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Natality Decline and Spatial Variation in Excess Death Rates During the 1918–1920 Influenza Pandemic in Arizona, United States

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A large body of epidemiologic research has concentrated on the 1918 influenza pandemic, but more work is needed to understand spatial variation in pandemic mortality and its effects on natality. We collected and analyzed 35,151 death records from Arizona for 1915–1921 and 21,334 birth records from Maricopa county for 1915–1925. We estimated the number of excess deaths and births before, during, and after the pandemic period, and we found a significant decline in the number of births occurring 9–11 months after peak pandemic mortality. Moreover, excess mortality rates were highest in northern Arizona counties, where Native Americans were historically concentrated, suggesting a link between ethnic and/or sociodemographic factors and risk of pandemic-related death. The relationship between birth patterns and pandemic mortality risk should be further studied at different spatial scales and in different ethnic groups.

1918–1920; Arizona; birth; excess mortality; influenza pandemic; Maricopa county; natality

Abbreviation: P&I, pneumonia and influenza.

The Spanish Flu of 1918–1920 was called "the mother of all pandemics" due to its devastating global mortality impact, estimated at 50 million deaths, or 1%–2% of the world population at the time (1, 2). The case fatality rate of this pandemic is estimated at approximately 2.5%—several-fold higher than that of typical seasonal influenza epidemics (1). Another salient feature of this pandemic is the atypical peak of mortality among young adults (3). Multiple pandemic waves occurred during 1918–1920, and areas in the Northern Hemisphere were more likely to experience a "herald wave" in early 1918 (1, 4–6). While our understanding of the mortality impact of this pandemic has improved in recent years, much less is known about the pandemic impact on natality. This is important given that influenza vaccination during pregnancy is currently being promoted. Further, more work is needed to disentangle the local circumstances that shaped pandemic mortality rates across different populations (7).

A lethal influenza pandemic may influence birth rate patterns (8–10) because pregnancy leads to physiological, hormonal, and immunologic changes that are known to heighten the risk of illness and death associated with influenza infection (11, 12). For instance, a cross-sectional study of pregnant women hospitalized during the 1918 influenza pandemic in Maryland, in the United States, found that about half of the pregnant women developed pneumonia, of whom 50% succumbed, with a case fatality rate of 27% (13). Also, a 1957 influenza pandemic study from Minnesota documented that about 50% of deaths among women of reproductive age occurred among pregnant women (14). Furthermore, recent studies have suggested a link between influenza infection in early pregnancy and an increased risk of fetal death (15). Accordingly, US and Scandinavian populations experienced a 5%–15% drop in natality rate 6–7 months after the 1918 pandemic, suggesting an increased risk of miscarriage in the first trimester (9). A similar association was reported during the 1957 pandemic (13, 16). However, prior studies of the 1918 pandemic have focused on highly aggregated national birth statistics, rather than detailed information available from individual birth certificates; further, no study has explored birth patterns in particularly hard hit and low-income populations.

Increasing epidemiologic evidence indicates that the 1918 pandemic was far from a "democratic disease." Indeed, differences in socioeconomic conditions or residual immunity acquired from prior exposure to related influenza viruses have been hypothesized to drive mortality differences (17–20). A seminal study proposed that national income differences could in

part explain an approximately 30-fold variation in 1918 pandemic mortality rates across 20 countries (7). Further work is needed to better understand the spatial heterogeneity in 1918 pandemic mortality impact at finer spatial scales.

In this paper we harness information from 35,151 individual death certificates to analyze differences in pandemic-related excess mortality rates across 13 counties of Arizona. Prior work has shown that the 1918–1920 pandemic killed about 0.8% of the population in Arizona (19), which is one of the highest pandemic mortality rates reported in the United States (21, 22). We also analyzed 21,334 individual birth certificates to quantify the impact of the 1918–1920 influenza pandemic on natality fluctuations in Maricopa county, the most populous county in Arizona state.

METHODS

Study setting

Arizona became a US state in 1912, a few years prior to the 1918 influenza pandemic, and did not become a US vital registration state until 1926 (23); therefore, alternative data sources have to be queried to explore mortality and natality during the pandemic period. Maricopa county is the largest county in this state. In 1920, Maricopa county represented 26.8% of the Arizona population (24). Between 1910 and 1920 the population of Maricopa county increased from 34,488 to 89,576 (see Figure 1 for a county map of Arizona).

