Prenatal loss of father during World War One is predictive of a reduced lifespan in adulthood

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Although early-life stress is known to alter health, its long-term consequences on mortality remain largely unknown. Thanks to unique French legislation established in 1917 for war orphans and children of disabled soldiers, we were able to study the adult mortality of individuals born in 1914–1916 whose fathers were killed during World War 1. Vital information and socio-demographic characteristics were extracted manually from historical civil registers for 5,671 children born between 1 August 1914 and 31 December 1916 who were granted the status of "*pupille de la Nation*" (orphan of the Nation). We used a database comprising 1.4 million deceased soldiers to identify war orphans and collect information on their fathers and then paired each orphan with a nonorphan from the same birth register matched for date of birth, sex, and mother's age at the infant's birth. Mortality between ages 31 and 99 y was analyzed for 2,365 orphan/nonorphan pairs. The mean loss of adult lifespan of orphans who had lost their father before birth was 2.4 y (95% CI: 0.7, 3.9 y) and was the result of increased mortality before age 65 y. Adult lifespan was not reduced when the father's death occurred after the infant's birth. These results support the notion that intrauterine exposure to a major psychological maternal stress can affect human longevity.

intrauterine programming | maternal bereavement | adult mortality | historical cohort | World War One

Multiple lines of evidence indicate that exposure to adverse environmental cues in the early stages of development may have durable effects on biological vulnerability at older ages (1, 2). Following D. J. Barker's seminal observations ("the womb may be more important than the home") in children born during 1911–1930 (3), the Fetal Origins of Adult Disease hypothesis (4) and the Developmental Origin of Health and Disease (DOHaD) hypothesis (5) have developed. Two main kinds of early-life adversities, undernutrition and psychic maternal stress, have been studied in humans. Indeed, exposure to famine during pregnancy can have long-range consequences on offspring's morbidities including cardiovascular, metabolic, and mental diseases (6–8). Psychic suffering of pregnant mothers has been associated with functional alteration in the offspring's hypothalamo–pituitary–adrenal (HPA) axis (9, 10) that may pave the way for psychic vulnerabilities (11), obesity (12), diabetes (13), and cardiovascular diseases (14).

Stressors in critical periods of development induce both immediate, reversible homeostatic mechanisms and whole-life modifications of the response to environmental challenges (15). The mechanisms implicated in early programming of adult disorders remain largely unknown, although epigenetics is likely involved (16, 17). The intrauterine and early postnatal periods are characterized by high epigenetic plasticity (18); thus, as shown in laboratory rodents, early-life stress can affect development by durably imprinting specific brain regions and other tissues through epigenetic modifications (19). Restraint stress (20) or repeated exposure of pregnant dams to an aggressive congener (21), poor maternal care (22), or separation of recently born pups from the mother (23, 24) were shown to result in tissue-specific changes in DNA methylation and in the activity of genes involved in the stress response (22–25); some of these effects are sexually dimorphic (26). Epigenetics, however, is only one of the many effectors of early-life stress that can act on brain development (19); for example, prenatal stress in rats induces a reduction of neurogenesis in specific brain regions (27).

Few studies have investigated the mortality consequences of early-life conditions, including caloric deprivation during gestation (28, 29), economic conditions at birth (30), and season of birth (31). For instance, males born at the height of the Finnish famine lost ∼1 y of life expectancy at age 40 y (29). To our knowledge, only two studies have related early psychological stress and adult mortality (32, 33). No increased mortality between age 27 and 69 y was found in the 1,726 members of the Helsinki Birth Cohort (born 1934–1944 and followed from 1971–2003) who were separated as children from their parents during the Second World War (32). In the 1958 British birth cohort, increased all-cause mortality before age 50 y was found for the 4,543 individuals who experienced events such as parental divorce or bereavement in early life (33).

World War I (WWI) has been described as a "vast human experiment in stress" (34). Based on universal conscription, the French army suffered heavy losses (∼1.4 million deaths). The great majority of casualties were men aged 18–35 years old in 1914 and were caused mainly by artillery bombardments (35). Every day, about 350 French women lost their husbands, an event found to top a list of 43 stressful life events (36).

