Pediatric Mortality in Males Versus Females in the United States, 1999–2008

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KEY WORDS

vital statistic, mortality risk, disease risk, sex difference, sex-linked genes

ABBREVIATIONS

CEC—Centers for Disease Control and Prevention
ICD-10—*International Classification of Diseases, 10th revision*
NCHS—National Center for Health Statistics
RR—relative risk
SEER—Surveillance, Epidemiology, and End Results

Ms Balsara assisted in the design of the study, performed data analysis, and drafted the initial manuscript; Dr Faerber assisted in the design of the study, performed data analysis, and edited the manuscript for key intellectual content; Dr Spinner assisted in the conceptualization of the study and edited the manuscript for key intellectual content; Dr Feudtner conceptualized and designed the study and edited the manuscript for key intellectual content; and all authors approved the final manuscript as submitted.

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WHAT'S KNOWN ON THIS SUBJECT: Adult males are known to have a greater overall likelihood of death than female adults. Among children, excess male mortality is known for specific conditions but not as a general phenomenon.

WHAT THIS STUDY ADDS: Males are more likely to die during childhood and adolescence than their female peers from not only injuries but also from a wide variety of medical conditions, suggesting the existence of either a female robustness factor or a male vulnerability factor.

abstract

OBJECTIVE: To evaluate whether differences between pediatric male and female mortality are due to differences in specific age ranges, specific disease categories, or differences in the risk of developing specific conditions versus the risk of dying once having developed the condition.

METHODS: Using 1999–2008 mortality data for all deaths of individuals <20 years of age from the Centers for Disease Control and Prevention's WONDER database, we calculated male-to-female relative risks (RRs), standardized to the 2000 US Census, by age and *International Classification of Diseases, 10th revision* (ICD-10), chapters. By using the Centers for Disease Control and Prevention's record of linked birth and infant death records between 1999 and 2007, we also calculated male-to-female RRs stratified by gestational age; and by using Surveillance, Epidemiology, and End Results cancer registries for 1999–2008, we calculated incidence and mortality RRs for the 7 leading types of cancer.

RESULTS: Males experience higher mortality rates in all age groups from birth to age 20 years (RR: 1.44; 95% confidence interval [CI]: 1.44–1.45) and among infant deaths in nearly all weekly gestational age strata (RR: 1.12; 95% CI: 1.11–1.12). Stratified by ICD-10 major disease categories, males experience higher mortality rates in 17 of 19 categories. For the 7 types of pediatric cancers, the overall pattern was similarly greater male incidence (RR: 1.13; 95% CI: 1.12–1.14), fatality rate (RR: 1.10; 95% CI: 1.07–1.13), and overall mortality (RR: 1.21; 1.18–1.25).

CONCLUSIONS: Under 20 years of age, males die more than females from a wide array of underlying conditions. The potential genetic and hormonal mechanisms for the mortality difference between males and females warrant investigation. *Pediatrics* 2013;132:1–8

That the average life span of females is longer than males is well known. In 2000, the World Health Organization reported that, worldwide, women compared with men live an average of 3.9 years longer.[1] The "female advantage" that is seen in greater life span is also noticeable in mortality rates. The ratio is greatest for ages 15 to 24 years, largely due to suicides, homicides, and accidents.[2] Less expected is the fact that not only are male mortality rates higher but they are consistently so at all ages.[3,4] Furthermore, this trend has been traced back until 1940 across the globe where the ratio of male-to-female mortality has almost unwaveringly remained above 1 throughout 22 affluent countries of the world.[4]

In the United States in 2002, 2003, and 2004, for example, males had greater mortality rates than females in 15 of the 16 leading causes of death.[5] Most commonly, these causes included heart disease, cancer, and kidney disease along with external causes such as homicide, suicide, and accidents.[6] Only in the case of Alzheimer disease did the male-to-female ratio of mortality rates dip below 1.[6] Similarly in 2010, the US Department of Health and Human Services, the Centers for Disease Control and Prevention (CDC), and the National Center for Health Statistics (NCHS) detailed the existence in the United States of excess male mortality in diseases of the heart, cerebrovascular diseases, malignant neoplasms, chronic lower respiratory diseases, influenza and pneumonia, chronic liver disease and cirrhosis, diabetes mellitus, HIV, unintentional injuries, suicide, and homicide since 1950.[7] Other studies have found significant male excess in infant deaths across numerous causes including sudden infant death syndrome, pre- and postnatal infection, and congenital malformations.[8–11]

