancy (773) – *not relevant to live births*
- ICD-10:
 - Disorders related to length of gestation and foetal growth (P05-P08) – *defined elsewhere*
 - Foetal death of unknown cause (P95) – *defined elsewhere*

Exclusion from hemorrhage:

- ICD-8
 - Delivery complicated by retained placenta (652) – *not directly relevant to neonatal health, included in ‘other maternal morbidity’*
 - Delivery complicated by other postpartum hemorrhage (653) – *not directly relevant to neonatal health, included in ‘other maternal morbidity’*
- ICD-10
 - Foetal death of unknown cause (O72) – *defined elsewhere*

Exclusion from placental disorders:

- ICD-8
 - Retained placenta (677.1) – *not directly relevant to neonatal health, included in ‘other maternal morbidity’*
- ICD-10
 - Retained placenta (O73) – *not directly relevant to neonatal health, included in ‘other maternal morbidity’*

Exclusion from **other maternal morbidity**:

- ICD-8:
 - Ectopic pregnancy (631) – *not relevant to live births*
 - Abortion (640-645) – *not relevant to live births*
 - Delivery without mention of complication (6500, 6501, 6509) – *not adverse*
 - Anaesthetic death in uncomplicated delivery (662) – *maternal mortality not assessed*
 - Maternal care (Y60-Y69) – *not adverse*
 - Healthy live-born infants (Y80-Y89) – *not adverse*
- ICD-10:
 - Pregnancy with abortive outcome (O00-O08) – *not relevant to live births*

- Maternal care or care for suspected abnormality (O28, O30, O32-36) – *not adverse*
- Multiple gestation (O30) – *not adverse*
- False labour (O47) – *not adverse*
- Preterm and long labour and delivery (O60, O48, O63) – *defined neonatally*
- Spontaneous Delivery (O80, O840) – *not adverse*
- Obstetric death (O95-O97) – *maternal mortality not assessed*

Important considerations:

1. Several disease groups contain codes used in other disease groups. This is because of the hierarchical structure of some of the codes in either in ICD-8 or ICD-10. For example, ICD-8 code 651 describes ‘Delivery complication by placenta previa or antepartum haemorrhage’. But its subcodes (e.g. 651.0 – 651.8 refer to types of assisted delivery or caesarean section). In this case, 650 codes could appear simultaneously for groups for maternal haemorrhage, assisted delivery and caesarean section. There are several more examples like this.
2. ICD-9 was not employed in Denmark, and so we only use ICD-8 (1973 – 1993) and ICD-10 (1994 - 2018) codes in this study.

2. Additional results from main analyses

Figure S3. Derivation of study population from source population of G3 grandchildren and G4 great-grandchildren (corresponding to **Table 1** in article)

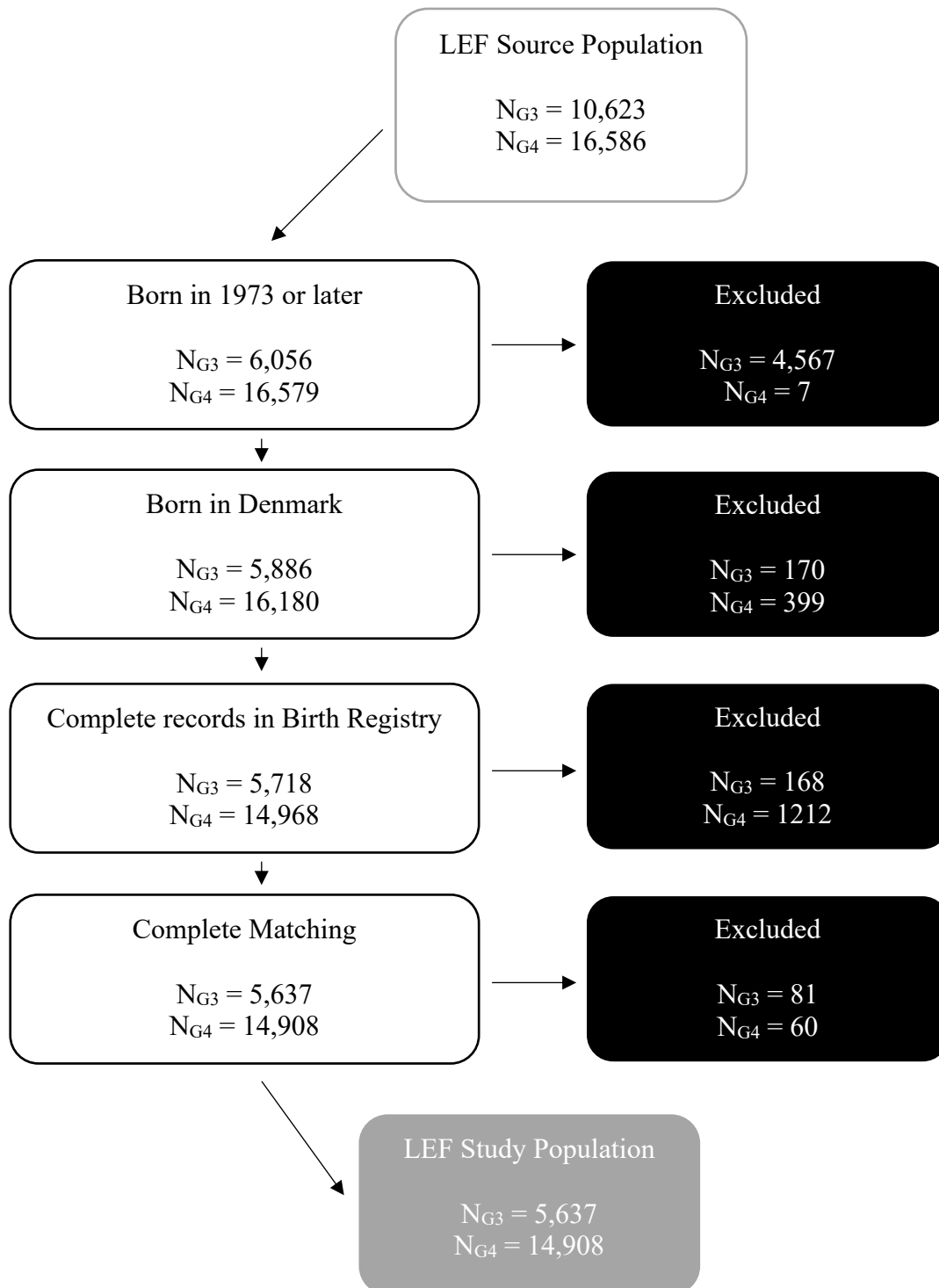


Table S4. Cox regression results for analyses of infant mortality, G3 grandchildren, G4 great-grandchildren and matched controls (corresponding to **Figure 3** in article)

Generation	Model	Adjustment	HR	95% CI	p
G3	LEF vs Matched Controls	Matched only	0.53	[0.36, 0.77]	0.0010
		Socioeconomic factors	0.55	[0.36, 0.82]	0.0033
	LEF Mother Subset	Matched only	0.55	[0.32, 0.94]	0.0295
		Socioeconomic factors	0.49	[0.24, 0.99]	0.0469
	LEF Father Subset	Matched only	0.51	[0.3, 0.87]	0.0137
		Socioeconomic factors	0.52	[0.3, 0.91]	0.0226
	Interaction	Matched only	1.06	[0.5, 2.28]	0.8717
		Socioeconomic factors	1.05	[0.46, 2.38]	0.9067
G4	LEF vs Matched Controls	Matched only	0.90	[0.7, 1.17]	0.4329
		Socioeconomic factors	0.98	[0.75, 1.27]	0.8701
	LEF Mother Subset	Matched only	0.93	[0.66, 1.31]	0.6913
		Socioeconomic factors	0.97	[0.68, 1.37]	0.8532
	LEF Father Subset	Matched only	0.86	[0.58, 1.28]	0.4576
		Socioeconomic factors	0.95	[0.63, 1.44]	0.8189
	Interaction	Matched only	1.08	[0.64, 1.82]	0.7642
		Socioeconomic factors	0.99	[0.58, 1.7]	0.9821
Direct	G3 compared to G4	Matched only	0.32	[0.16, 0.64]	0.0012
		Socioeconomic factors	0.37	[0.19, 0.73]	0.0040

Comparisons of infant mortality in G3 grandchildren, G4 great-grandchildren and matched controls. Matching criteria included sex, birth year, birth season, maternal birth year, parity and mother's place of birth. Further adjustment for parental socioeconomic factors included highest attained education level, total gross income, and marital status. 'Direct comparison' describes analyses that compared G3 grandchildren to G4 great-grandchildren directly within the time periods where the two generations had overlapping birth cohorts (approx. 1973-2010, see Figure 1). Data are presented as hazard ratios with 95% confidence intervals, and HRs < 1 indicate lower hazards of the outcome in LEF descendants compared to general population matched controls, except in 'Direct comparison' where it indicates lower hazards in G3 descendants compared to G4 descendants. P-values describe a two-sided Wald hypothesis test, without adjustment for multiple testing. Abbreviations: G3 (Generation 3), G4 (Generation 4), LEF (Longevity-enriched Family), HR (hazard ratio), CI (confidence interval).

Table S5. Logistic regression results for analyses comparing neonatal morbidities in G3 grandchildren, G4 great-grandchildren, and matched controls, with adjusted p-values (corresponding to **Figure 4** in article)

Generation	Neonatal Outcome	Adjustment	OR	95% CI	p	p _{adjusted}
G3	Preterm Birth	Matched only	0.82	[0.72, 0.93]	0.0014	0.0170
		Socioeconomic factors	0.82	[0.72, 0.93]	0.0016	0.0191
	Small for Gestational Age	Matched only	0.83	[0.76, 0.9]	0.0000	0.0003
		Socioeconomic factors	0.85	[0.78, 0.93]	0.0003	0.0041
	Large for Gestational Age	Matched only	0.92	[0.82, 1.02]	0.1255	0.4460
		Socioeconomic factors	0.91	[0.81, 1.01]	0.0849	0.5096
	Low APGAR Score	Matched only	0.78	[0.55, 1.11]	0.1609	0.4460
		Socioeconomic factors	0.74	[0.51, 1.07]	0.1106	0.5630
	Birth Trauma	Matched only	0.79	[0.56, 1.12]	0.1945	0.4460
		Socioeconomic factors	0.85	[0.59, 1.21]	0.3589	0.7178
	Respiratory Disorders	Matched only	0.76	[0.66, 0.88]	0.0002	0.0026
		Socioeconomic factors	0.76	[0.66, 0.88]	0.0003	0.0036
	Congenital Malformation	Matched only	0.93	[0.79, 1.11]	0.4460	0.4460
		Socioeconomic factors	0.94	[0.78, 1.12]	0.4691	0.7404
	Other Neonatal Morbidity	Matched only	0.87	[0.79, 0.96]	0.0071	0.0706
		Socioeconomic factors	0.87	[0.79, 0.97]	0.0079	0.0790
G4	Preterm Birth	Matched only	0.96	[0.91, 1.02]	0.2003	0.6084
		Socioeconomic factors	0.98	[0.92, 1.04]	0.5445	0.6965
	Small for Gestational Age	Matched only	0.90	[0.85, 0.94]	0.0000	0.0002
		Socioeconomic factors	0.93	[0.89, 0.98]	0.0058	0.0698
	Large for Gestational Age	Matched only	1.06	[1, 1.11]	0.0321	0.2887
		Socioeconomic factors	1.04	[0.99, 1.1]	0.0959	0.6353
	Low APGAR Score	Matched only	1.06	[0.9, 1.26]	0.4899	0.6084
		Socioeconomic factors	1.08	[0.91, 1.29]	0.3698	0.6965
	Birth Trauma	Matched only	0.94	[0.76, 1.18]	0.6084	0.6084
		Socioeconomic factors	0.96	[0.76, 1.2]	0.6965	0.6965
	Respiratory Disorders	Matched only	0.92	[0.87, 0.98]	0.0078	0.0855
		Socioeconomic factors	0.94	[0.89, 1]	0.0491	0.4182
	Congenital Malformation	Matched only	0.92	[0.84, 1.01]	0.0730	0.4674
		Socioeconomic factors	0.94	[0.86, 1.02]	0.1506	0.6807
	Other Neonatal Morbidity	Matched only	0.91	[0.86, 0.96]	0.0005	0.0071
		Socioeconomic factors	0.93	[0.88, 0.98]	0.0060	0.0723

Comparisons of neonatal outcomes in G3 grandchildren, G4 great-grandchildren and matched controls. Matching criteria included sex, birth year, birth season, maternal birth year, parity and mother's place of birth. Adjustment for parental socioeconomic factors included highest attained education level, total gross income, and marital status. Data are presented as odds ratios with 95% confidence intervals, and ORs < 1 indicate lower odds of the outcome in LEF descendants compared to general population matched controls. Basic p-values describe a two-sided Wald hypothesis test, and adjusted p-values are corrected for multiple testing using the Hommel method (n = 14 outcomes). Abbreviations: G3 (Generation 3), G4 (Generation 4), OR (odds ratio), CI (confidence interval).