We studied the adult mortality of individuals whose fathers were killed during WWI. Our working hypothesis was that the father's death, known to be associated with maternal stress of extreme psychic intensity, could program orphans for various disorders, leading to an increased mortality in adulthood. Further, we hypothesized that if specific in utero programming did take place, it could be revealed by a decreased lifespan observed only in orphans whose fathers died before they were born (prenatal orphans). Depending on the mechanisms involved, male and female offspring might not have been equally affected.

Significance

The First World War was a historical experiment for early-life stress. Fathers of hundreds of thousands of children of all ages were killed during the conflict. The Developmental Origins of Health and Disease hypothesis predicts long-term effects of early-life stress. We collected historical data on French orphans born 1914–1916 and their fathers' military records and compared the orphans' mortality in adulthood (age 31–99 y) with that of matched nonorphans. We found a strong decrease in lifespan, reflecting increased mortality before age 65 y, in persons whose fathers died before, not after, their birth. These results support the notion that maternal psychological stress in pregnancy decreases adult longevity in offspring.

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We chose the design of a historical (non-concurrent) cohort study to test the relation between the loss of father and the mortality outcome. We took advantage of a specific legal status created in July 1917 and granted upon request to war orphans from 1918 onwards (37) that enabled state assistance and financial support if needed. The children, named "*pupilles de la Nation*" (orphans of the Nation), were said to be "adopted by the Nation," an event noted on their birth certificate (Fig. 1*A*). By law, adoption, marriage, divorce, and, since 1945, death also were systematically inscribed on birth certificates, no matter where they occurred. Any French city hall continuously updates its birth registers, receiving systematic notifications from the ∼36,000 other city halls covering France and consulates abroad (death and marriage notifications) and from civil tribunals and law firms (adoptions and divorces).

We identified and computerized the birth certificates of 5,671 *pupilles de la Nation* born between 1914 and 1916 in two large cities, Paris and Bordeaux. The dates of death of *pupilles* who died after 1945 were known by the notifications on their birth certificates. For the 3,210 *pupilles* identified as war orphans, we retrieved the dates and causes of paternal death in the publicly available database of all military deaths that occurred between 3 August 1914 and 1 June 1919 (Fig. 1*B*). After we excluded those whose father died from disease, we compared the adult lifespan of orphans with that of non-*pupille* individuals (i.e., matched nonorphans, MNOs) drawn from the same birth registers. An orphan and an MNO were matched by sex, mother's age (± 2 y), district, and date of birth. The flowchart of the study is shown in Fig. S1. The adult lifespan of 2,365 orphan/MNO pairs alive at age 31 y was analyzed. Lifespan comparisons with MNOs were performed separately for prenatal and postnatal orphans.

Results

Baseline Characteristics of Subjects. Table 1 shows the characteristics of the 2,365 pairs (see Table S1 for detailed characteristics); 27.7% (95% CI: 25.9, 29.6%) of orphans were prenatal orphans, and 72.3% (95% CI: 70.4, 74.1%) were postnatal orphans.

Dates of birth of MNOs matched those of orphans. The distribution of dates of birth of prenatal and postnatal orphans showed differences (Fig. S2). The monthly number of orphans fell in May 1915. Although the dates of birth of postnatal orphans were uniformly distributed before May 1915, a peak in prenatal orphans occurred in February–April 1915 (see legend of Fig. S2).

The paternal occupation score (range: 1–6) was 2.60 (95% CI: 2.46, 2.74) in prenatal orphans and 2.70 (95% CI: 2.58, 2.82) in their MNOs (median P of the χ^2 test over the 10 datasets obtained by multiple imputation = 0.02). This orphan/MNO difference was similar in postnatal orphan/MNO pairs [postnatal orphans: 2.62 (95% CI: 2.55, 2.69); MNOs: 2.75 (95% CI: 2.68, 2.83)]. The illegitimacy rate was lower in orphans than in MNOs (Table 1): 4.0% (95% CI: 2.7, 5.8%) in prenatal orphans, 11.7% (95% CI: 10.2, 13.3%) in postnatal orphans, and 15.9% (95% CI:13.2. 18.9%) and 17.3% (95% CI:15.6, 19.2%) in their respective MNOs.