Despite this abundance of research, however, the picture of gender-related mortality differences remains fragmented, incomplete, and underappreciated; the female advantage has mostly been studied in adults, with the exception of a few specific pediatric conditions, and with a vague notion that the differences among younger persons chiefly arise due to males engaging in riskier behaviors and dying of injuries.[3] To advance our understanding of gender-related mortality disparities, we organized our study around 2 main questions. First, is the overall mortality risk for males elevated due to an extreme elevation of risk for just a few causes of death or is it due to a more general elevation of risk across many conditions? To answer this question, we examined US national mortality data for each chapter of the *International Classification of Diseases, 10th revision* (ICD-10). Second, is the elevation of mortality risk due to an increased risk of developing life-threatening conditions, or (after developing the condition) an increased risk of dying from these conditions, or a combination of the 2 processes? To answer this question we examined mortality due to cancer and complications of premature birth, gathering disease incidence data from the CDC National Program of Cancer Registries and the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program for cancer data and the linked infant birth/death records in the CDC's WONDER database for gestational age and prematurity data.

METHODS

Data Sources

Mortality Data for All Persons <20 Years of Age

Total and cause-specific mortality data from 1999 to 2007 were obtained from the CDC's WONDER program (wonder.cdc.gov). Mortalities are based on death certificates of US residents on which a single underlying cause of death is identified. These causes of death are categorized according to ICD-10 chapters, omitting chapter XV (pregnancy, childbirth, and puerperium) because males are not at risk for these conditions.

Infant Mortality Data

Infant death data were taken from the NCHS and CDC database of linked birth and death records for the years 1999–2007 in which ICD-10 codes were available (wonder.cdc.gov/lbd.html). This data source yielded the unadjusted number of deaths and births as well as the weighted number of deaths per 1000 births for each gestational age and gender stratum for the years spanning 1999 to 2007. The death rates are weighted to account for the 2% to 3% of infant death records that cannot be linked to corresponding birth certificates.

Cancer Incidence and Mortality Data

Cancer incidence and mortality data from 1999 to 2008 were obtained from the National Program of Cancer Registries (www.cdc.gov/cancer/npcr) and the SEER program (seer.cancer.gov). Incidence analyses focused on 7 cancers: (1) leukemia, (2) cancers of the brain and nervous system, (3) lymphomas, (4) cancers of the endocrine system, (5) cancers of soft tissue including the heart, (6) cancers of bone and joints, and (7) cancers of the digestive system. These 7 cancers account for 79% of cancer incidence and 89% of cancer deaths in children under the age of 20 years. Cancer incidences are classified according to the ICD-10 subchapter and are counted in multiple categories if >1 primary cancer occurs. Cancer death data are obtained from death certificates in 50 states and the District of Columbia and are made available by the National Vital Statistics System at the NCHS. To be consistent with the cancer incidence data, the cancer sites in the mortality data were

classified on the basis of the revised SEER recodes from January 27, 2003. Counts (number of cases) for both incidence and mortality (overall and cause-specific) are reported by gender and age group and are suppressed by the CDC database if <16 years of age.

Statistical Analysis

Stratified Relative Risk Ratio Analyses for Pediatric and Infant Mortality

Relative risks (RRs) were used to measure the risk of death in male children compared with the risk of death for female children. By using the mortality data for all children, RR ratios were computed within each ICD chapter using (1) the death counts available from the CDC and (2) the total number of male and female children <20 years who were alive according to the 2000 census. We calculated RRs stratified by age (<1 year, 1–4 years, 5–9 years, 10–14 years, and 15–19 years) to examine how the RR of mortality varied by age.

To generate RRs using infant mortality data, we used the gestational age–specific birth and death counts. We calculated RRs by weekly gestational age with collapsed groups of <20 weeks and >44 weeks and an additional category for unknown gestational age.

Stratified Analysis for Cancer Incidence and Mortality

The final analyses sought to separate the 2-step process of getting a disease and dying from the disease. We first calculated population-level gender- and age-specific incidence rate ratios for the 7 cancers, as classified by ICD-10 subchapters. We then computed the mortality proportion on the basis of the number of observed deaths and the number of incident diagnoses. Finally, we computed the population-level mortality incidence ratio of observed deaths to the overall population in each gender and age stratum. For each gender and age stratum and cancer type, we computed the RR (with 95% confidence interval [CI]) to examine the relationship between gender and incidence of, or death from, each cancer type. Pooled Mantel-Haenszel rate ratios within each age and cancer stratum were also provided.

Statistical Software

All data management and analyses were conducted by using Stata 12.1 (StataCorp, College Station, TX).