Table S6. Logistic regression results for analyses comparing maternal morbidities in mothers of G3 grandchildren, G4 great-grandchildren, and matched controls, with adjusted p-values (corresponding to **Figure 4** in article)

Generation	Maternal Outcome	Adjustment	OR	95% CI	p	p _{adjusted}
G3	Assisted Delivery	Matched only	0.87	[0.79, 0.96]	0.0066	0.0658
		Socioeconomic factors	0.87	[0.79, 0.96]	0.0051	0.0509
	Cesarean Section	Matched only	0.87	[0.67, 1.12]	0.2822	0.4460
		Socioeconomic factors	0.86	[0.66, 1.13]	0.2769	0.7037
	Preeclampsia and Eclampsia	Matched only	0.94	[0.81, 1.08]	0.3962	0.4460
		Socioeconomic factors	0.95	[0.82, 1.09]	0.4592	0.7404
	Placental Disorders	Matched only	0.77	[0.58, 1.03]	0.0746	0.4460
		Socioeconomic factors	0.77	[0.57, 1.03]	0.0819	0.4912
	Hemorrhage	Matched only	0.87	[0.77, 0.98]	0.0200	0.1799
		Socioeconomic factors	0.86	[0.76, 0.98]	0.0185	0.1667
G4	Assisted Delivery	Matched only	0.98	[0.93, 1.02]	0.3266	0.6084
		Socioeconomic factors	0.98	[0.93, 1.02]	0.3385	0.6965
	Cesarean Section	Matched only	0.95	[0.89, 1.02]	0.1343	0.6084
		Socioeconomic factors	0.95	[0.89, 1.02]	0.1592	0.6807
	Preeclampsia and Eclampsia	Matched only	0.89	[0.81, 0.98]	0.0172	0.1604
		Socioeconomic factors	0.90	[0.82, 0.99]	0.0316	0.3156
	Placental Disorders	Matched only	0.94	[0.78, 1.14]	0.5252	0.6084
		Socioeconomic factors	0.93	[0.76, 1.13]	0.4676	0.6965
	Hemorrhage	Matched only	0.95	[0.89, 1.01]	0.1013	0.6010
		Socioeconomic factors	0.96	[0.9, 1.02]	0.1859	0.6965
	Other Maternal Morbidity	Matched only	1.03	[1.01, 1.04]	0.0042	0.0467
		Socioeconomic factors	1.03	[1.01, 1.04]	0.0050	0.0594

Comparisons of maternal outcomes in G3 grandchildren, G4 great-grandchildren and matched controls. Matching criteria included sex, birth year, birth season, maternal birth year, parity and mother's place of birth. Adjustment for parental socioeconomic factors included highest attained education level, total gross income, and marital status. Data are presented as odds ratios with 95% confidence intervals, and ORs < 1 indicate lower odds of the outcome in LEF descendants compared to general population matched controls. Basic p-values describe a two-sided Wald hypothesis test, and adjusted p-values are corrected for multiple testing using the Hommel method (n = 14 outcomes). Abbreviations: G3 (Generation 3), G4 (Generation 4), OR (odds ratio), CI (confidence interval).

Table S7. Logistic regression results for analyses comparing exposure to maternal smoking in G3 grandchildren, G4 great-grandchildren and matched controls (corresponding to **Figure 5** in article)

Generation	Outcome	Adjustment	Odds Ratio	95% CI	p
G3	Overall	Matched only	0.80	[0.69, 0.92]	0.0016
		Socioeconomic factors	0.85	[0.74, 0.98]	0.0283
	LEF Mother	Matched only	0.71	[0.56, 0.9]	0.0049
		Socioeconomic factors	0.74	[0.58, 0.94]	0.0153
	LEF Father	Matched only	0.85	[0.72, 1.02]	0.0816
		Socioeconomic factors	0.91	[0.75, 1.1]	0.3269
G4	Overall	Matched only	0.75	[0.71, 0.79]	0.0000
		Socioeconomic factors	0.85	[0.81, 0.9]	0.0000
	LEF Mother	Matched only	0.70	[0.65, 0.76]	0.0000
		Socioeconomic factors	0.82	[0.76, 0.89]	0.0000
	LEF Father	Matched only	0.79	[0.73, 0.85]	0.0000
		Socioeconomic factors	0.89	[0.82, 0.96]	0.0017

Comparisons of exposure to maternal smoking in G3 grandchildren, G4 great-grandchildren and matched controls. Matching criteria included sex, birth year, birth season, maternal birth year, parity and mother's place of birth. Adjustment for parental socioeconomic factors included highest attained education level, total gross income, and marital status. Data are presented as odds ratios with 95% confidence intervals, and ORs < 1 imply lower odds of exposure to maternal smoking in LEF descendants compared to general population matched controls. P-values describe a two-sided Wald hypothesis test, without adjustment for multiple testing. Abbreviations: G3 (Generation 3), G4 (Generation 4), OR (Odds Ratio), CI (confidence interval), LEF (Longevity-enriched Family).

Table S8. Logistic regression results for analyses comparing highest attained education level in parents of G3 grandchildren, G4 great-grandchildren and matched controls (corresponding to **Figure 6** in article)

Model	Generation	Education Level	Odds Ratio	95% CI
Multinomial	G3	Primary or Lower Secondary	1.00	[NA, NA]
		Upper Secondary	1.19	[1.07, 1.31]
		Short Cycle Tertiary	1.58	[1.35, 1.86]
		Bachelor or Equivalent	1.42	[1.27, 1.58]
		Master, Doctoral or Equivalent	1.55	[1.36, 1.77]
	G4	Primary or Lower Secondary	1.00	[NA, NA]
		Upper Secondary	1.46	[1.33, 1.59]
		Short Cycle Tertiary	1.45	[1.3, 1.62]
		Bachelor or Equivalent	1.76	[1.61, 1.92]
		Master, Doctoral or Equivalent	1.99	[1.81, 2.18]
Ordinal	G3	Odds of higher education level	1.28	[1.21, 1.36]
	G4		1.34	[1.29, 1.39]
	G3 vs G4		1.05	[0.95, 1.16]

Comparisons of highest attained education level for parents of G3 grandchildren, G4 great-grandchildren and matched controls. Matching criteria included sex, birth year, birth season, maternal birth year, parity and mother's place of birth. Data in both panels are presented as odds ratios with 95% confidence intervals, and ORs > 1 indicate higher education levels in parents of LEF descendants versus parents of general population matched controls. P-values describe a two-sided Wald hypothesis test, without adjustment for multiple testing. Abbreviations: G3 (Generation 3), G4 (Generation 4), OR (odds ratio), CI (confidence interval), LEF (Longevity-enriched Family).

Items S9-S12 assess differences in overall neonatal and maternal morbidities. We employed two definitions for composite measures of neonatal and maternal morbidity based on the individual measures of morbidity included in our study (**Figure 4** of the article). What contrasts these two sets of definitions is the exclusion or inclusion of the ‘other morbidity’ categories. This was due to the difficulty of interpreting the ‘other’ category as they included all adverse ICD codes not included in the other categories, and capture highly diverse clinical phenomena in terms of both aetiology and severity.

Neonatal morbidity definition 1: Any occurrence of preterm birth, small for gestational age, large for gestational age, low APGAR score, birth trauma, respiratory disorders, or congenital malformation. *Excluded: Other neonatal morbidity.*

Maternal morbidity definition 1: Any occurrence of assisted delivery, caesarean section, preeclampsia and eclampsia, placental disorders, or haemorrhage. *Excluded: Other maternal morbidity.*

Neonatal morbidity definition 2: Any occurrence of preterm birth, small for gestational age, large for gestational age, low APGAR score, birth trauma, respiratory disorders, congenital malformation, or other neonatal morbidity. *Excluded: none.*

Maternal morbidity definition 2: Any occurrence of assisted delivery, caesarean section, preeclampsia and eclampsia, placental disorders, haemorrhage, or other maternal morbidity. *Excluded: none.*

Interpretation: G3 and G4 grandchildren have lower risk of neonatal morbidity according to both definitions (Definition 1: $OR_{G3} = 0.89$, $OR_{G4} = 0.96$; Definition 2: $OR_{G3} = 0.89$, $OR_{G4} = 0.95$). Mothers of G3 and G4 grandchildren also have lower risk of maternal morbidity according to definition 1. However, an advantage was only observed in mothers of G3 grandchildren with definition 2 (Definition 1: $OR_{G3} = 0.90$, $OR_{G4} = 0.95$; Definition 2: $OR_{G3} = 0.95$, $OR_{G4} = 1.00$). A general pattern emerges in both analyses suggesting that maternal factors may dominate paternal factors in the transmission of advantage in maternal morbidities. However, the evidence was more mixed in neonatal morbidities, with contrasting findings in G3 grandchildren and G4 grandchildren. In the manuscript we use definition 1 as our main outcome, due to the ambiguity of the ‘other morbidity’ categories.

Figure S9. Analyses comparing composite neonatal and maternal morbidities in G3 grandchildren, G4 great-grandchildren, matched controls, and their parents (definition 1)

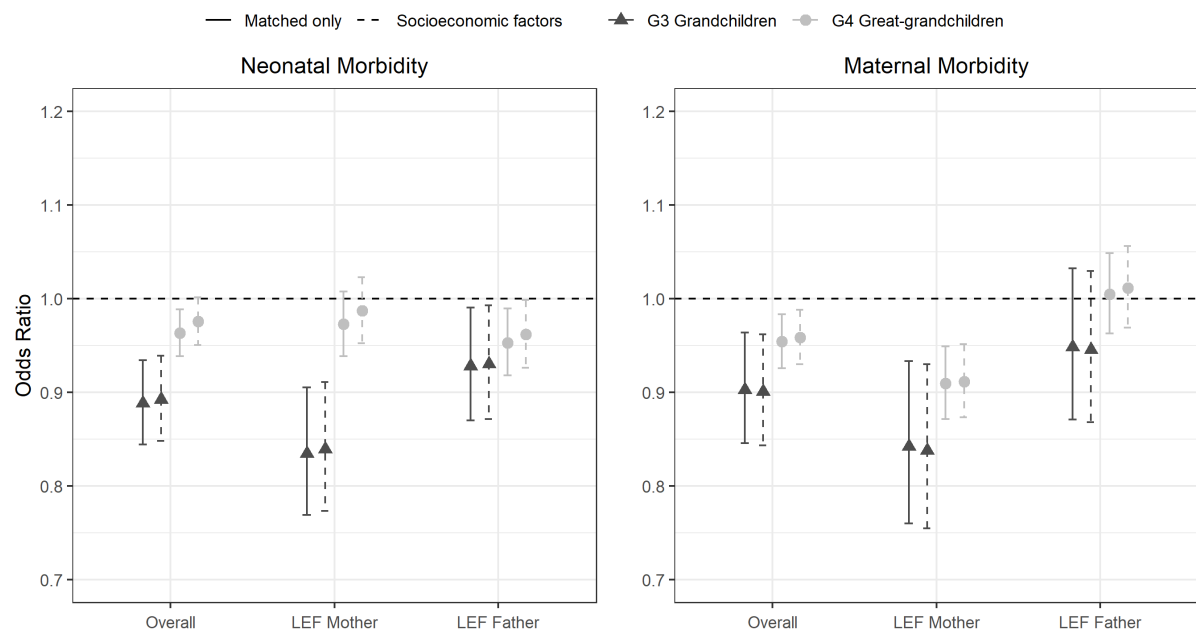
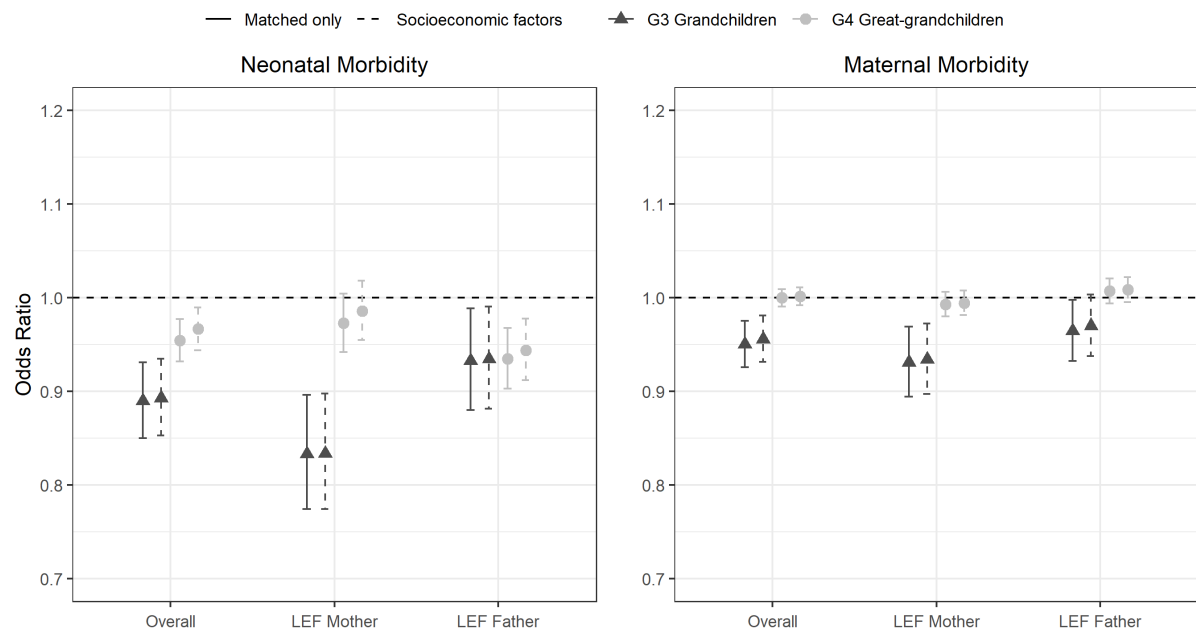