Difference in Adult Lifespan Between Orphans and MNOs. Adult lifespan was different in prenatal orphans and their MNOs (Wilcoxon test: $P = 8.1 \times 10^{-3}$). No difference was found between postnatal orphans and their MNOs (Wilcoxon test: $P = 0.99$). Prenatal and postnatal orphans had different losses of lifespan (permutation test: $P = 0.03$). Mean lifespan was 75.9 y (95% CI: 74.6, 77.1 y) in prenatal orphans vs. 78.2 y (95% CI: 77.1, 79.3 y) in their MNOs and was 76.7 y (95% CI: 76.0, 77.4 y) in postnatal orphans vs. 77.0 y (95% CI: 76.3, 77.7 y) in their MNOs. The mean lifespan of prenatal orphans was 2.4 y (95% CI: 0.7, 3.9 y) less than that of their MNOs. The difference was 0.3 y (95% CI: −0.8, 1.3 y) in postnatal orphans. Using a Generalized Additive Model (GAM) to control for legitimacy, parental occupation, and age, the adjusted difference between orphans and MNOs was 2.0 y (95% CI: 0.1, 4.0 y) higher in prenatal than in postnatal pairs.

The observed difference lifespan in orphan/MNO prenatal pairs was stronger in males [males: 3.1 y (95% CI: 0.8, 5.4 y); females: 1.3 y (95% CI: −1.1, 3.5 y)]. However, the male/female difference in effects did not achieve significance (permutation test: $P = 0.29$).

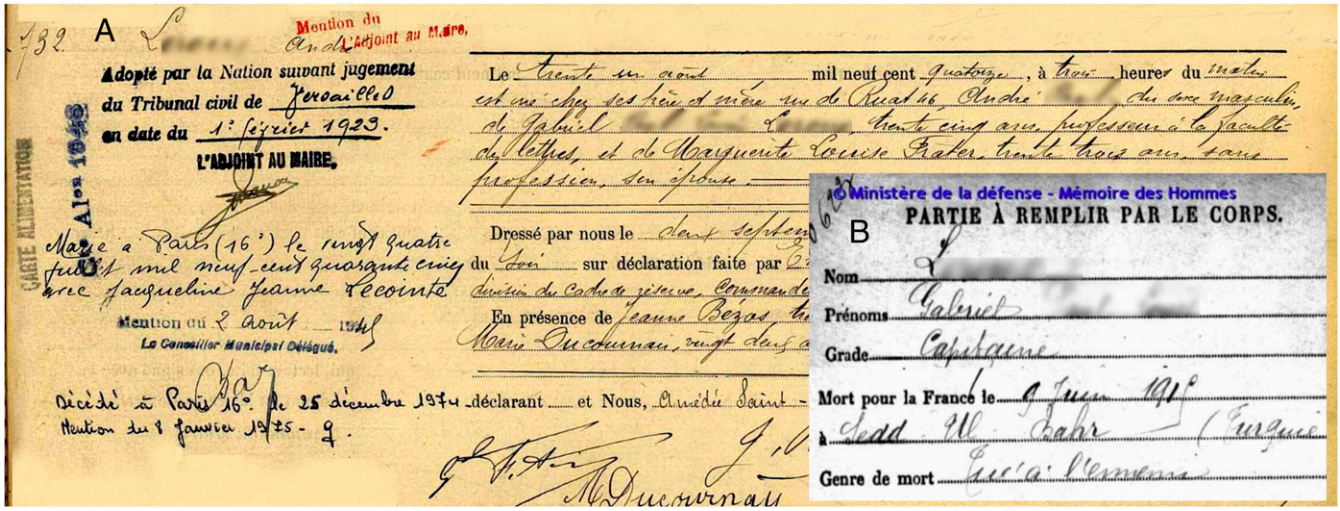

Fig. 1. Historical material used: Examples of an orphan's birth certificate (*A*) and the military record of the orphan's father (*B*). (*A*) Birth certificate of a *pupille de la Nation*, André L., born of Gabriel L. on 31 August, 1914, in Bordeaux. The tribunal of the city of Versailles granted him *pupille de la Nation* status in 1923. That information was automatically transmitted by the Versailles tribunal to the city hall of Bordeaux and was transcribed by a civil servant in the upper left margin of the birth certificate. Similarly, notification of André L.'s marriage (in 1945) and death (in 1974) were transmitted (both by the city hall of the 16th district of Paris) to the city hall of Bordeaux, which noted these life events on the left margin of the birth certificate a few days after they occurred (© archives Bordeaux métropole – Bordeaux 1 E 427). (*B*) We searched for the father of André L., Gabriel L., by name and age in the database of French soldiers who died during WW1 (available at www.memoiredeshommes.sga.defense.gouv.fr/en/article.php?larub=80). The database yielded the image of the father's record (selected sections are shown). Gabriel L. was killed in action on 9 June 1915.