Arizona is unique because of its large population of Native Americans and its historical concentration of tuberculosis sanatoriums, due to a dry and arid climate (25). Arizona is one of 4 states with more than 100,000 Native Americans (26). Well-known Native American tribes in Arizona include Apache, Hopi, Maricopa, Navajo, Papago, Pima, Yavapai, and Yuma. More than 20 Native American reservations have covered one-fourth of the state's surface area. Of these, the Navajo and the Tohono O'odham are the largest reservations in the United States (27). The Navajo reservation include areas in the Apache, Navajo, and Coconino counties, whereas the Tohono O'odham reservation lies in central Pima and includes southwestern Pinal and southeastern Maricopa counties. Overall, the northeastern part of Arizona has a higher residence of Native Americans (28, 29).

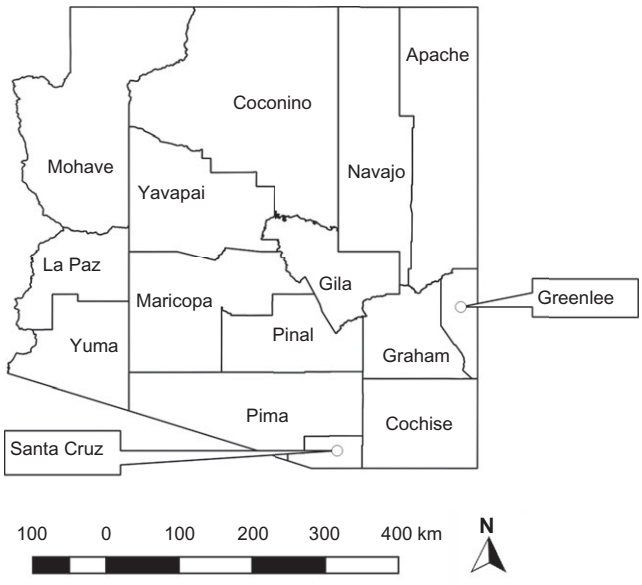

Figure 1. Counties in the US state of Arizona.

The state of Arizona had one of the highest tuberculosis death rates (25), the highest infant mortality rate, and, in its capital city (Phoenix), some of the "worst slums" in the country (30, 31). During 1918–1920, many minority households relied on irrigation canals for drinking water and for bathing (30). Infant mortality rates among black persons, Hispanics, and Native Americans were 2–3 times higher than among white persons (30, 32).

Data sources

The *Arizona Genealogy Database* (http://genealogy.az.gov/) is a freely available online resource of all birth records generated during the years 1855–1941 and all death certificates recorded during the years 1870–1996 for the state of Arizona. We manually retrieved a total of 21,334 birth records from January 1915 to December 1925 for Maricopa county, Arizona, from this database. For each birth record, we retrieved the date of birth and compiled monthly birth time series, as in a previous study (see Chandra and Yu (10)).

Similarly, to assess the timing and mortality impact of the 1918–1920 influenza pandemic, we manually retrieved a total of 35,151 individual death records from January 1915 to December 1921 for Arizona. For each death record, we compiled date of death, county of death, cause of death, and age at death. We then created weekly and monthly time series of deaths attributed to pneumonia and influenza (P&I) and to all causes, which are traditionally used to monitor the impact of influenza.

We also derived the overall and age-specific population estimates of the 13 Arizona counties from 1915 to 1925 by linear interpolation of estimates available for decennial censuses in 1910, 1920, and 1930 (24, 33). Two counties, Greenlee and Lapaz, were excluded from analysis due to lack of population data.

Statistical analysis

Pandemic period and excess deaths. To define the pandemic period, we determined the most likely period of pandemic influenza activity from the time series of weekly P&I death rates, the most specific indicator of influenza. We first estimated baseline mortality levels by fitting cyclical Serfling regression models to P&I deaths in noninfluenza weeks as in previous studies (19, 34). Periods of pandemic influenza circulation corresponded to those weeks in 1918–1921 where the observed total P&I mortality rate exceeded the upper 95% confidence limit of the baseline level (19, 21, 34). These pandemic periods were used to assess mortality and natality estimation for different counties, sexes, age groups, and causes of death (19). For each county, we estimated excess mortality rates for total population as well as children (<5 years) during the main pandemic wave (October to December) of 1918. We also classified our study period into 3 categories—before the pandemic, during the pandemic, and after the pandemic—based on observed P&I mortality patterns (we return to this later). We

Table 1. Three Study Periods, Maricopa County, Arizona, 1915–1921

Period	Definition	Dates	*t* (Month No.)[a]
1	Before the pandemic	January 1915 to March 1918	1–39
2	Pandemic	April 1918 to April 1920 + 10 months	40–(64 + 10)[b]
3	After the pandemic	March 1921 to December 1925	75–132

[a] *t* is a running number for month, starting from January 1915 (*t* = 1 for January 1915).
[b] A lag up to 10 months was considered between influenza activity and birth, to fully account for pregnancy.

added 10 months to the pandemic period to account for the duration of pregnancy, in line with the expected delay between pandemic activity and birth outcomes (10).