RESULTS

Mortality rate data from 1999 to 2008 revealed that the number of male deaths exceeded the number of female deaths for all pediatric age categories (Fig 1). A total of 34 577 more male infants died than female infants: 6461 more males among 1 to 4 year olds, 3691 among 5 to 9 year olds, 8221 among 10 to 14 year olds, and 58 425 more male deaths among 15 to 19 year olds, totaling 76 698 more male deaths.

Comparing male and female mortality by using age-stratified RRs for all causes of death (excluding ICD-10 codes 000-099: pregnancy, childbirth, and puerperium) further indicates an excess male mortality (Fig 2), measured in both an overall RR of 1.44 (95% CI: 1.44–1.45) and in each age stratum. As expected, the RR is most pronounced in adolescents and young adults aged 15 to 19 years (2.39; 95% CI: 2.37–2.42), but

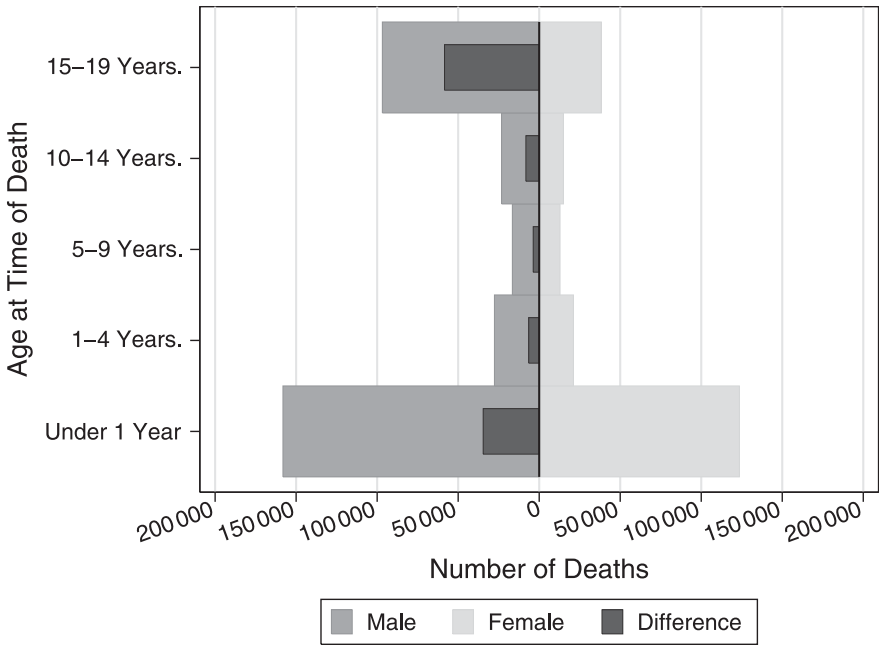

FIGURE 1
Excess number of pediatric male-to-female deaths by age. Data source: CDC WONDER database, 1999–2008.

even at a minimum, the RR is 1.20 (95% CI: 1.19–1.21) for children <1 year old.

Among infant deaths, data stratified by gestational age (Fig 3) indicate an overall RR of 1.12 (95% CI: 1.12–1.13) with a greater proportion of male compared with female deaths among all weekly gestational age strata >24 weeks.

Stratifying the pediatric population by the 19 ICD-10 major disease category chapters (Fig 4), the overall RR of 1.45 (95% CI: 1.45–1.46) is due to the significantly elevated excess male risk in 14 of 19 chapters. Two exceptions to the overall pattern of excess male mortality, namely, diseases of the musculoskeletal system and connective tissue (RR: 0.61; 95% CI: 0.54–0.69) and diseases of the skin and subcutaneous tissue (RR: 0.84; 95% CI: 0.62–1.13), are largely due to lupus (ICD-10 codes M320–M329). Females accounted for 278 (82.7%) of the 336 deaths attributed to systemic lupus erythematosus; similarly, 35 (38%) of 93 female deaths from diseases of skin and subcutaneous tissues were attributed to discoid lupus erythematosus (ICD-10 code L93.0). Other ICD-10 chapters exhibit relatively small numbers of deaths, including diseases of the eye and adnexa (15 females, 21 males) and diseases of the ear and mastoid process (49 females, 56 males), both of which show male excess.

External causes of morbidity and mortality account for 25.14% of all deaths in persons <20 years of age. Because males, particularly in the 15- to19-year-old age group, are significantly more likely to die of trauma and injuries (both accidental and nonaccidental), in a sensitivity analysis we removed fatalities attributed to ICD-10 chapter 20, "External causes of morbidity and mortality" (ICD-10 codes V01–Y98), from the analysis to determine whether these causes of death accounted for the gender differences. Even after omitting deaths due to external causes, the overall RR of males versus females dying remains unfavorable toward males (RR: 1.22; 95% CI: 1.21–1.23).