Figure S10. Analyses comparing composite neonatal and maternal morbidities in G3 grandchildren, G4 great-grandchildren, matched controls, and their parents (definition 2)



Comparisons of neonatal and maternal composite outcomes in G3 grandchildren, G4 great-grandchildren and matched controls according two definitions. Matching criteria included sex, birth year, birth season, maternal birth year, parity and mother's place of birth. Adjustment for parental socioeconomic factors included highest attained education level, total gross income, and marital status. Data are presented as odds ratios with 95% confidence intervals, and ORs < 1 indicate lower odds of the outcome in LEF descendants compared to general population matched controls. P-values describe a two-sided Wald hypothesis test, without adjustment for multiple testing. Abbreviations: G3 (Generation 3), G4 (Generation 4), OR (odds ratio), LEF (longevity-enriched family).

Table S11. Logistic regression results for analyses comparing composite neonatal and maternal morbidity in G3 grandchildren, G4 great-grandchildren, matched controls, and their parents (definition 1)

Neonatal morbidity - Outcome Definition 1					
Generation	Model	Adjustment	Odds Ratio	95% CI	p
G3	Overall	Matched only	0.89	[0.84, 0.93]	0.0000
		Socioeconomic factors	0.89	[0.85, 0.94]	0.0000
	LEF Mother	Matched only	0.83	[0.77, 0.91]	0.0000
		Socioeconomic factors	0.84	[0.77, 0.91]	0.0000
	LEF Father	Matched only	0.93	[0.87, 0.99]	0.0246
		Socioeconomic factors	0.93	[0.87, 0.99]	0.0302
	Overall	Matched only	0.96	[0.94, 0.99]	0.0044
		Socioeconomic factors	0.98	[0.95, 1]	0.0625
G4	LEF Mother	Matched only	0.97	[0.94, 1.01]	0.1271
		Socioeconomic factors	0.99	[0.95, 1.02]	0.4755
	LEF Father	Matched only	0.95	[0.92, 0.99]	0.0119
		Socioeconomic factors	0.96	[0.93, 1]	0.0429

Maternal morbidity - Outcome Definition 1					
Generation	Model	Adjustment	Odds Ratio	95% CI	p
G3	Overall	Matched only	0.90	[0.85, 0.96]	0.0022
		Socioeconomic factors	0.90	[0.84, 0.96]	0.0019
	LEF Mother	Matched only	0.84	[0.76, 0.93]	0.0010
		Socioeconomic factors	0.84	[0.75, 0.93]	0.0009
	LEF Father	Matched only	0.95	[0.87, 1.03]	0.2211
		Socioeconomic factors	0.95	[0.87, 1.03]	0.1985
	Overall	Matched only	0.95	[0.93, 0.98]	0.0024
		Socioeconomic factors	0.96	[0.93, 0.99]	0.0065
G4	LEF Mother	Matched only	0.91	[0.87, 0.95]	0.0000
		Socioeconomic factors	0.91	[0.87, 0.95]	0.0000
	LEF Father	Matched only	1.00	[0.96, 1.05]	0.8224
		Socioeconomic factors	1.01	[0.97, 1.06]	0.5993

Comparisons of neonatal and maternal composite outcomes in G3 grandchildren, G4 great-grandchildren and matched controls. Matching criteria included sex, birth year, birth season, maternal birth year, parity and mother's place of birth. Adjustment for parental socioeconomic factors included highest attained education level, total gross income, and marital status. Data are presented as odds ratios with 95% confidence intervals, and ORs < 1 indicate lower odds of the outcome in LEF descendants compared to general population matched controls. P-values describe a two-sided Wald hypothesis test, without adjustment for multiple testing. Abbreviations: G3 (Generation 3), G4 (Generation 4), OR (odds ratio), CI (confidence interval), LEF (longevity-enriched family).

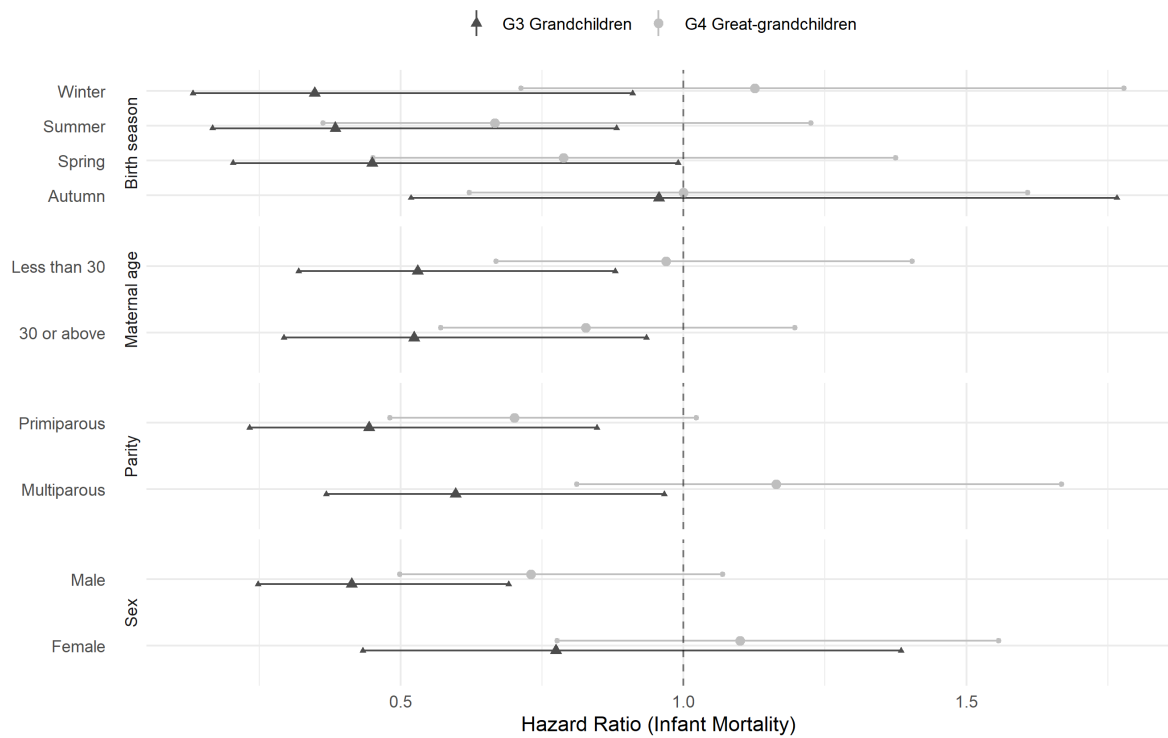
Table S12. Logistic regression results for analyses comparing composite neonatal and maternal morbidity in G3 grandchildren, G4 great-grandchildren, matched controls and their parents (definition 2)

Neonatal morbidity - Outcome Definition 2					
Generation	Model	Adjustment	Odds Ratio	95% CI	p
G3	Overall	Matched only	0.89	[0.85, 0.93]	0.0000
		Socioeconomic factors	0.89	[0.85, 0.93]	0.0000
	LEF Mother	Matched only	0.83	[0.77, 0.9]	0.0000
		Socioeconomic factors	0.83	[0.77, 0.9]	0.0000
	LEF Father	Matched only	0.93	[0.88, 0.99]	0.0187
		Socioeconomic factors	0.93	[0.88, 0.99]	0.0231
	Overall	Matched only	0.95	[0.93, 0.98]	0.0001
		Socioeconomic factors	0.97	[0.94, 0.99]	0.0048
G4	LEF Mother	Matched only	0.97	[0.94, 1]	0.0920
		Socioeconomic factors	0.99	[0.95, 1.02]	0.3920
	LEF Father	Matched only	0.93	[0.9, 0.97]	0.0001
		Socioeconomic factors	0.94	[0.91, 0.98]	0.0012

Maternal morbidity - Outcome Definition 2					
Generation	Model	Adjustment	Odds Ratio	95% CI	p
G3	Overall	Matched only	0.95	[0.93, 0.98]	0.0001
		Socioeconomic factors	0.96	[0.93, 0.98]	0.0006
	LEF Mother	Matched only	0.93	[0.89, 0.97]	0.0005
		Socioeconomic factors	0.93	[0.9, 0.97]	0.0009
	LEF Father	Matched only	0.96	[0.93, 1]	0.0375
		Socioeconomic factors	0.97	[0.94, 1]	0.0802
	Overall	Matched only	1.00	[0.99, 1.01]	0.9875
		Socioeconomic factors	1.00	[0.99, 1.01]	0.7545
G4	LEF Mother	Matched only	0.99	[0.98, 1.01]	0.3071
		Socioeconomic factors	0.99	[0.98, 1.01]	0.4210
	LEF Father	Matched only	1.01	[0.99, 1.02]	0.2818
		Socioeconomic factors	1.01	[1, 1.02]	0.2058

Comparisons of neonatal and maternal composite outcomes in G3 grandchildren, G4 great-grandchildren and matched controls. Matching criteria included sex, birth year, birth season, maternal birth year, parity and mother's place of birth. Adjustment for parental socioeconomic factors included highest attained education level, total gross income, and marital status. Data are presented as odds ratios with 95% confidence intervals, and ORs < 1 indicate lower odds of the outcome in LEF descendants compared to general population matched controls. P-values describe a two-sided Wald hypothesis test, without adjustment for multiple testing. Abbreviations: G3 (Generation 3), G4 (Generation 4), OR (odds ratio), LEF (longevity-enriched family), CI (confidence interval).

Figure S13. Post-hoc analyses of infant mortality by discrete subgroups of the matching criteria



Post-hoc comparisons of infant mortality in G3 grandchildren, G4 great-grandchildren and matched controls by discrete groupings of the matching criteria. Matching criteria included sex, birth year, birth season, maternal birth year, parity and mother's place of birth. Further adjustment for parental socioeconomic factors included highest attained education level, total gross income, and marital status. Data are presented as hazard ratios with 95% confidence intervals, and HRs < 1 indicate lower hazards of the outcome in LEF descendants compared to general population matched controls. P-values describe a two-sided Wald hypothesis test, without adjustment for multiple testing. Abbreviations: G3 (Generation 3), G4 (Generation 4), LEF (Longevity-enriched Family), HR (hazard ratio).