Table 1. Baseline characteristics of the 2,365 studied orphan/MNO pairs

Variable	Prenatal orphans (n = 656)	MNOs (n = 656)	Postnatal orphans (n = 1,709)	MNOs (n = 1,709)
Date of birth, mean	28 April 1915	27 April 1915	1 April 1915	2 April 1915
Sex, *n* (%)				
Female	319 (48.6)	319 (48.6)	814 (47.6)	814 (47.6)
Male	337 (51.4)	337 (51.4)	895 (52.4)	895 (52.4)
Legitimacy, *n* (%)				
Legitimate	630 (96.0)	552 (84.1)	1,509 (88.3)	1,413 (82.7)
Illegitimate	26 (4.0)	104 (15.9)	200 (11.7)	296 (17.3)
Paternal OS (95% CI)	2.60 (2.46, 2.74)	2.70 (2.58, 2.82)	2.62 (2.55, 2.69)	2.75 (2.68, 2.83)
Maternal OS (95% CI)	4.42 (4.26, 4.59)	4.70 (4.53, 4.86)	4.44 (4.34, 4.54)	4.62 (4.52, 4.72)
Maternal age, mean (SD)	25.8 (4.3)	26.2 (4.5)	25.6 (4.9)	26.4 (5.0)
Paternal age, mean (SD)	28.7 (4.3)	30.4 (5.7)	28.5 (4.9)	30.6 (6.2)
Status at age 99, *n* (%)				
Dead	630 (96.0)	637 (97.1)	1,645 (96.3)	1,632 (95.5)
Alive	26 (4.0)	19 (2.9)	64 (3.7)	77 (4.5)

OS, occupation score (*Methods*).

We examined the possibility of an increased effect of father's death in early pregnancy (first trimester vs. pooled second and third trimesters) or late pregnancy (third trimester vs. pooled first and second trimesters). No difference in orphan/MNO lifespan was found when the father's death occurred during early pregnancy (permutation test: $P = 0.80$), but the orphan/MNO difference reached 4.1 y (95% CI: 1.5, 6.7 y) when the father's death occurred during the third trimester vs. 1.2 y (95% CI: −0.8, 3.2 y) when the father's death occurred during the first/second trimester (permutation test: $P = 0.07$) (Fig. 2). For postnatal orphans, the mean difference between the orphans and the MNOs was similar when the father's death occurred in the first year of postnatal life or after age 1 y (permutation test: $P = 0.59$) (Fig. 2) and when the father's death occurred before or after 6 mo of age (permutation test: $P = 0.94$).

Evolution of Differences in Lifespan with Age. A larger proportion of prenatal orphans (150/656) than their MNOs (107/656) died before age 65 y ($P = 3.5 \times 10^{-3}$). No difference was found in remaining lifespan for prenatal orphans and MNOs alive at age 65 y (Fig. 3), indicating that the 2.4-y difference in remaining life expectancy at age 31 y reflected increased mortality between the ages of 31 and 65 y.

Sensitivity Analyses. Because of the difference in the proportion of legitimate children in orphans and MNOs, the analyses were performed on the subset of orphan/MNO pairs in which both members were legitimate. The difference between prenatal and postnatal pairs was maintained: The mean loss of lifespan of orphans was 2.7 y (95% CI: 0.9, 4.4 y) in prenatal legitimate pairs and was 0.2 y (95% CI: −0.9, 1.4 y) in postnatal legitimate pairs (permutation test: $P = 0.03$). In the multivariate analysis restricted to legitimate pairs, the difference with MNOs was 2.6 y (95% CI: 0.4, 4.7 y) greater in prenatal than in postnatal orphans.

Results remained consistent when rematched pairs were removed (*Methods*), when the analysis was restricted to Paris, when median, not mean, differences were analyzed, when only pairs born before May 1915 (i.e., conceived before the beginning of the war) were included, or when the longevity of those still alive at age 99 y was imputed and included in the analyses.