To examine whether excess male mortality was due to greater risk of males developing the condition that subsequently became the underlying cause of mortality or due to a greater risk among persons with the condition that males would die of the condition, we studied persons <20 years of age with cancer for whom both population-level incidence rate and mortality rate data are available. Males exceed females in terms of both cancer incidence (72 441 male incident cases, 61 948 female incident cases) and mortality (12 316 male deaths, 9476 female deaths). Focusing on 7 leading types of cancer (bone and joints, brain and other nervous system, soft tissue including heart, digestive system, endocrine system, lymphomas, and leukemia; these comprise 89% of all cancer deaths), the age-stratified pooled incidence rate ratio of males to females is 1.13 (95% CI: 1.12–1.14) indicating greater male incidence (Table 1), but with variation in the incidence rate ratio among the 7 cancers. The fatality ratio (ie, the number of deaths divided by the number of incident cases within each age- and gender-specific stratum) was 1.10 (95% CI: 1.07–1.13), which indicated that, overall, males with cancer were more likely to die of cancer than were females with cancer (although this finding was not consistent across all of the cancer types). Finally, with regard to the mortality incidence ratio (ie, the number of deaths divided by the total number of persons in the age and gender subpopulation), males exhibit excess mortality (RR: 1.21; 95% CI: 1.18–2.25), indicating that the combination of greater incidence risk and greater mortality proportion resulted in greater overall population-level risk, and this pattern was consistent for all 7 types of cancer.

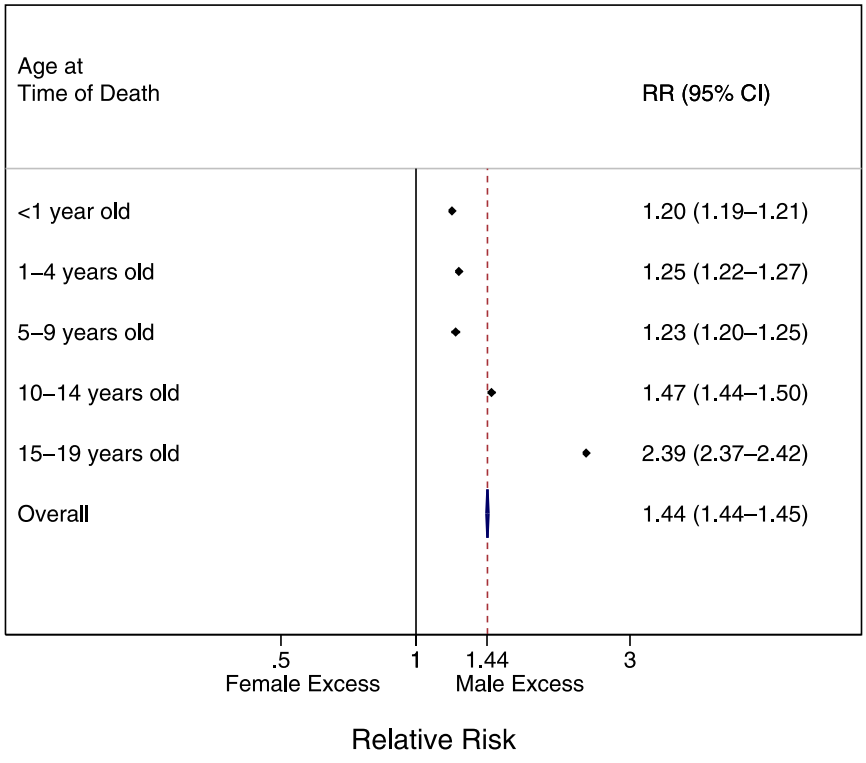

FIGURE 2
Excess pediatric male-to-female mortality by age. RR indicates relative risk of death of males compared with females within each age group stratum. Data source: CDC WONDER database, 1999–2008.