Table S14. Post-hoc Cox regression results for analyses of infant mortality by discrete subgroups of the matching criteria

Generation	Variable	Subgroup	HR	95% CI	p
G3	Maternal Parity	Primiparous	0.44	[0.23, 0.85]	0.0137
		Multiparous	0.60	[0.37, 0.97]	0.0356
	Maternal Age	Less than 30	0.53	[0.32, 0.88]	0.0140
		30 or above	0.52	[0.29, 0.93]	0.0285
	Sex of child	Male	0.41	[0.25, 0.69]	0.0007
		Female	0.77	[0.43, 1.38]	0.3881
	Birth season	Winter	0.35	[0.13, 0.91]	0.0313
		Spring	0.45	[0.2, 0.99]	0.0473
		Summer	0.38	[0.17, 0.88]	0.0240
		Autumn	0.96	[0.52, 1.77]	0.8870
	Maternal Parity	Primiparous	0.70	[0.48, 1.02]	0.0652
		Multiparous	1.16	[0.81, 1.67]	0.4102
G4	Maternal Age	Less than 30	0.97	[0.67, 1.4]	0.8695
		30 or above	0.83	[0.57, 1.2]	0.3142
	Sex of child	Male	0.73	[0.5, 1.07]	0.1063
		Female	1.10	[0.78, 1.56]	0.5912
	Birth season	Winter	1.13	[0.71, 1.78]	0.6105
		Spring	0.79	[0.45, 1.37]	0.4014
		Summer	0.67	[0.36, 1.23]	0.1916
		Autumn	1.00	[0.62, 1.61]	1.0000

Post-hoc comparisons of infant mortality in G3 grandchildren, G4 great-grandchildren and matched controls by discrete groupings of the matching criteria. Matching criteria included sex, birth year, birth season, maternal birth year, parity and mother's place of birth. Further adjustment for parental socioeconomic factors included highest attained education level, total gross income, and marital status. Data are presented as hazard ratios with 95% confidence intervals, and HRs < 1 indicate lower hazards of the outcome in LEF descendants compared to general population matched controls. P-values describe a two-sided Wald hypothesis test, without adjustment for multiple testing. Abbreviations: G3 (Generation 3), G4 (Generation 4), LEF (Longevity-enriched Family), HR (hazard ratio), CI (confidence interval).

Table S15. Correlation matrix plot between all the covariates employed in the main analysis of our study

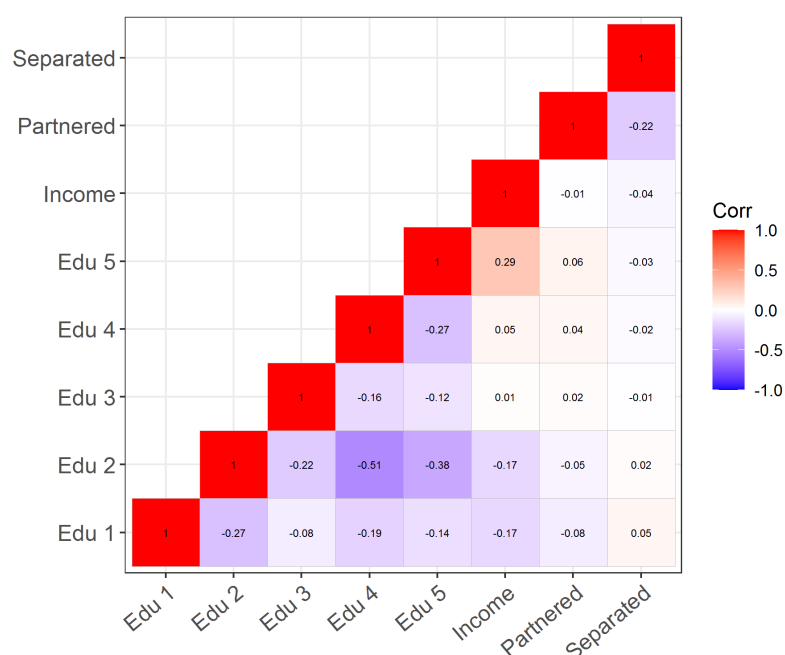


Table S16. Variance inflation factors (VIFs) for fully adjusted regression models analysing infant survival

Generation	Covariate	VIF	Df	$VIF^{1/(2 \cdot Df)}$
G3	LEF	1.07	1	1.034
	Highest education level	1.59	4	1.059
	Total gross income	1.59	1	1.260
	Marital Status	1.14	2	1.034
G4	LEF	1.07	1	1.034
	Highest education level	1.59	4	1.059
	Total gross income	1.59	1	1.260
	Marital Status	1.14	2	1.034

Interpretation: The largest correlation between the covariates employed in our main analysis was between education groups 2 and 4 ($r = -0.51$). The largest variance inflation factor in our fully adjusted models of infant survival were for highest education level and total gross income ($VIF = 1.59$), suggesting a very low risk of model instability due to multicollinearity.

Table S17. Cox regression results for analyses of infant mortality demonstrating the effect of individually adjusting for the covariates employed in our main analyses

Generation	Adjustment	HR	95% CI	p
G3	Matched only	0.53	[0.36, 0.77]	0.0010
	Parental education	0.55	[0.37, 0.81]	0.0027
	Parental income	0.54	[0.37, 0.8]	0.0022
	Parental marital status	0.53	[0.36, 0.78]	0.0014
	All socioeconomic factors	0.55	[0.36, 0.82]	0.0033
G4	Matched only	0.90	[0.69, 1.16]	0.4073
	Parental education	0.94	[0.72, 1.22]	0.6265
	Parental income	0.92	[0.71, 1.2]	0.5505
	Parental marital status	0.92	[0.71, 1.2]	0.5468
	All socioeconomic factors	0.97	[0.74, 1.27]	0.8355

Comparisons of infant mortality in G3 grandchildren, G4 great-grandchildren and matched controls by adjustment for individual covariates. Matching criteria included sex, birth year, birth season, maternal birth year, parity and mother's place of birth. Data are presented as hazard ratios with 95% confidence intervals, and HRs < 1 indicate lower hazards of the outcome in LEF descendants compared to general population matched controls. P-values describe a two-sided Wald hypothesis test, without adjustment for multiple testing. Abbreviations: G3 (Generation 3), G4 (Generation 4), LEF (Longevity-enriched Family), HR (hazard ratio), CI (confidence interval).

Items S18-S20 describe the results of analyses adjusting for a range of additional socioeconomic factors that were not included in our main analyses due to a lower quality of their measurement or underlying data. These additional covariates are described below.

First, we included occupation of their parents based on DISCO-88 and DISCO-08 codes – the Danish version of the International Standard Classification of Occupations. However, occupation data was only available in our study since 1993 in the register for work classification (Arbejdsklassifikationmodulet). There is also no ordinal ranking of the occupations in these classification schemes. For these reasons, we defined individual occupation as the most frequently observed occupation after age 30 for each parent. However, combining both maternal and paternal data where available would result in a categorical variable too large to use in our models without creating considerable model instability, when used in combination with the other covariates included in our study. Therefore, we defined a socioeconomically informative summary measure of occupation that considers both maternal and paternal data by creating a binary variable that is equal to 1 if at least one parent is in skilled work (Managerial Work, High Skilled Work, or Intermediate Skilled Work), and 0 otherwise. However, we used more granular subgroups in our sensitivity analyses that considered maternal and paternal derived covariates individually, rather than their combined impact (Table S3.10 of the Supplementary Appendix).

Second, we included a measure of urban density at the level of individual municipalities in Denmark. This data was derived from a EU wide project conducted in 2007. We then linked this data with the municipality of birth for the participants of our study. The main limitation to this data is it represents a static representation of urban density in 2007, whereas the participants of our study were born between a wider range including 1973 – 2018. Therefore, although this variable is still informative, it may not perfectly capture urban density in all settings. The variable we created based on this data stratified population density according to 6 levels: 1. Sparsely populated area with small city, 2. Sparsely populated area with medium or average city, 3. Medium populated area with small city, 4. Medium populated area with average city, 5. Medium populated area with large city, 6. Densely populated area with large city.

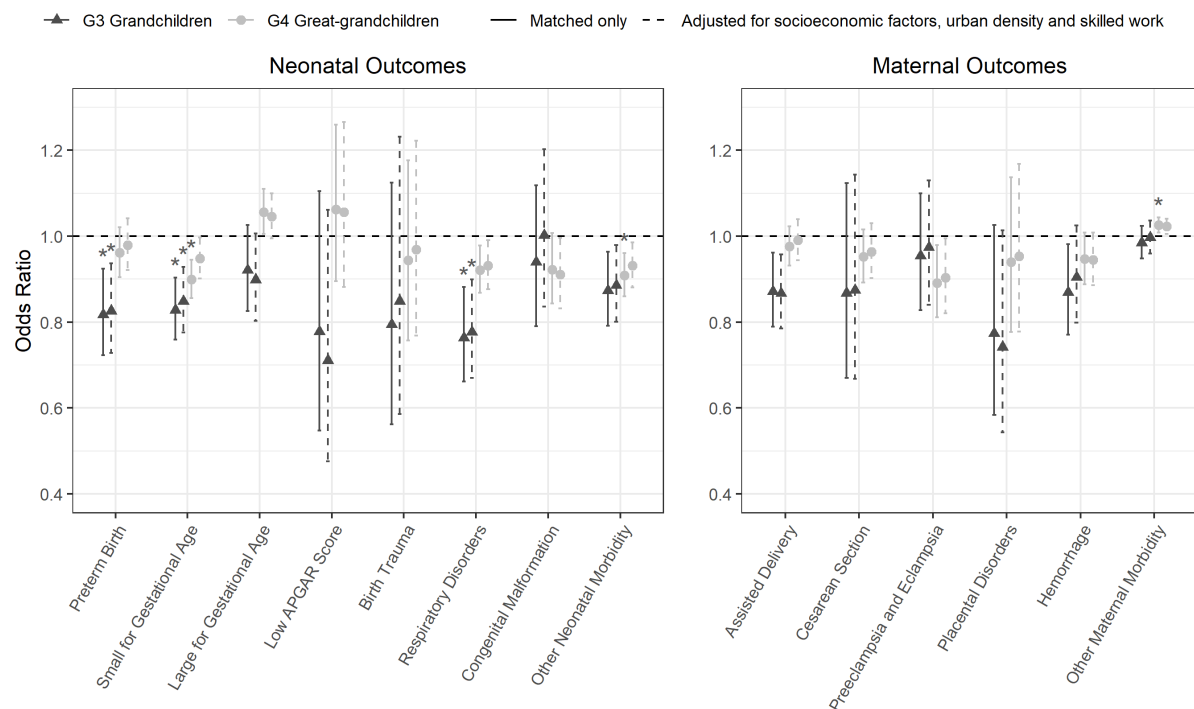
Interpretation: Our results were robust to further adjustment for further adjustment for additional socioeconomic factors, suggesting a limited role of these factors in the mechanisms underlying the exceptional infant phenotype. For example, our G3 infant survival analyses controlling for education, income and marital status as in the main paper provide a hazard ratio of 0.55. After adjusting for skilled work and urban density, this was largely unchanged at 0.59. For G4, their association changed from 0.97 to 0.94. Similar results were found when considering the analyses of individual neonatal and maternal morbidities.

Table S18. Cox regression results for analyses of infant mortality with an expanded set of socioeconomic covariates, including urban density and parental occupation

Generation	Adjustment	HR	95% CI	p
G3	Socioeconomic factors, baseline	0.55	[0.36, 0.82]	0.0033
	Socioeconomic factors and urban density	0.56	[0.37, 0.85]	0.0069
	Socioeconomic factors and skilled work	0.56	[0.37, 0.86]	0.0074
	Socioeconomic factors, urban density and skilled work	0.59	[0.39, 0.9]	0.0148
G4	Socioeconomic factors, baseline	0.97	[0.74, 1.27]	0.8355
	Socioeconomic factors and urban density	0.95	[0.72, 1.25]	0.7105
	Socioeconomic factors and skilled work	0.96	[0.73, 1.26]	0.7514
	Socioeconomic factors, urban density and skilled work	0.94	[0.72, 1.25]	0.6873

Comparisons of infant mortality in G3 grandchildren, G4 great-grandchildren and matched controls by level of adjustment including additional covariates. Matching criteria included sex, birth year, birth season, maternal birth year, parity and mother's place of birth. Data are presented as hazard ratios with 95% confidence intervals, and HRs < 1 indicate lower hazards of the outcome in LEF descendants compared to general population matched controls. P-values describe a two-sided Wald hypothesis test, without adjustment for multiple testing. Abbreviations: G3 (Generation 3), G4 (Generation 4), LEF (Longevity-enriched Family), HR (hazard ratio), CI (confidence interval).