Discussion

All persons in the current study were born in 1914–1916, at a time when most mothers faced uncertainty about safety and nutrition and an increased workload. Those whose spouse survived may have lost a brother or friend. Those who lost their spouse were not always informed immediately (*SI Text*). Our main finding was a large difference of 2.4 y in adult lifespan between prenatal orphans and MNOs because of increased mortality before age 65 y. In contrast, postnatal orphans and their MNOs had quasi-identical lifespans. Both findings are of interest in the context of the DOHaD hypothesis.

It is known that early mortality selection may mask the negative long-term effects of an early-life adversity by enriching the proportion of more robust individuals in the studied population (30). A striking example is the Finnish famine, when selection induced by the immediate threefold increase in mortality was strong enough to mask a 1-y decrease in adult life expectancy (28, 29). Had preferential mortality been present among WWI

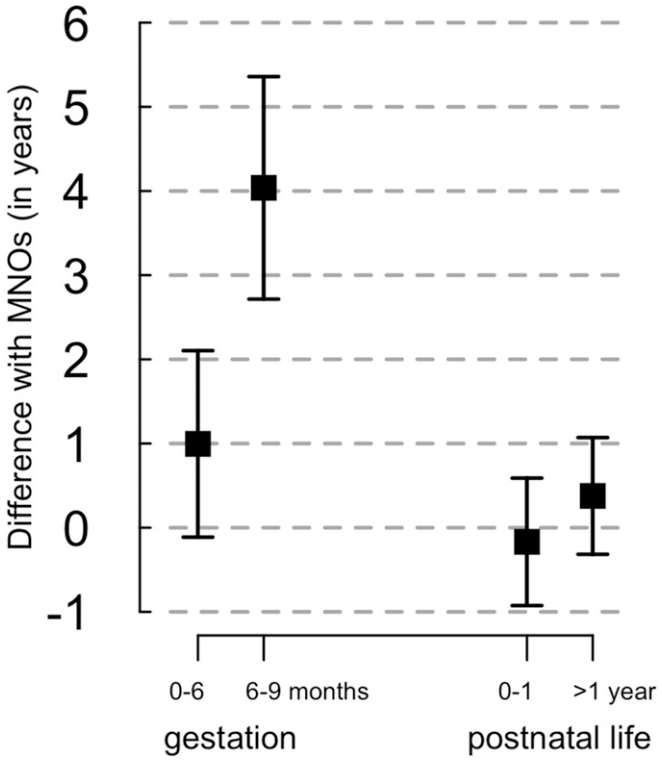

Fig. 2. Mean difference in lifespan between war orphans and MNOs according to age at father's death. Data are shown as mean ± SE.

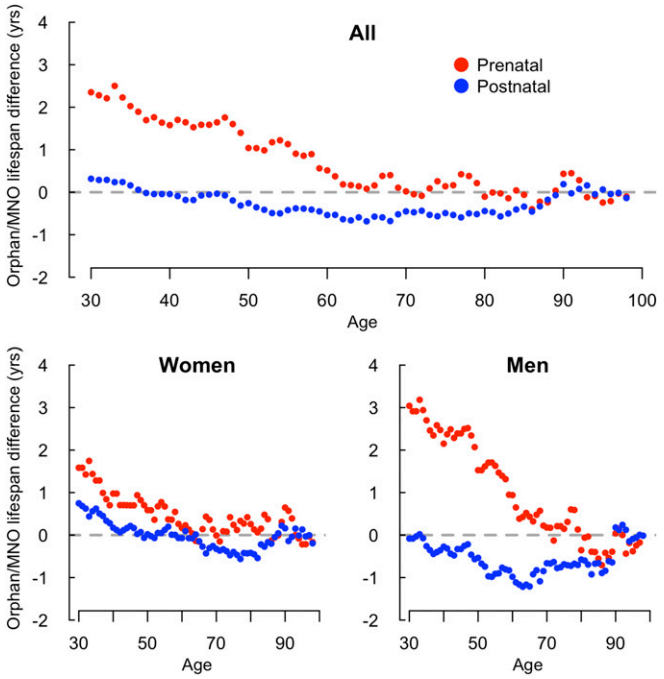

Fig. 3. Variation with age of the difference between orphan and MNO remaining lifespans, by sex.

orphans before they reached age 31 y, a more robust proportion of them would have been selected, strengthening our finding of a loss of lifespan in prenatal orphans.