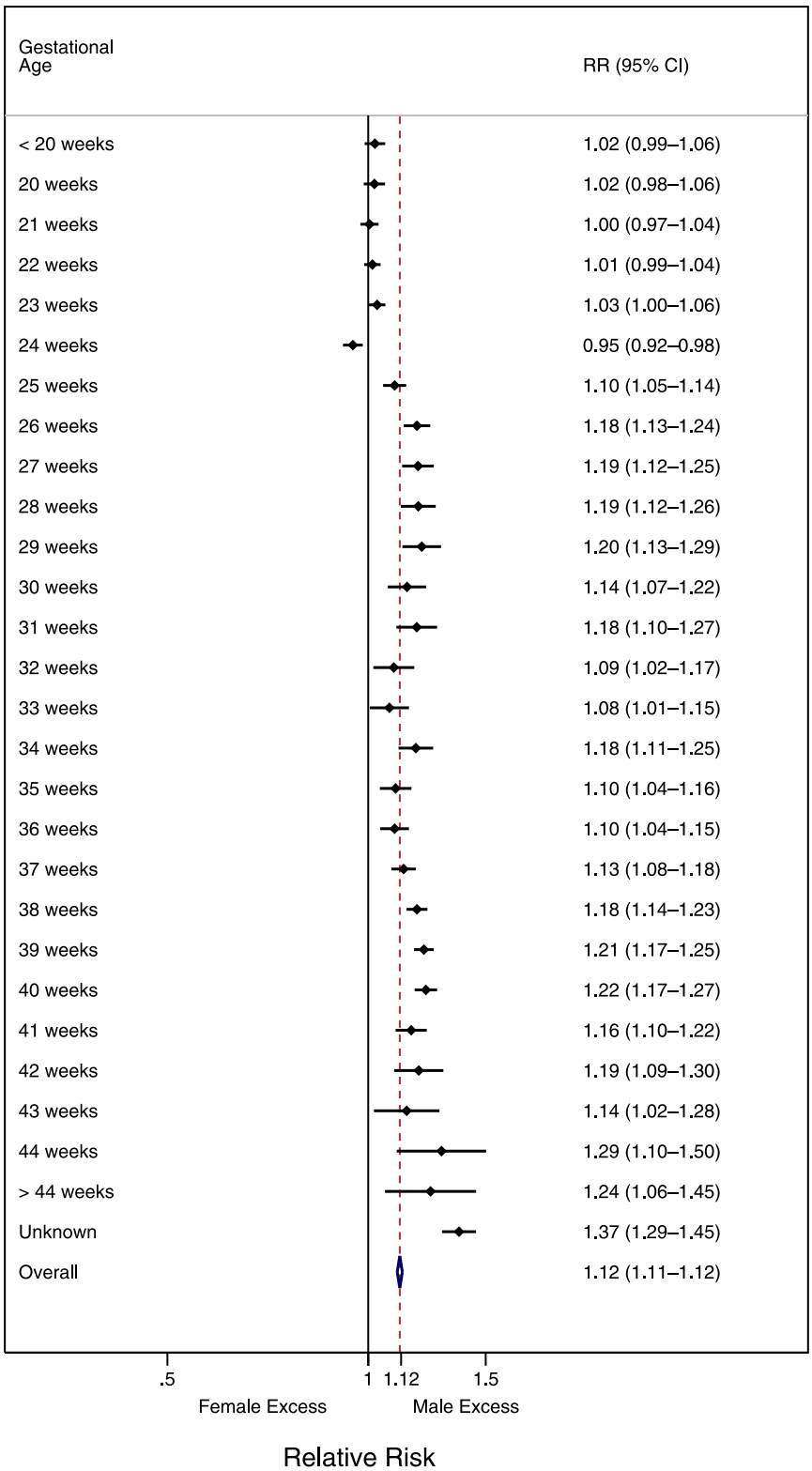

FIGURE 3

Excess infant male-to-female mortality by gestational age. RR indicates relative risk of death of males compared with females within each gestational age stratum. Data source: CDC WONDER database, 1999–2007, and linked infant birth/death records, 1999–2008.

DISCUSSION

Our analysis of the gender difference in mortality among persons <20 years of age suggests the existence of a "male syndrome." We observed an overall female survival advantage that starts early in life and exists across many diverse causes of mortality. In each 5-year-span age group, males are at significantly greater risk and the number of males who died between 1999 and 2008 exceeded the number of females by thousands. When stratifying by ICD-10 code for underlying cause of death, in only 2 of the 19 general disease categories do females have statistically significant higher mortality rates. In both of these instances (namely, diseases of the musculoskeletal system and connective tissue and diseases of the skin and subcutaneous tissue), lupus, an autoimmune disease known for higher prevalence in women, is responsible.[12,13] When stratifying infant deaths by estimated gestational age, after 24 weeks, females exhibit a constant advantage (overall RR: 1.12; 95% CI: 1.11–1.12). Finally, focusing on cancer-related deaths, although females may have reduced incidence or mortality risks within age groups or cancer types, the overall pattern still inclines toward greater male incidence and mortality.