Figure S19. Analyses of neonatal and maternal morbidity with an expanded set of socioeconomic covariates, including urban density and parental occupation



Comparisons of neonatal and maternal outcomes in G3 grandchildren, G4 great-grandchildren and matched controls. Matching criteria included sex, birth year, birth season, maternal birth year, parity and mother's place of birth. Adjustment for parental socioeconomic factors included highest attained education level, total gross income, marital status, urban density and skilled work. Data are presented as odds ratios with 95% confidence intervals, and ORs < 1 indicate lower odds of the outcome in LEF descendants compared to general population matched controls. Asterisk (*) indicates statistical significance at the 5% level in a two-sided hypothesis test after correction for multiple testing using the Hommel method (n = 14 outcomes). Abbreviations: G3 (Generation 3), G4 (Generation 4), OR (odds ratio).

Table S20. Logistic regression results for analyses of neonatal and maternal morbidities with an expanded set of socioeconomic covariates, including urban density and parental occupation

Generation	Neonatal Outcome	Adjustment	OR	95% CI	p	Padjusted
G3	Preterm Birth	Matched only	0.82	[0.72, 0.92]	0.0013	0.0157
		Socioeconomics, urban & skilled work	0.83	[0.73, 0.94]	0.0029	0.0323
	Small for Gestational Age	Matched only	0.83	[0.76, 0.9]	0.0000	0.0003
		Socioeconomics, urban & skilled work	0.85	[0.78, 0.93]	0.0004	0.0050
	Large for Gestational Age	Matched only	0.92	[0.83, 1.03]	0.1359	0.5183
		Socioeconomics, urban & skilled work	0.90	[0.8, 1.01]	0.0632	0.4011
	Low APGAR Score	Matched only	0.78	[0.55, 1.11]	0.1609	0.5183
		Socioeconomics, urban & skilled work	0.71	[0.48, 1.06]	0.0954	0.5724
	Birth Trauma	Matched only	0.79	[0.56, 1.12]	0.1945	0.5183
		Socioeconomics, urban & skilled work	0.85	[0.59, 1.23]	0.3885	0.9782
	Respiratory Disorders	Matched only	0.76	[0.66, 0.88]	0.0002	0.0030
		Socioeconomics, urban & skilled work	0.78	[0.67, 0.9]	0.0008	0.0098
	Congenital Malformation	Matched only	0.94	[0.79, 1.12]	0.4863	0.5183
		Socioeconomics, urban & skilled work	1.00	[0.84, 1.2]	0.9782	0.9782
	Other Neonatal Morbidity	Matched only	0.87	[0.79, 0.96]	0.0071	0.0714
		Socioeconomics, urban & skilled work	0.89	[0.8, 0.98]	0.0177	0.1772
G4	Preterm Birth	Matched only	0.96	[0.9, 1.02]	0.1990	0.6084
		Socioeconomics, urban & skilled work	0.98	[0.92, 1.04]	0.5054	0.7892
	Small for Gestational Age	Matched only	0.90	[0.86, 0.94]	0.0000	0.0004
		Socioeconomics, urban & skilled work	0.95	[0.9, 1]	0.0379	0.3030
	Large for Gestational Age	Matched only	1.06	[1.01, 1.11]	0.0305	0.2731
		Socioeconomics, urban & skilled work	1.05	[0.99, 1.1]	0.0807	0.5648
	Low APGAR Score	Matched only	1.06	[0.9, 1.26]	0.4899	0.6084
		Socioeconomics, urban & skilled work	1.06	[0.88, 1.27]	0.5506	0.7892
	Birth Trauma	Matched only	0.94	[0.76, 1.18]	0.6084	0.6084
		Socioeconomics, urban & skilled work	0.97	[0.77, 1.22]	0.7892	0.7892
	Respiratory Disorders	Matched only	0.92	[0.87, 0.98]	0.0071	0.0785
		Socioeconomics, urban & skilled work	0.93	[0.88, 0.99]	0.0243	0.2188
	Congenital Malformation	Matched only	0.92	[0.84, 1.01]	0.0709	0.4643
		Socioeconomics, urban & skilled work	0.91	[0.83, 1]	0.0414	0.3311
	Other Neonatal Morbidity	Matched only	0.91	[0.86, 0.96]	0.0007	0.0088
		Socioeconomics, urban & skilled work	0.93	[0.88, 0.99]	0.0137	0.1506

Generation	Maternal Outcome	Adjustment	OR	95% CI	p	p _{adjusted}
G3	Assisted Delivery	Matched only	0.87	[0.79, 0.96]	0.0060	0.0604
		Socioeconomics, urban & skilled work	0.87	[0.78, 0.96]	0.0050	0.0548
	Cesarean Section	Matched only	0.87	[0.67, 1.12]	0.2822	0.5183
		Socioeconomics, urban & skilled work	0.87	[0.67, 1.14]	0.3267	0.9782
	Preeclampsia and Eclampsia	Matched only	0.95	[0.83, 1.1]	0.5183	0.5183
		Socioeconomics, urban & skilled work	0.97	[0.84, 1.13]	0.7298	0.9782
	Placental Disorders	Matched only	0.77	[0.58, 1.03]	0.0746	0.4539
		Socioeconomics, urban & skilled work	0.74	[0.54, 1.01]	0.0612	0.4011
	Hemorrhage	Matched only	0.87	[0.77, 0.98]	0.0230	0.2073
		Socioeconomics, urban & skilled work	0.90	[0.8, 1.02]	0.1146	0.6876
	Other Maternal Morbidity	Matched only	0.99	[0.95, 1.02]	0.4421	0.5183
		Socioeconomics, urban & skilled work	1.00	[0.96, 1.04]	0.8937	0.9782
G4	Assisted Delivery	Matched only	0.98	[0.93, 1.02]	0.3168	0.6084
		Socioeconomics, urban & skilled work	0.99	[0.94, 1.04]	0.7082	0.7892
	Cesarean Section	Matched only	0.95	[0.89, 1.02]	0.1361	0.6084
		Socioeconomics, urban & skilled work	0.96	[0.9, 1.03]	0.2777	0.7892
	Preeclampsia and Eclampsia	Matched only	0.89	[0.81, 0.98]	0.0172	0.1546
		Socioeconomics, urban & skilled work	0.90	[0.82, 0.99]	0.0385	0.3083
	Placental Disorders	Matched only	0.94	[0.78, 1.14]	0.5252	0.6084
		Socioeconomics, urban & skilled work	0.95	[0.78, 1.17]	0.6451	0.7892
	Hemorrhage	Matched only	0.95	[0.89, 1.01]	0.0910	0.5462
		Socioeconomics, urban & skilled work	0.95	[0.89, 1.01]	0.0899	0.6291
	Other Maternal Morbidity	Matched only	1.03	[1.01, 1.04]	0.0034	0.0408
		Socioeconomics, urban & skilled work	1.02	[1.01, 1.04]	0.0109	0.1241

Comparisons of neonatal and maternal outcomes in G3 grandchildren, G4 great-grandchildren and matched controls. Matching criteria included sex, birth year, birth season, maternal birth year, parity and mother's place of birth. Adjustment for parental socioeconomic factors included highest attained education level, total gross income, marital status, urban density and skilled work. Data are presented as odds ratios with 95% confidence intervals, and ORs < 1 indicate lower odds of the outcome in LEF descendants compared to general population matched controls. Basic p-values describe a two-sided Wald hypothesis test, and adjusted p-values are corrected for multiple testing using the Hommel method (n = 14 outcomes). Abbreviations: G3 (Generation 3), G4 (Generation 4), OR (odds ratio), CI (confidence interval).

Table S21. Absolute risk differences between G3 and G4 descendants of longevity-enriched sibships and matched controls across outcomes measuring neonatal and maternal morbidities, composites of morbidity, and maternal smoking

Generation	Neonatal Outcomes	Risk Difference	95% CI	p
G3	Preterm Birth	-1.81	[-2.9, -0.70]	0.0014
	Small for Gestational Age	-2.51	[-3.95, -1.09]	0.0006
	Large for Gestational Age	-0.57	[-1.77, 0.64]	0.3561
	Low APGAR Score	-0.24	[-0.6, 0.12]	0.1912
	Birth Trauma	-0.19	[-0.53, 0.14]	0.2542
	Respiratory Disorders	-1.34	[-2.15, -0.53]	0.0012
	Congenital Malformation	-0.20	[-0.85, 0.45]	0.5489
	Other Neonatal Morbidity	-1.36	[-2.48, -0.25]	0.0167
G4	Preterm Birth	-0.38	[-0.92, 0.16]	0.1689
	Small for Gestational Age	-1.17	[-1.81, -0.54]	0.0003
	Large for Gestational Age	0.60	[-0.03, 1.23]	0.0638
	Low APGAR Score	0.07	[-0.12, 0.25]	0.4930
	Birth Trauma	-0.03	[-0.18, 0.11]	0.6493
	Respiratory Disorders	-0.61	[-1.12, -0.09]	0.0206
	Congenital Malformation	-0.28	[-0.64, 0.08]	0.1253
	Other Neonatal Morbidity	-0.82	[-1.38, -0.26]	0.0042

Generation	Maternal Outcomes	Risk Difference	95% CI	p
G3	Assisted Delivery	-1.34	[-2.43, -0.25]	0.0163
	Cesarean Seciton	-0.25	[-0.74, 0.25]	0.3220
	Preeclampsia and Eclampsia	-0.19	[-1.01, 0.63]	0.6470
	Placental Disorders	-0.34	[-0.75, 0.07]	0.1035
	Hemorrhage	-0.96	[-1.88, -0.03]	0.0421
	Other Maternal Morbidity	-0.67	[-2.52, 1.19]	0.4810
G4	Assisted Delivery	-0.25	[-0.87, 0.37]	0.4323
	Cesarean Seciton	-0.36	[-0.86, 0.15]	0.1714
	Preeclampsia and Eclampsia	-0.36	[-0.71, -0.01]	0.0428
	Placental Disorders	-0.05	[-0.22, 0.12]	0.5901
	Hemorrhage	-0.36	[-0.86, 0.14]	0.1543
	Other Maternal Morbidity	1.16	[0.18, 2.14]	0.0206

Generation	Other Outcomes	Risk Difference	95% CI	p
G3	Any Neonatal Morbidity	-2.38	[-3.72, -1.04]	0.0005
	Any Maternal Morbidity	-1.48	[-2.63, -0.34]	0.0112
	Maternal Smoking	-4.24	[-7.66, -0.82]	0.0150
G4	Any Neonatal Morbidity	-1.07	[-2.00, -0.14]	0.0238
	Any Maternal Morbidity	-1.19	[-2.05, -0.33]	0.0067
	Maternal Smoking	-4.20	[-4.95, -3.45]	0.0000

Comparisons of neonatal and maternal outcomes in G3 grandchildren, G4 great-grandchildren and matched controls. Matching criteria included sex, birth year, birth season, maternal birth year, parity and mother's place of birth. Adjustment for parental socioeconomic factors included highest attained education level, total gross income, marital status, urban density and skilled work. Data are presented as absolute risk differences with 95% confidence intervals, and ORs < 1 indicate lower odds of the outcome in LEF descendants compared to general population matched controls. P-values describe a two-sided delta-method Wald hypothesis test, without further adjustment for multiple testing. Abbreviations: G3 (Generation 3), G4 (Generation 4), OR (odds ratio), CI (confidence interval).

3. Sensitivity and Robustness Analyses

Items S22 and S23 describe sensitivity analyses we undertook to assess the robustness of our ‘overlapping generations’ analyses, where we compared G3 grandchildren to G4 great-grandchildren directly within their overlapping birth cohort periods. The analyses below introduce controls into the mix and use them in specific analyses as negative controls. In all these analyses, the full matching criteria was used as adjustment covariates. Below we provide the rationale for each analysis and our interpretation:

LEF-G3 vs LEF G4: This analysis is what was presented in the main paper.