In fact, orphans and MNOs followed a similar path of adversities except for the father's death. Because adoptions by the Nation started in 1918, only orphans alive in 1918 could become *pupilles*, precluding a direct study of infant and child mortality. However, there is no evidence for any selective pressure comparable to a famine in the early life of WWI orphans. When the Spanish influenza pandemic started in France in August 1918 (38), the studied orphans and MNOs were 1.5–4 y old. We see no reason to postulate that the Spanish flu struck significantly more war orphans than MNOs. Indirect evidence against a significant early-mortality selection also comes from the examination of paternal occupations. The odds ratio of survival in the Finnish famine was ∼2.5 between rich and poor families (39). In contrast, we observed only minimal differences in the occupations of the fathers of the war orphans who survived to adulthood and the fathers of their MNOs (Table 1 and Table S1).

Our rule for recruiting MNOs aimed at limiting confounding factors. An orphan and the MNO were born in the same district. In 87.8% of the orphan/MNO pairs, the difference in dates of birth was less than 2 wk, guaranteeing that an orphan and the MNO faced a comparable external environment and food supply at the earliest stages of development. Matching of date and district of birth also was critical because of the migrations induced by the war. In particular, refugees from the invaded regions of the northeast, including pregnant women, progressively settled in Paris (40), thereby modifying the area of recruitment (Fig. S3*C*).

We searched for variables that might have influenced both the offspring's lifespan and the paternal risk of death at war. The risk of death affected all strata of society because of universal conscription and depended on three key factors: age, health, and occupation. Men aged ≥35 y in 1914 were assigned to less exposed units (territorial regiments) (35). Because paternal age was not always available on birth certificates, we matched MNOs and orphans by maternal age, with which paternal age is associated. This matching ensured that mean paternal age was comparable in MNOs and orphans (Table 1). After thorough medical examination, French men in poor health were declared unfit for military service or were assigned to units not involved in combat. Thus fathers of orphans were men in good health. Another source of confounding might be that specific occupations at all levels of the social ladder protected a fraction of citizens from combat (e.g., railroad workers, policemen, physicians). Our detailed classification of paternal occupations in six socioeconomic categories showed only minimal differences between fathers of orphans and of MNOs (Table 1). Heterogeneity that might remain within categories is unlikely to be different in prenatal and postnatal pairs, so it could not account for the observed difference in loss of adult lifespan.

Because the *pupille de la Nation* status was granted upon request, we checked to confirm that the non-*pupille* individuals initially drawn to serve as MNOs were not war orphans (Fig. S1). We found that only 1% of the MNOs alive at age 31 y actually were war orphans who did not become *pupilles* (Table S2). There was also the question of legitimacy. A strikingly low illegitimacy rate (4.0%) was observed in prenatal orphans (Table 1), perhaps because, for unmarried couples, the early death of the partner made recognition of the child impossible. For mothers who had no definite proof of paternity (letters or other evidence), the lack of recognition made application to the *pupille* status impossible. We found that legitimacy cannot explain the difference in lifespan, because this difference also was observed in the analysis performed on legitimate children only.

Our main argument for our belief that potential confounding factors were unlikely to explain our observation is that we observed no association between postnatal father's death and reduced lifespan. Similarly, the decreased lifespan found in prenatal orphans could not be explained by degraded familial socioeconomic status, because we observed no loss of lifespan in the postnatal orphans, who faced comparable conditions in childhood and adolescence.

Finally, maternal stress during pregnancy appears the most plausible cause for the reduced lifespan of prenatal orphans. Glucocorticoids are a major candidate for programming the womb and the fetal HPA axis during prenatal stress (41). The maternal HPA axis undergoes dramatic changes during pregnancy. Although cortisol levels rise threefold by the third trimester, placental 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) maintains low concentrations of cortisol in the fetal circulation until late in gestation (42). This hypocortisolic fetal milieu seems crucial for fetal HPA axis maturation and regulation of steroidogenesis (43). Placental 11β-HSD2 is more active in females (44) and is sensitive to maternal stress, which causes a greater transfer of glucocorticoids from mother to fetus. A reduction in placental levels of 11β-HSD2 occurs during late gestation, allowing an increased transfer of maternal glucocorticoids to the fetus and exacerbation of the effects of maternal stress on the fetus (45, 46). Because maternal cortisol levels are much higher than fetal levels, even moderate changes in placental 11β-HSD2 can significantly modify the glucocorticoid exposure of the fetus. The increase in fetal glucocorticoid levels can lead to fundamental changes in gene regulation and fetal development in many developing organs and in the HPA axis, in particular (47, 48).