These findings should be interpreted with both the strengths and weaknesses of our study in mind. The population basis of the study and the comparison of rates by age and underlying cause of death enable a broader view of the male syndrome phenomenon. Inquiry into the mortality gender differential should distinguish between the risk of becoming an incidence case and the risk of dying from a condition once contracted. In this regard, we used the population-level incident data available from the CDC's infant linked birth/death files, for which the estimated gestational age at birth essentially identifies an infant as an incident case of premature birth,

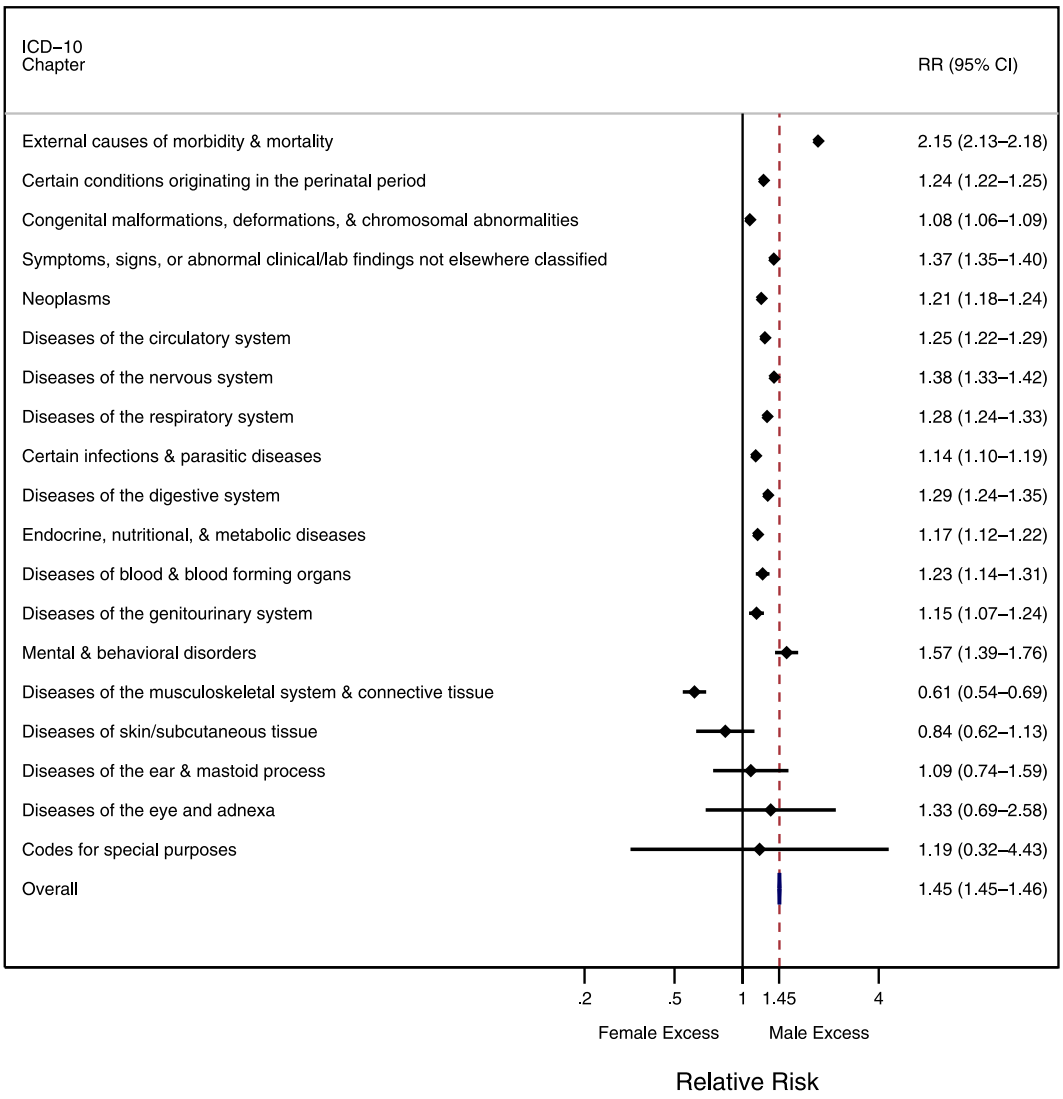

FIGURE 4
Excess male-to-female mortality by ICD-10 chapter. RR indicates relative risk of death of males compared with females within each ICD-10 chapter stratum. Data source: CDC WONDER database, 1999–2008.

and from SEER, which routinely tracks incident cancer diagnoses and deaths. Regarding weaknesses, the accuracy of ICD-10 coding for Underlying Cause of Death in death certificate data is subject to 8 sources of coding errors,[14] but these errors are unlikely to be associated with the decedent's gender and thus not the source of the observed gender difference. Without reliably coded population-level data regarding disease incidence for conditions other than premature birth or cancer, our examination of the paradox between female morbidity and mortality (whereby adult females have been shown to be more likely to contract a number of conditions but less likely to die of them[15–18]) is limited. Finally, although the differential mortality rates may be modified by social, cultural, or economic factors, we did not have data elements to examine these possibilities.