LEF-G3 vs Control-G4: Since we see no difference in infant mortality between G4 great-grandchildren and their controls (See **Figure 3**), we hypothesised that comparing G3 grandchildren to the matched controls of the G4 great-grandchildren in the same overlapping period analysis, we would observe the same estimate as when comparing to the G4 great-grandchildren directly. This hypothesis was confirmed (LEF-G3 vs LEF G4 HR = 0.32, LEF-G3 vs Control-G4 HR = 0.33).

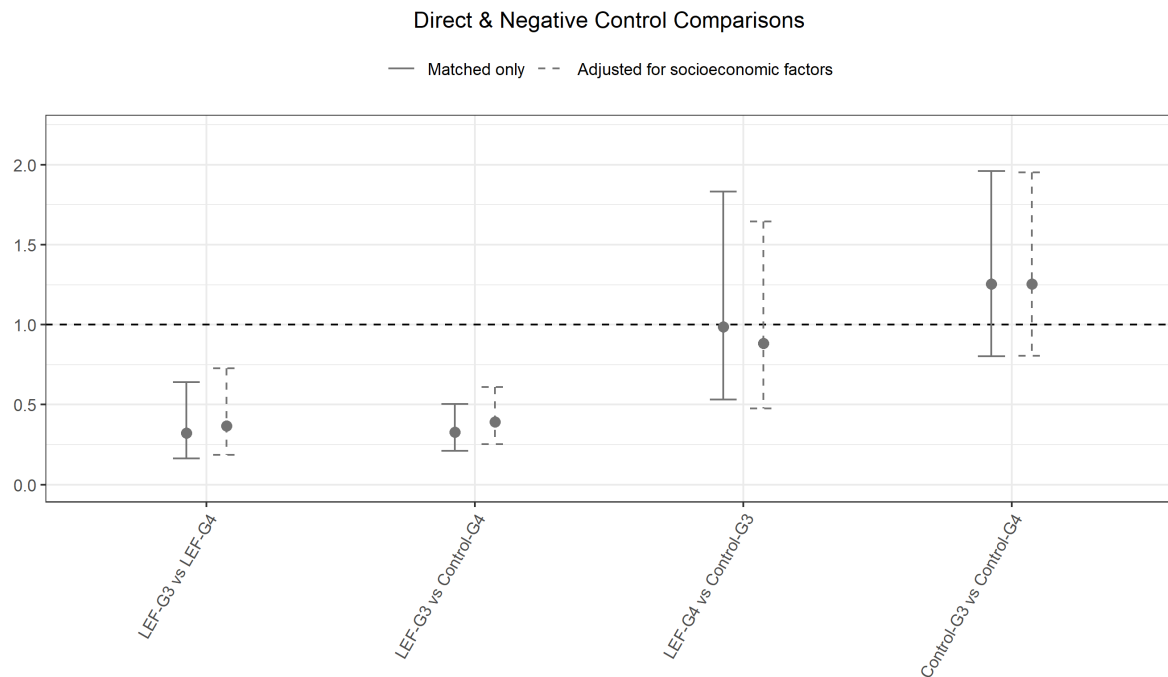
LEF-G4 vs Control-G3: Similarly, since G4 great-grandchildren exhibit no advantage compared to the general population, we would expect to observe no advantage when comparing them in the overlapping generation analysis to the matched controls of G3 grandchildren. This hypothesis was confirmed (LEF-G4 vs Control G3 HR = 0.99).

Control-G3 vs Control-G4: The above analyses establish that the selected controls behave in such a way to imply that direct comparisons between G3 grandchildren and G4 great-grandchildren would be unbiased. Similarly, the findings also imply that if we compared matched controls of G3 grandchildren to matched controls of G4 great-grandchildren, we would observe no mortality differences. This hypothesis was again validated (Control-G3 vs Control-G4 HR = 1.21).

If the trend for increased mortality in G3 controls vs G4 controls 3 is to be interpreted literally despite large confidence intervals, this would imply that our analyses are biased towards generation 4 having a survival advantage. This in turn would suggest that our estimates showing a survival advantage in G3 compared to G4 may be conservative. However, we do not think this is likely, given the results of the other negative control analyses. Nonetheless, this possibility does conserve our interpretation of a strong dilution of the survival advantage between generations G3 and G4 in longevity-enriched families.

Overall, these findings suggest that our direct comparison analyses in the main article are capable of accurately inferring patterns in intergenerational transmission of infant survival advantages, independent of both secular trends in the background population, and methodological and statistical considerations.

Figure S22. Negative control analyses using overlapping generations and matched controls



Comparisons of infant mortality in G3 grandchildren, G4 great-grandchildren and matched controls in overlapping birth cohorts (approx. 1973 to 2010). Baseline adjustment criteria included sex, birth year, birth season, maternal birth year, parity and mother's place of birth. Further adjustment for parental socioeconomic factors included highest attained education level, total gross income, and marital status. Data are presented as hazard ratios with 95% confidence intervals, and HRs < 1 indicate lower hazards of the outcome in group X in a X vs Y comparison. Abbreviations: G3 (Generation 3), G4 (Generation 4), LEF (Longevity-enriched Family), HR (hazard ratio), CI (confidence interval).

Table S23. Cox regression results for negative control analyses using overlapping generations and matched controls

Model	Adjustment	HR	95% CI	p
LEF-G3 vs LEF-G4	Matched only	0.32	[0.16, 0.64]	0.0012
LEF-G3 vs LEF-G4	Socioeconomic factors	0.37	[0.19, 0.73]	0.0041
LEF-G3 vs Control-G4	Matched only	0.33	[0.21, 0.5]	0.0000
LEF-G3 vs Control-G4	Socioeconomic factors	0.39	[0.25, 0.61]	0.0000
LEF-G4 vs Control-G3	Matched only	0.99	[0.53, 1.83]	0.9666
LEF-G4 vs Control-G3	Socioeconomic factors	0.88	[0.47, 1.64]	0.6955
Control-G3 vs Control-G4	Matched only	1.25	[0.8, 1.96]	0.3192
Control-G3 vs Control-G4	Socioeconomic factors	1.25	[0.8, 1.95]	0.3181

Comparisons of infant mortality in G3 grandchildren, G4 great-grandchildren and matched controls in overlapping birth cohorts (approx. 1973 to 2010). Baseline adjustment criteria included sex, birth year, birth season, maternal birth year, parity and mother's place of birth. Further adjustment for parental socioeconomic factors included highest attained education level, total gross income, and marital status. Data are presented as hazard ratios with 95% confidence intervals, and HRs < 1 indicate lower hazards of the outcome in the first listed group. P-values describe a two-sided Wald hypothesis test, without adjustment for multiple testing. Abbreviations: G3 (Generation 3), G4 (Generation 4), LEF (Longevity-enriched Family), HR (hazard ratio), CI (confidence interval).

Table S24. Logistic regression results for analyses of congenital malformations with varying windows of opportunity for the diagnosis

Generation	Time Window	Adjustment	Odds Ratio	95% CI	p
G3	< 28 days	Matched only	0.93	[0.79, 1.11]	0.4460
		Socioeconomic factors	0.94	[0.78, 1.12]	0.4691
	< 60 days	Matched only	0.98	[0.84, 1.16]	0.8355
		Socioeconomic factors	0.99	[0.83, 1.16]	0.8648
	< 90 days	Matched only	1.00	[0.85, 1.17]	0.9838
		Socioeconomic factors	1.00	[0.85, 1.18]	0.9738
	< 365 days	Matched only	0.98	[0.85, 1.14]	0.8099
		Socioeconomic factors	0.99	[0.85, 1.15]	0.9110
	< 730 days	Matched only	0.97	[0.85, 1.12]	0.7037
		Socioeconomic factors	0.99	[0.86, 1.14]	0.8559
G4	> 730 days	Matched only	0.97	[0.87, 1.08]	0.5587
		Socioeconomic factors	0.99	[0.88, 1.1]	0.8244
	< 28 days	Matched only	0.92	[0.84, 1.01]	0.0730
		Socioeconomic factors	0.94	[0.86, 1.02]	0.1506
	< 60 days	Matched only	0.93	[0.86, 1.01]	0.1007
		Socioeconomic factors	0.95	[0.87, 1.03]	0.1847
	< 90 days	Matched only	0.93	[0.86, 1.01]	0.0700
		Socioeconomic factors	0.94	[0.87, 1.02]	0.1211
	< 365 days	Matched only	0.95	[0.89, 1.01]	0.1174
		Socioeconomic factors	0.96	[0.9, 1.02]	0.1939
	< 730 days	Matched only	0.97	[0.91, 1.03]	0.2514
		Socioeconomic factors	0.98	[0.92, 1.04]	0.4408
	> 730 days	Matched only	1.00	[0.95, 1.05]	0.9107
		Socioeconomic factors	1.01	[0.96, 1.06]	0.6058

Comparisons of congenital malformation risk in G3 grandchildren, G4 great-grandchildren and matched controls by opportunity-window definition. Matching criteria included sex, birth year, birth season, maternal birth year, parity and mother's place of birth. Adjustment for parental socioeconomic factors included highest attained education level, total gross income, and marital status. Adjustment for parental socioeconomic factors included highest attained education level, total gross income, and marital status. Data are presented as odds ratios with 95% confidence intervals, and ORs < 1 indicate lower odds of the outcome in LEF descendants compared to general population matched controls. Basic p-values describe a two-sided Wald hypothesis test, without adjustment for multiple testing. Abbreviations: G3 (Generation 3), G4 (Generation 4), OR (odds ratio), CI (confidence interval).

Interpretation: No differences were observed across any of the diagnostic windows for assessing congenital malformations. Descendants of longevity-enriched sibships do not exhibit a lower risk of congenital malformations, at least in generations 3 and 4.

Table S25. Cox regression results for analyses of infant mortality when adjusting for paternal immigration status and age at birth

Generation	Adjustment	HR	95% CI	p
G3	Matched only	0.61	[0.41, 0.91]	0.0147
	Socioeconomics	0.64	[0.42, 0.97]	0.0350
	Socioeconomics, Paternal Age	0.63	[0.41, 0.97]	0.0345
	Socioeconomics, Danish Father	0.62	[0.4, 0.96]	0.0328
	Socioeconomics, Paternal Age, Danish Father	0.61	[0.39, 0.96]	0.0319
G4	Matched only	0.95	[0.73, 1.24]	0.7129
	Socioeconomics	1.01	[0.77, 1.32]	0.9525
	Socioeconomics, Paternal Age	1.01	[0.77, 1.33]	0.9319
	Socioeconomics, Danish Father	1.00	[0.76, 1.3]	0.9714
	Socioeconomics, Paternal Age, Danish Father	1.00	[0.76, 1.31]	0.9867

Comparisons of infant mortality in G3 grandchildren, G4 great-grandchildren and matched controls by adjustment for paternal covariates. Matching criteria included sex, birth year, birth season, maternal birth year, parity and mother's place of birth. Data are presented as hazard ratios with 95% confidence intervals, and HRs < 1 indicate lower hazards of the outcome in LEF descendants compared to general population matched controls. P-values describe a two-sided Wald hypothesis test, without adjustment for multiple testing. Abbreviations: G3 (Generation 3), G4 (Generation 4), LEF (Longevity-enriched Family), HR (hazard ratio), CI (confidence interval).

Interpretation: Note that the matched only estimate (HR = 0.61) is slightly different to the baseline estimate provided in the main study (HR = 0.53). This is because the above analyses only include children whose father's place of birth and age at conception is known. Overall, we observe that there were no differences in any of the estimates after adjusting for paternal age, paternal place of birth, or both.