Some of these changes may relate to the powerful effects of glucocorticoids on the epigenome (49), which can imprint male and female fetuses for life. Indeed, durable epigenetic imprints involving genes expressed in regions of the HPA axis may have a long-lasting influence on the expression of these genes and cause an altered cortisol reactivity to future stress in later life (50). Human studies have shown that maternal psychological trauma during pregnancy can influence the offspring's epigenome, notably the human glucocorticoid receptor gene (*NR3C1*) that mediates the effects of fetal cortisol on HPA-axis development. Precisely, the *NR3C1* locus was found to be hypermethylated in children whose mothers suffered from depression and anxiety during the third trimester of their pregnancy (51). Women's experience of

intimate partner violence during pregnancy also has been associated with increased *NR3C1* methylation in their adolescent offspring (52). When women were exposed to the Tutsi genocide during pregnancy, their children had higher methylation of the *NR3C1* exon 1F than offspring from nonexposed women (53). *NR3C1* is not the only locus where DNA methylation is modified by maternal stress. Other methylation changes in offspring exposed to maternal depression were detectable in the immune system at birth and persisted until adulthood in the hippocampus, a known regulator of HPA activity (54).

Remarkably, the methylation status of the *NR3C1* promoter was found to be more sensitive to maternal depression in late pregnancy (55). This finding is consistent with our observation of a trend for a greater increase in adult mortality when the father's death occurred during the third trimester of intrauterine life. Trimester-specific early-life adversities may have differential effects on particular systems. In this respect, psychic maternal stress is unlikely to have the same effects on offspring health as famine, which is known to favor late development of diseases if it occurs during early gestation. It is important to note that programming mechanisms remain out of reach in humans, notably with regard to the tissue-specific nature of epigenetic modifications, because the tissues of interest, such as the hippocampus, hypothalamus, or pituitary, escape investigation. Nevertheless epigenetic imprints probably represent a critical component of the programming process and could be partly responsible for the long-range effects of antenatal glucocorticoid exposure on neurologic, cardiovascular, and metabolic function through their persistent effects on the HPA axis (56). Epigenetic programming of neuroendocrine and behavioral phenotypes has some sex specificity (26). It is conceivable that imprints in the HPA axis following the father's death could be perpetuated in subsequent generations through the female lineage and pregnancies.

In conclusion, our study of the consequences of maternal bereavement during WWI, a single stress of extreme psychic intensity, allowed us to study the effects of the loss of the father at specific moments of child development and to compare the whole-life adult mortality of persons whose mothers had experienced this stress with that of matched individuals born at the same time and place to mothers who had not experienced this particular stress. Although we were not able to dissect the causes of the increased mortality in orphans, our study contributes to the assessment of the health impact of severe maternal psychic stress during pregnancy.

Methods

Identification of *Pupilles de la Nation* on the Birth Registers. All *pupilles de la Nation* born in 17 districts of Paris between 1 August 1914 and 31 December 1916 and in the four districts of Bordeaux from 1 August 1914 to 31 December 1915 (Table S3) were identified by the "adopted by the Nation" notification that was systematically inscribed on their birth certificates following adoption. Vital information available on birth certificates was computerized; see *SI Text* for details. The Commission Nationale de l'Informatique et des Libertés (57) authorized us to access and analyze those data (registration number 915774).

Choice of MNOs. MNOs were used for comparison of orphans' lifespans. Because MNOs were selected before the identification of war orphans among *pupilles* (see below), an MNO was paired to each *pupille*, whether the *pupille* was an orphan or the child of a disabled soldier. The MNO of a *pupille* was selected from the same birth register and was the closest (going upward in the birth register, from the *pupille*'s certificate) non-*pupille* same-sex birth with an age difference $\leq$2 y between the MNO's mother and the *pupille*'s mother.

Claiming the status of *pupille de la Nation* required a proof of dead soldier's paternity of the child. Therefore, a child whose father's identity was unknown could not become a *pupille*, whatever his father's war experience. *Pupilles* were legitimate children or children who were born illegitimate but later were recognized by their father or by judgment (in cases in which the father died before recognition but where definite proof of paternity existed). MNOs with an unknown father therefore were excluded from the analysis.