Further research is warranted to better understand the mechanisms that account for this pervasive female advantage across age and cause of death and in children. To date, the literature concerning the gender disparity in mortality rates has often focused on behavioral factors, such as the greater rates of smoking that result in more ischemic heart disease and cardiovascular deaths in adult males.[19] Studies have also examined differences in infant and pediatric mortality rates across underdeveloped, developing, and developed countries, postulating the effects of biased gender attitudes and differential impact of technological advances (which have curbed the number of deaths due to childbirth and other conditions that historically have a female excess).[9,20] The mortality difference between males

TABLE 1 Cancer Incidence, Mortality Proportion, and Mortality Incidence Stratified by Cancer Type and Age, 1999–2008

Cancer Type and Age	Disease Incidence			Fatality Ratio			Mortality Incidence		
	Dx/Pop	95% CI	P (χ^2)	Deaths/Dx	95% CI	P (χ^2)	Deaths/Pop	95% CI	P (χ^2)
Leukemia			<.001			.326			.002
<1 year	1.00	0.92–1.11		0.94	0.73–1.20		0.95	0.74–1.21	
1–4 years	1.18	1.13–1.22		0.98	0.88–1.10		1.17	1.04–1.31	
5–9 years	1.15	1.10–1.21		1.08	0.97–1.20		1.24	1.11–1.38	
10–14 years	1.23	1.17–1.30		1.01	0.91–1.11		1.24	1.12–1.37	
15–19 years	1.55	1.47–1.64		0.93	0.85–1.02		1.45	1.32–1.58	
M-H pooled	1.23	1.20–1.26		0.99	0.94–1.04		1.27	1.21–1.34	
Brain and nervous system			.009			.037			<.001
<1 year	0.98	0.88–1.09		1.15	0.83–1.60		1.13	0.81–1.57	
1–4 years	1.10	1.05–1.16		1.02	0.90–1.15		1.12	0.99–1.27	
5–9 years	1.14	1.08–1.20		0.89	0.81–0.98		1.01	0.92–1.11	
10–14 years	1.10	1.04–1.16		0.99	0.89–1.10		1.08	0.97–1.20	
15–19 years	1.20	1.13–1.28		1.12	0.99–1.27		1.35	1.19–1.52	
M-H pooled	1.12	1.09–1.15		0.99	0.94–1.04		1.11	1.06–1.18	
Lymphomas			<.001			.028			.351
<1 year	1.07	0.75–1.53		N/A			N/A		
1–4 years	1.90	1.68–2.15		0.88	0.53–1.51		1.68	1.01–2.87	
5–9 years	2.40	2.20–2.62		0.99	0.71–1.40		2.37	1.70–3.35	
10–14 years	1.55	1.46–1.64		1.36	1.06–1.75		2.10	1.63–2.71	
15–19 years	1.16	1.12–1.21		1.54	1.32–1.80		1.78	1.53–2.09	
M-H pooled	1.41	1.37–1.46		1.37	1.21–1.54		1.92	1.71–2.16	
Endocrine system			<.001			<.001			.624
<1 year	1.24	1.10–1.41		0.96	0.59–1.60		1.20	0.73–1.99	
1–4 years	1.24	1.13–1.36		0.91	0.79–1.06		1.13	0.97–1.32	
5–9 years	1.02	0.88–1.18		1.26	1.08–1.47		1.28	1.10–1.50	
10–14 years	0.59	0.53–0.66		1.74	1.34–2.25		1.03	0.80–1.33	
15–19 years	0.28	0.26–0.30		4.19	2.94–5.99		1.18	0.83–1.69	
M-H pooled	0.58	0.56–0.61		1.25	1.14–1.36		1.18	1.07–1.29	
Soft tissue including heart			.065			.931			.510
<1 year	0.97	0.87–1.09		1.03	0.54–1.96		1.00	0.52–1.91	
1–4 years	0.95	0.86–1.05		1.17	0.88–1.56		1.11	0.83–1.48	
5–9 years	1.08	0.96–1.22		1.07	0.83–1.38		1.16	0.90–1.49	
10–14 years	0.96	0.87–1.06		1.02	0.82–1.26		0.98	0.79–1.22	
15–19 years	1.10	1.02–1.20		1.12	0.96–1.31		1.24	1.06–1.45	
M-H pooled	1.02	0.97–1.06		1.09	0.99–1.21		1.14	1.03–1.26	
Bone and joints			<.001			.755			<.001
<1 year	0.77	0.44–1.23		N/A			N/A		
1–4 years	1.13	0.89–1.44		N/A			N/A		
5–9 years	1.01	0.89–1.13		0.85	0.61–1.17		0.85	0.62–1.17	
10–14 years	1.03	0.95–1.11		0.97	0.82–1.15		0.99	0.84–1.17	
15–19 years	1.69	1.57–1.82		0.94	0.83–1.07		1.59	1.41–1.80	
M-H pooled	1.26	1.20–1.32		0.94	0.86–1.03		1.30	1.18–1.42	
Digestive system			.093			.932			.711
<1 year	1.09	0.95–1.26		1.20	0.69–2.12		1.31	0.75–2.32	
1–4 years	1.18	1.06–1.32		1.41	1.07–1.87		1.67	1.27–2.21	
5–9 years	0.96	0.78–1.18		1.61	1.03–2.54		1.54	0.99–2.44	
10–14 years	0.93	0.78–1.11		1.32	0.92–1.92		1.23	0.85–1.78	
15–19 years	1.01	0.90–1.13		1.41	1.12–1.79		1.43	1.13–1.80	
M-H pooled	1.06	1.00–1.13		1.40	1.22–1.61		1.46	1.27–1.68	
All 7 above cancers			<.001			<.001			<.001
<1 year	1.04	0.99–1.09		1.01	0.86–1.20		1.05	0.89–1.24	
1–4 years	1.17	1.14–1.20		1.00	0.94–1.07		1.02	0.95–1.09	
5–9 years	1.23	1.20–1.27		0.94	0.89–1.99		1.16	1.10–1.23	
10–14 years	1.14	1.11–1.17		1.02	0.96–1.08		1.16	1.10–1.23	
15–19 years	1.05	1.03–1.08		1.38	1.31–1.46		1.45	1.38–1.53	
M-H pooled	1.13	1.12–1.14		1.10	1.07–1.13		1.21	1.18–1.25	