Table S26. Logistic regression results for analyses assessing alternative outcomes using weight at birth

Generation	Outcome	Adjustment	Coefficient	95% CI	pval
G3	SGA	Matched only	0.83	[0.76, 0.9]	0.0000
		Socioeconomic factors	0.85	[0.78, 0.93]	0.0003
	vSGA	Matched only	0.80	[0.7, 0.9]	0.0002
		Socioeconomic factors	0.84	[0.74, 0.95]	0.0050
	eSGA	Matched only	0.66	[0.53, 0.83]	0.0003
		Socioeconomic factors	0.71	[0.57, 0.89]	0.0035
	LBW	Matched only	0.83	[0.76, 0.9]	0.0000
		Socioeconomic factors	0.85	[0.78, 0.92]	0.0001
	vLBW	Matched only	0.82	[0.63, 1.06]	0.1352
		Socioeconomic factors	0.88	[0.66, 1.16]	0.3604
G4	eLBW	Matched only	0.86	[0.54, 1.36]	0.5151
		Socioeconomic factors	1.09	[0.65, 1.83]	0.7399
	SGA	Matched only	0.90	[0.85, 0.94]	0.0000
		Socioeconomic factors	0.93	[0.89, 0.98]	0.0058
	vSGA	Matched only	0.87	[0.81, 0.93]	0.0001
		Socioeconomic factors	0.91	[0.85, 0.97]	0.0067
	eSGA	Matched only	0.85	[0.75, 0.96]	0.0114
		Socioeconomic factors	0.89	[0.78, 1.01]	0.0699
	LBW	Matched only	0.90	[0.83, 0.97]	0.0078
		Socioeconomic factors	0.93	[0.86, 1.01]	0.0824
	vLBW	Matched only	0.82	[0.63, 1.06]	0.1352
		Socioeconomic factors	1.15	[0.95, 1.39]	0.1556
	eLBW	Matched only	1.03	[0.76, 1.41]	0.8328
		Socioeconomic factors	1.05	[0.76, 1.44]	0.7813

Comparisons of congenital malformation risk in G3 grandchildren, G4 great-grandchildren and matched controls by opportunity-window definition. Matching criteria included sex, birth year, birth season, maternal birth year, parity and mother's place of birth. Adjustment for parental socioeconomic factors included highest attained education level, total gross income, and marital status. Adjustment for parental socioeconomic factors included highest attained education level, total gross income, and marital status. Data are presented as odds ratios with 95% confidence intervals, and ORs < 1 indicate lower odds of the outcome in LEF descendants compared to general population matched controls. Basic p-values describe a two-sided Wald hypothesis test, without adjustment for multiple testing. Abbreviations: G3 (Generation 3), G4 (Generation 4), OR (odds ratio), CI (confidence interval), SGA (small for gestational age), vSGA (very small for gestational age), eSGA (extremely small for gestational age), LBW (low birth weight), vLBW (very low birth weight), eLBW (extremely low birth weight).

SGA: Less than -1.282 SDs below the expected intrauterine weight for gestational age (10th percentile)

vSGA: Less than -1.645 SDs below the expected intrauterine weight for gestational age (5th percentile)

eSGA: Less than -2.326 SDs below the expected intrauterine weight for gestational age (1st percentile)

LBW: Less than 2500g at birth

vLBW: Less than 1500g at birth

eLBW: Less than 1000g at birth

Interpretation: Degree of advantage increased in both grandchildren and great-grandchildren when decreasing the percentile for intrauterine weights. For example, G3 grandchildren were 34% less likely to be extremely small for gestational age compared to controls, compared to 17% less likely for just being small for gestational age.

Table S27. Regression results for analyses of key neonatal indicators as continuous rather than dichotomized outcomes

Generation	Outcome	Adjustment	Beta	95% CI	pval
G3	APGAR Score	Matched only	0.0281782	[0, 0.06]	0.0523
		Socioeconomic factors	0.0231367	[-0.01, 0.05]	0.1099
	Birth Weight	Matched only	44.80734	[25.33, 64.29]	0.0000
		Socioeconomic factors	38.481118	[19, 57.96]	0.0001
	Gestational Age	Matched only	1.0636207	[0.52, 1.61]	0.0001
		Socioeconomic factors	0.9746737	[0.43, 1.52]	0.0005
G4	APGAR Score	Matched only	-0.011083	[-0.03, 0]	0.1370
		Socioeconomic factors	-0.0142523	[-0.03, 0]	0.0568
	Birth Weight	Matched only	32.326314	[20.51, 44.14]	0.0000
		Socioeconomic factors	23.500446	[11.7, 35.3]	0.0001
	Gestational Age	Matched only	0.5010705	[0.22, 0.78]	0.0004
		Socioeconomic factors	0.3826203	[0.11, 0.66]	0.0068

Comparisons of continuous neonatal outcomes in G3 grandchildren, G4 great-grandchildren and matched controls. Matching criteria included sex, birth year, birth season, maternal birth year, parity and mother's place of birth. Adjustment for parental socioeconomic factors included highest attained education level, total gross income, and marital status. Data are presented as regression coefficients from linear regression with 95% confidence intervals, and Beta > 0 indicate increased mean value of the outcome in LEF descendants compared to general population matched controls. P-values describe two-sided t-tests, without adjustment for multiple testing. Abbreviations: G3 (Generation 3), G4 (Generation 4), OR (odds ratio), CI (confidence interval).

APGAR Score: Measured on a scale of 0-10

Birth Weight: Measured in grams

Gestational Age: measured in weeks

Interpretation: All estimates are supportive of findings presented in the main article.

Table S28. Cox regression analyses for analyses of infant mortality including weakly matched sets who were previously unable to be matched according to the full matching criteria

Cohort	Generation	Adjustment	HR	95% CI	p
Main Cohort	G3	Matched only	0.53	[0.36, 0.77]	0.0010
		Parental education	0.55	[0.38, 0.8]	0.0019
	G4	Matched only	0.90	[0.7, 1.17]	0.4329
		Parental education	0.94	[0.73, 1.23]	0.6658
Fully Matched	G3	Matched only	0.55	[0.38, 0.8]	0.0014
		Parental education	0.58	[0.4, 0.83]	0.0031
	G4	Matched only	0.89	[0.69, 1.15]	0.3882
		Parental education	0.94	[0.73, 1.21]	0.6303

Comparisons of infant mortality in G3 grandchildren, G4 great-grandchildren and matched controls with additional matched sets. Matching criteria included sex, birth year, birth season, maternal birth year, parity and mother's place of birth for the main cohort, and sex, birth year and maternal birth year for the new matches. Data are presented as hazard ratios with 95% confidence intervals, and HRs < 1 indicate lower hazards of the outcome in LEF descendants compared to general population matched controls. P-values describe a two-sided Wald hypothesis test, without adjustment for multiple testing. Abbreviations: G3 (Generation 3), G4 (Generation 4), LEF (Longevity-enriched Family), HR (hazard ratio), CI (confidence interval).

Interpretation: Of the 141 unable to matched initially, we were able to match 137 of them with just birth year, maternal birth year and sex. Four were unable to be matched at all even with this basic criterion. When appending our new matched sets to our main data and reperforming the survival analyses, only minor changes in our estimates were observed (0.53 -> 0.55 in G3 grandchildren, 0.90 -> 0.89 in G4 great-grandchildren). We conclude that the unmatched persons excluded from our main cohort were missing at random and do not affect our inferences.

Table S29. Missingness of data in key outcomes derived from the Medical Birth Registry stratified by infant mortality

Outcome	Infant Mortality	Not Missing	Missing	% Missing
Birth Weight	Alive	60743	642	1.05
	Dead	302	16	5.03
Gestational Age	Alive	54311	7074	11.52
	Dead	256	62	19.50
APGAR Score	Alive	55046	6339	10.33
	Dead	241	77	24.21
Maternal Smoking	Alive	39696	21689	35.33
	Dead	152	166	52.20

Interpretation: Several of the outcomes used in our study which were derived from the Medical Birth Registry had patterns of missingness that were not random. For birth weight, gestational age, APGAR score, and maternal smoking, the rate of missingness was higher in children who died in the first year of life. Since children descending from longevity-enriched sibships have a lower rate of infant mortality ($HR = 0.53$), this implies our analyses assessing differences in adverse outcomes such as low birth weight, low gestational age, low APGAR score, and maternal smoking, are affected by a bias that goes in the direction of the observed advantages in these outcomes being conservative.

Table S30. Cox regression results for analyses of infant mortality with alternative definitions of covariate controls based on education and income data

Generation	Adjustment	HR	95% CI	p
G3	Fully adjusted model, baseline	0.55	[0.36, 0.82]	0.0033
	With income as breadwinner gross income	0.56	[0.38, 0.84]	0.0047
	With income as total net income	0.53	[0.35, 0.8]	0.0026
	With income as breadwinner net income	0.57	[0.39, 0.85]	0.0062
	With education as years of education	0.55	[0.36, 0.82]	0.0033
G4	Fully adjusted model, baseline	0.97	[0.74, 1.27]	0.8355
	With income as breadwinner gross income	0.96	[0.73, 1.25]	0.7438
	With income as total net income	0.98	[0.75, 1.28]	0.8777
	With income as breadwinner net income	0.96	[0.74, 1.26]	0.7854
	With education as years of education	0.97	[0.74, 1.27]	0.7405

Comparisons of infant mortality in G3 grandchildren, G4 great-grandchildren and matched controls by adjustment for alternative covariate definitions. Matching criteria included sex, birth year, birth season, maternal birth year, parity and mother's place of birth. Data are presented as hazard ratios with 95% confidence intervals, and HRs < 1 indicate lower hazards of the outcome in LEF descendants compared to general population matched controls. P-values describe a two-sided Wald hypothesis test, without adjustment for multiple testing. Abbreviations: G3 (Generation 3), G4 (Generation 4), LEF (Longevity-enriched Family), HR (hazard ratio), CI (confidence interval).

Interpretation: Our findings were robust to various definitions of measuring income in our study, including in either net or gross terms, or as total versus breadwinner (highest of two) income among the sets of parents in our study. Moreover, our findings were also robust to measuring highest attained education level numerically in terms of number of years spent in formal education.

Table S31. Cox regression results for analyses of infant mortality with maternal versus paternal definitions of covariates based on parental education, income, and occupation

Generation	Covariate source	Adjustment	HR	95% CI	p
G3	Maternal	Baseline, matched only	0.53	[0.36, 0.77]	0.0010
		Marital status, maternal education, and maternal income	0.59	[0.4, 0.87]	0.0082
		Marital status, maternal education, maternal income and maternal occupation	0.59	[0.4, 0.88]	0.0104
		Marital status, maternal education, maternal income, maternal occupation and urban density	0.62	[0.41, 0.93]	0.0197
	Paternal	Baseline	0.61	[0.41, 0.91]	0.0147
		Marital status, paternal education, and paternal income	0.64	[0.42, 0.98]	0.0378
		Marital status, paternal education, paternal income and paternal occupation	0.60	[0.38, 0.95]	0.0295
		Marital status, paternal education, paternal income, paternal occupation and urban density	0.62	[0.38, 0.99]	0.0465
G4	Maternal	Baseline	0.90	[0.69, 1.16]	0.4073
		Marital status, maternal education, and maternal income	0.95	[0.72, 1.24]	0.6947
		Marital status, maternal education, maternal income and maternal occupation	0.95	[0.72, 1.25]	0.7142
		Marital status, maternal education, maternal income, maternal occupation and urban density	0.93	[0.7, 1.22]	0.5870
	Paternal	Baseline	0.95	[0.73, 1.24]	0.7129
		Marital status, maternal education, and maternal income	0.98	[0.74, 1.3]	0.9043
		Marital status, maternal education, maternal income and maternal occupation	0.99	[0.74, 1.31]	0.9282
		Marital status, maternal education, maternal income, maternal occupation and urban density	0.97	[0.73, 1.29]	0.8315

Comparisons of infant mortality in G3 grandchildren, G4 great-grandchildren and matched controls by adjustment for maternal and paternal covariate definitions. Matching criteria included sex, birth year, birth season, maternal birth year, parity and mother's place of birth. Data are presented as hazard ratios with 95% confidence intervals, and HRs < 1 indicate lower hazards of the outcome in LEF descendants compared to general population matched controls. P-values describe a two-sided Wald hypothesis test, without adjustment for multiple testing. Note that baseline paternal estimates is a subset of the entire cohort due to incomplete linkage to fathers in the Civil Registration System (See Table S3.4). Abbreviations: G3 (Generation 3), G4 (Generation 4), LEF (Longevity-enriched Family), HR (hazard ratio), CI (confidence interval).

Interpretation: Our results are robust to adjustment for individually measured maternal and paternal covariates. Moreover, our findings are robust to adjustment for a more granular definition of parental occupation based on the following DISCO-88 and DISCO-08 classifications: 1. Management or skilled work, 2. Office work, sales and service, 3. Craftsmanship, Agriculture, Forestry and Fishing, and 4. Other manual work.