Longevity Information Available on Birth Certificates. The date of death has been systematically recorded on French birth certificates since 29 March 1945. Wherever and whenever death occurs, the civil registration service at the place of death notifies the civil registration service at the place of birth, so that the birth certificate is updated within a few weeks, at most, after death. For individuals who die abroad, the information is transmitted to the place of birth by the local French consulate. Thus 31–99 y is the range within which the age at death is known for all included individuals, from the youngest (born December 1916) to the oldest (born August 1914) (see *SI Text* for details).

Identification of War Orphans Among *Pupilles de la Nation*. A *pupille de la Nation* is the child of a soldier who died or was disabled (injured or ill) during the war. To identify orphans, we searched for the father of each *pupille de la Nation* in an online database (58) (available at www.memoiredeshommes.sga.defense.gouv.fr/en/article.php?larub=80), which records all French soldiers who died during WWI (see *SI Text* and Fig. S4). We similarly searched for the father of each MNO in the database of French soldiers who died during WWI. The 35 MNOs alive at age 31 y who were identified as war orphans were excluded from the analysis (Fig. S1).

Rematching. A total of 987 orphans alive at age 31 y were rematched to an available MNO of same sex and same district of birth (Fig. S1) because the initial MNO had died before age 31 y, was identified as a war orphan, or had an unknown father. When several MNOs were available for rematching, we selected the one with the date of birth closest to that of the orphan. Each available MNO was used only once in rematching. Rematching was performed after a random permutation of the 987 orphans. Rematching was successful for 985 of the 987 orphans, yielding 2,365 orphan/MNO pairs in the final dataset analyzed.

Classification of Parental Occupations. We computed an ordinal score of paternal occupations based on the following six categories: *i*) worker; *ii*) craftsman; *iii*) employee; *iv*) shopkeeper; *v*) middle class, and *vi*) upper class. Similarly, we defined eight categories of maternal occupations: *i*) servant; *ii*) worker; *iii*), craftswoman; *iv*) employee; *v*) housekeeper; *vi*) shopkeeper; *vii*) housewife, and *viii*) middle and upper class. The maternal occupation at the time of birth was available on 99.4% of birth certificates. The paternal occupation was available for 97.2% of legitimate children.

Statistical Analysis. To impute the unavailable paternal and maternal occupations and those we could not classify, we performed multivariate imputation by chained equations (MICE) (59) using district and date of birth, sex, status (alive/dead) at age 31 y, parental occupations, legitimacy, and maternal age. We created 10 completed datasets. The parental occupation scores and regression coefficients obtained on the 10 datasets then were combined following Rubin's rules (60).

The main outcome analyzed was the lifespan of those died between the ages of 31 and 99 y. We tested for differences in the distribution of lifespans between orphans and MNOs using paired Wilcoxon signed-ranked tests on pairs in which the lifespan of both members was measured (i.e., both died between the ages of 31 and 99 y). The presence of differences was assessed separately for prenatal orphan/MNO and postnatal orphan/MNO pairs. We computed the mean lifespan of each group: prenatal orphans, MNOs of prenatal orphans, postnatal orphans, and MNOs of postnatal orphans. Bootstrapped 95% CIs were based on B = 1,000 replicates. To test the hypothesis that mean losses of lifespan were different in prenatal orphans and postnatal orphans, permutation tests were performed on prenatal and postnatal pairs. For each orphan/MNO pair, prenatal or postnatal, in which both members died between the ages of 31 and 99 y, an orphan/MNO difference in lifespan, δ, was determined. We ran P = 10,000 permutations on the prenatal/postnatal variable to estimate the null distribution of differences of means between prenatal and postnatal pairs.

Finally, the δs were regressed in a GAM (61) on status (postnatal/prenatal pair) with control for six categorical variables (paternal occupation, maternal occupations, legitimacy) and paternal and maternal ages (modeled by cubic regression splines with 5 df and evenly spaced knots; smoothing parameters determining the effective df were selected to minimize the unbiased risk estimator score).

Analyses were repeated for prenatal orphans according to the prenatal trimester of the father's death, and six sensitivity analyses were performed (*SI Text*).

All analyses were performed in R v3.0.3, with the package *mice* for multiple imputation (62) and the package *mgcv* for GAM regressions (63).

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