Dx, incident diagnoses; M-H pooled, Mantel-Haenszel pooled estimate across the age strata; Pop, population at risk.

and females is thus attributed to a complex web of factors that include acquired risks (lifestyle, risks encountered in work or leisure activities, health habits), health-reporting behavior, illness behavior, health care utilization, and biology.[17,18,20,21] Even these studies, however, acknowledge that in developed nations where women are educated, gender biases are lessened, and medical technology is advanced, there is likely an underlying biologically based difference between male and female mortality.[9]

What are the possible biological mechanisms, which are often cited but, remarkably, little explored?[3] Two sets of hypotheses are worth pursuing. First, males and females differ substantially regarding their respective human sex chromosome composition.[22] Whereas the X chromosome has 836 active protein-coding genes, the Y chromosome has 52 active genes (of which 25 are specific to males only, whereas 27 genes are in the Y chromosome's pseudoautosomal region and are also found on the X chromosome). Because most X chromosome genes are present in only 1 copy in males, the risk of recessive disease vulnerability is increased. Furthermore, meiotic pairing is more challenging for the X/Y chromosomal pair than for the X/X pair, and the majority of the Y chromosome cannot undergo meiotic recombination, diminishing the ability for repair of genetic errors, and thus increasing the risk of deleterious genes. Second, males and females experience during childhood a variety of hormonal differences stemming from male-specific genes and the male developmental pathway, which in turn may result in differential risk of either disease development or fatality rate among males with a disease. Whatever the factors are contributing to the mortality difference, they appear to influence not only the occurrence of disease or conditions but also the ability to survive with the condition, acting perhaps as a robustness enhancer that is present to a greater degree in females and that appears to be beneficial across a broad array of diverse conditions.

CONCLUSIONS

Male infants, children, adolescents, and young adults experience an elevate risk of mortality compared with females. This excess mortality is attributable to a wide variety of conditions, and this effect appears to be due to elevated risk both of contracting high-mortality conditions and, once afflicted, dying of these conditions. The mechanisms underlying these phenomena warrant investigation.

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