Items S32 and S33 describe the results of analyses assessing the risk of being small for gestational age after adjusting for socioeconomic factors, as well as maternal smoking. In our primary analyses in the main manuscript, maternal smoking was not adjusted for as a mediator of the observed effects, due to the fact that it was only available since 1991, and this would exclude a large portion of the G3 from such analyses, which is problematic for analysis of rarer outcomes such as infant mortality. Here we demonstrate the effect of maternal smoking on the risk of being small for gestational age. This outcome was chosen because it is one of the few where an advantage was observed in G4 and is one of the primary endpoints used in epidemiological research as a sensitive indicator of neonatal health. Note that all the analyses presented here, including the baseline ‘unadjusted matched only’ analyses for both generations, are subset on those without missing maternal smoking data. This removes all of those born before 1991 and is why the confidence intervals are so wide in the G3 analyses compared to what is presented in the main manuscript.

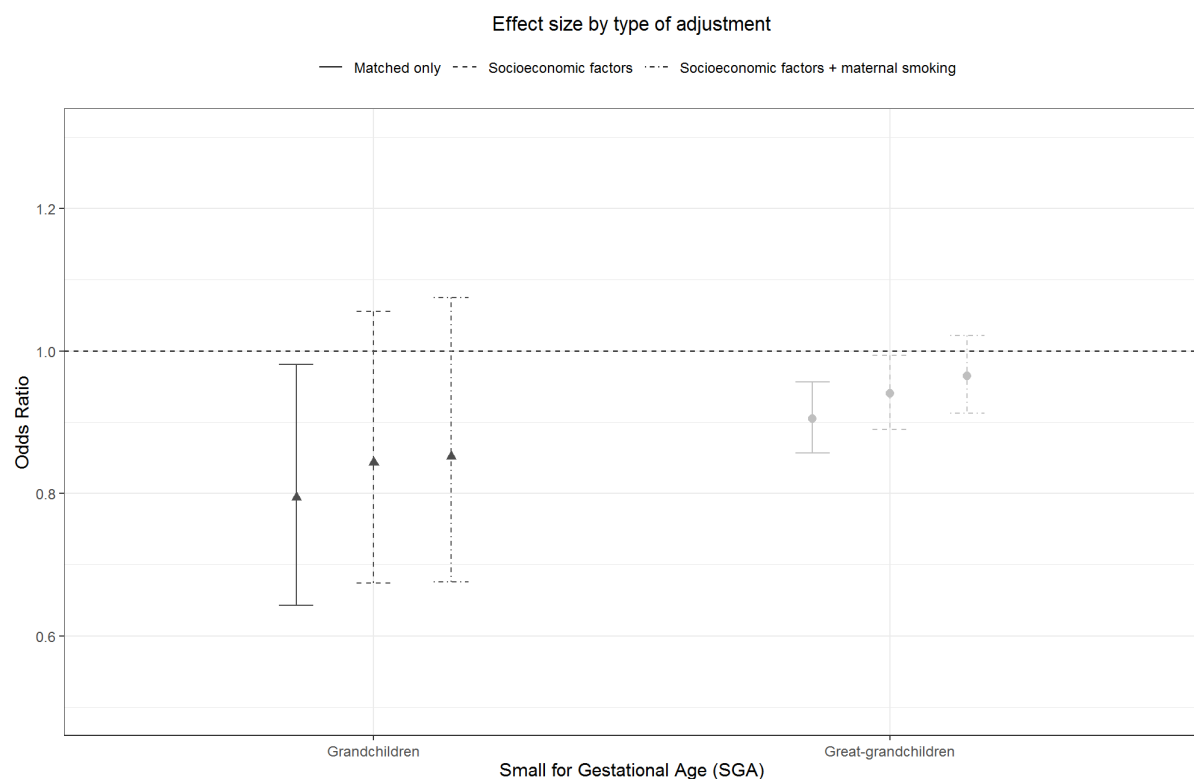
Interpretation: In generation G3, the size of the estimates are comparable between models adjusting for socioeconomic status and those adjusting for both socioeconomic status and maternal smoking. An attenuating effect was observed in generation G4 such that the direct effect after adjusting for maternal smoking was no longer statistically significant. However, the estimate was already marginal after adjusting for socioeconomic status and the absolute change in the estimate is very modest (0.94 to 0.97). These analyses suggest that maternal smoking did not materially influence the association between being a descendent of a longevity-enriched sibship and the risk of being born small for gestational age.

Table S32. Logistic regression results for analyses of size for gestational age with adjustment for maternal smoking

Generation	Adjustment	OR	95% CI	p
G3	Matched only	0.79	[0.64, 0.98]	0.0326
	Socioeconomic factors	0.84	[0.67, 1.06]	0.1375
	Socioeconomic factors + maternal smoking	0.85	[0.68, 1.08]	0.1772
G4	Matched only	0.91	[0.86, 0.96]	0.0004
	Socioeconomic factors	0.94	[0.89, 0.99]	0.0301
	Socioeconomic factors + maternal smoking	0.97	[0.91, 1.02]	0.2200

Comparisons of small for gestational age risk in G3 grandchildren, G4 great-grandchildren and matched controls. Matching criteria included sex, birth year, birth season, maternal birth year, parity and mother's place of birth. Adjustment for parental socioeconomic factors included highest attained education level, total gross income, and marital status. Additional adjustment was also made for maternal smoking. Data are presented as odds ratios with 95% confidence intervals, and ORs < 1 indicate lower odds of the outcome in LEF descendants compared to general population matched controls. Basic p-values describe a two-sided Wald hypothesis test, without adjustment for multiple testing. Abbreviations: G3 (Generation 3), G4 (Generation 4), OR (odds ratio), CI (confidence interval).

Figure S33. Analyses of size for gestational age with adjustment for maternal smoking



Comparisons of small for gestational age risk in G3 grandchildren, G4 great-grandchildren and matched controls. Matching criteria included sex, birth year, birth season, maternal birth year, parity and mother's place of birth. Adjustment for parental socioeconomic factors included highest attained education level, total gross income, and marital status. Additional adjustment was also made for maternal smoking. Data are presented as odds ratios with 95% confidence intervals, and ORs < 1 indicate lower odds of the outcome in LEF descendants compared to general population matched controls. Abbreviations: G3 (Generation 3), G4 (Generation 4), OR (odds ratio), CI (confidence interval).

Item S34. Modified E-value analyses of infant mortality

We now describe the results of an E-value analysis for analyses of infant mortality. An E-value is typically used to assess the extent to which an association between an exposure of interest could be explained away by a potential set of unobserved confounders. Although our results statistically adjusting for, the methodology used in E-values can be applied in our setting for similar argumentation.

For generation G3, our E-value analysis ($E = 3.07$) results suggest that a set of mediators would have to operate through pathways independent of parental education, income and marital status, and increase the risk of infant mortality by 3.07 times and be 3.07 times as prevalent in matched controls than G3 descendants, to fully explain the effect of being a G3 descendent of a longevity-enriched sibship. For G4, the E-value is 1.17. These findings are unchanged when adjusting for our expanded set of socioeconomic controls including occupation and urban density, resulting in E-values of 2.78 and 1.29 for G3 and G4 respectively. The socioeconomic covariates adjusted for in our study are those documented to be of high epidemiological importance for early life health outcomes, and there are unlikely to be other socioeconomic factors that could fully explain away our findings which are independent of those already adjusted for. These findings support the conclusion that the exceptional infant phenotype observed in our study does not seem to be mediated by socioeconomic and related factors.

Item S35. Assessment of model overfitting and prediction generalization in analyses of infant survival

We assessed the robustness of our primary results to overfitting by using penalised Cox penalized regression methods in the *glmnet* package in R, estimated by penalized partial likelihood, with 10-fold cross validation, using Harrel's C index as a performance measure. Since these models were not compatible with our matched cohort design, we instead used the eligible source population prior to the matching stage and matching criteria were instead employed as covariates. We report hazard ratios for the coefficient of interest (belonging to a longevity-enriched family) and Harrel's C index for three models, and where appropriate, the estimated values of λ . Due to statistical issues with conducting inference in penalized regression models, most packages generally do not report uncertainty measures alongside their estimated covariate parameters, and so we were unable to report them for the *glmnet* analyses presented below (see exception at the end, re *selectiveInference*). We estimated the following models:

1. Cox proportional hazard regression model estimated in the source population adjusted for sex and birth year as covariates, no penalization or cross validation.
2. Cox proportional hazard regression model estimated in the source population adjusted for sex, birth year, and all primary demographic and socioeconomic covariates, with cross validation, but with the penalization parameter forced to $\lambda = 0$ (equivalent to unpenalized Cox proportional hazard regression).
3. Cox proportional hazard regression model estimated in the source population adjusted for sex, birth year and all primary demographic and socioeconomic covariates, with penalization parameter set to its optimal value $\lambda = \lambda^*$ as determined by 10-fold cross-validation.

We conducted the above analyses using three types of penalized regression models: Lasso, Ridge, and Elastic Net. The results of these analyses are reported in the below tables.

Model type: Lasso Regression	Penalization and Prediction Accuracy		Effect Coefficient	
	λ^1	Harrell's C-index ²	Hazard Ratio	95% CI
G3 grandchildren vs general population				
Basic model, unpenalized ³	.	.	0.56	NA
Extended model, unpenalized, cross-validated ⁴	.	0.63	0.61	NA
Extended mode, penalized, cross-validated ⁵	0.0000028	0.63	0.61	NA
G4 great-grandchildren vs general population				
Basic model, unpenalized ³	.	.	0.86	NA
Extended model, unpenalized, cross-validated ⁴	.	0.63	0.92	NA
Extended model, penalized, cross-validated ⁵	0.0000030	0.63	0.92	NA

Model type: Ridge Regression	Penalization and Prediction Accuracy		Effect Coefficient	
	λ^1	Harrell's C-index ²	Hazard Ratio	95% CI
G3 grandchildren vs general population				
Basic model, unpenalized ³	.	.	0.56	NA
Extended model, unpenalized, cross-validated ⁴	.	0.63	0.61	NA
Extended model, penalized, cross-validated ⁵	0.000182	0.63	0.61	NA
G4 great-grandchildren vs general population				
Basic model, unpenalized ³	.	.	0.86	NA
Extended model, unpenalized, cross-validated ⁴	.	0.63	0.92	NA
Extended model, penalized, cross-validated ⁵	0.000178	0.63	0.92	NA

Model type: Elastic Net Regression	Penalization and Prediction Accuracy		Effect Coefficient	
	λ^1	Harrell's C-index ²	Hazard Ratio	95% CI
G3 grandchildren vs general population				
Basic model, unpenalized ³	.	.	0.56	NA
Extended model, unpenalized, cross-validated ⁴	.	0.63	0.61	NA
Extended model, penalized, cross-validated ⁵	0.0000040	0.63	0.61	NA
G4 great-grandchildren vs general population				
Basic model, unpenalized ³	.	.	0.86	NA
Extended model, unpenalized, cross-validated ⁴	.	0.63	0.92	NA
Extended model, penalized, cross-validated ⁵	0.0000041	0.63	0.92	NA

¹ λ is the shrinkage/regularisation/penalization parameter. When $\lambda = 0$, equivalent to unpenalized regression.

² Harrell's C-index measured via 10-fold cross-validation

³ Baseline model with the minimum covariates required to meaningfully interpret effects: sex and birth year.

⁴ Full model with all demographic and socioeconomic covariates, estimated without penalization.

⁵ Full model with all demographic and socioeconomic covariates, estimated with cross-validated penalization.

The consistency of both the effect estimates and the cross-validated C-index metric between the penalized and unpenalized models suggest that our models are not susceptible to overfitting or lack of prediction generalization.

We also used the selectiveInference package in R to perform post-variable-selection inference using Lasso models. However, this method has several limitations. The results are shown in the below table.

Model type: Selective Inference Lasso	Penalization and Prediction Accuracy		Effect Coefficient	
	λ^1	Harrell's C-index ²	HR	95% CI
G3 grandchildren vs general population				
Extended model, penalized, cross-validated ³	0.0000028	0.63	0.61	[0.42, 0.96]
G4 great-grandchildren vs general population				
Extended model, penalized, cross-validated ³	0.0000030	0.63	0.92	[0.72, 1.83]

¹ λ is the shrinkage/regularisation/penalization parameter. When $\lambda = 0$, equivalent to unpenalized regression.

² Harrell's C-index measured via 10-fold cross-validation

³ Full model with all demographic and socioeconomic covariates, estimated with cross-validated penalization.