Estimation of seasonally and trend-adjusted excess births and deaths. After removing the seasonality and long-term trend components using moving averages, the residual components of the birth and death time series were extracted to capture the corresponding birth and death counts associated with the pandemic. We then estimated the cross-correlation coefficients of P&I deaths and births to identify temporal associations between pandemic influenza and natality at different lags, as in previous studies (10, 35, 36). We estimated these coefficients to identify temporal associations between monthly deaths and births during the pandemic period.

The following definition of cross-correlation coefficient was used (35):

$$r_{\mathrm{db}}(k) = \frac{C_{db}}{S_d S_b},$$

where

$$C_{\mathrm{db}}(k) = \begin{cases} \frac{1}{n}\sum_{t=1}^{n-k} (d_t - \bar{d})(b_{t+k} - \bar{b}), k = 0,\ 1,\ 2, \cdots,\ 12 \\ \frac{1}{n}\sum_{t=1}^{n+k} (b_t - \bar{b})(d_{t-k} - \bar{d}), k = 0, -1, -2, \cdots, -12 \end{cases},$$

where, d_t, b_t, and k represent deaths in month t, births in month t, and the time difference between the birth and death series (i.e., the number of time lags or leads), respectively. In this study, cross-correlations with lags or leads of up to 12 months ($-12 \le k \le 12$) were estimated for the period of 1915–1921. Then, we employed the augmented Dickey-Fuller test for stationarity analysis, Mann-Kendall test for trend analysis, and null hypotheses of zero cross-correlation for each of the estimated correlation coefficients.

All *P* values reported are 2-sided. Statistical analyses were performed in SAS, version 9.4 (SAS Institute Inc., Cary, North Carolina), and R, version 3.2.3 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Pandemic waves

Based on the time series of P&I deaths, 4 different pandemic waves were identified in Arizona: spring 1918 (April 1918), fall 1918 (October to December 1918), winter 1919 (January to April 1919), and winter 1920 (February to April 1920). Accordingly, we defined our 3 study periods as follows: 1) before the pandemic (January 1915 to March 1918); 2) pandemic (April 1918 to April 1920 plus 10 months); and 3) after the pandemic (March 1921 to December 1925) (Table 1).

Seasonally and trend-adjusted excess births and deaths, Maricopa county

Figure 2 displays the time series of seasonally and trend-adjusted excess births and deaths for Maricopa county, Arizona, between 1915 and 1921, stratified by sex. A small peak in births was observed immediately after pandemic mortality peaked in males and females, while deep troughs in births occurred about 10 months after the peak in pandemic mortality. To formally test the time scale of the association between pandemic activity and births, we calculated the cross-correlation between excess births and sex-specific P&I deaths in individuals aged 10–49 years. We found a significant negative association between influenza deaths in males at time *t* and births 9–10 months later, and 10–11 months later for female deaths (Figure 3). A natality dip of approximately 43% was observed in July 1919; dips of this size were not seen at any other time point during 1915–1921.

Spatial analysis of pandemic excess mortality according to time period

The total excess mortality rates according to mortality outcomes, sex, and pandemic waves are shown in Table 2. For the total pandemic period, total P&I excess death rates per 10,000 population were 98.3 for males and 75.9 for females. For both males and females, the highest P&I and all-cause death rates were recorded during the main pandemic wave in fall 1918. In relative terms, during the pandemic period the observed P&I mortality rates were about 5 times and 4 times above the baseline for males and females, respectively (Table 2). The mortality rate ratio of male to female deaths was 1.23.

We also estimated county-specific excess mortality rates for all ages and for children aged <5 years for 13 counties in Arizona that provided appropriately stratified data (Table 3). We found that northern counties had higher excess P&I and all-cause mortality overall and for children aged <5 years. Northern counties Apache, Coconino, Mohave, and Navajo had significantly higher excess P&I mortality for children aged <5 years (mean rank = 10.50) compared with other counties (all other counties categorized as "others"; mean rank = 5.44) (Mann-Whitney *U* test, $P < 0.05$). However, there was no statistically significant mortality

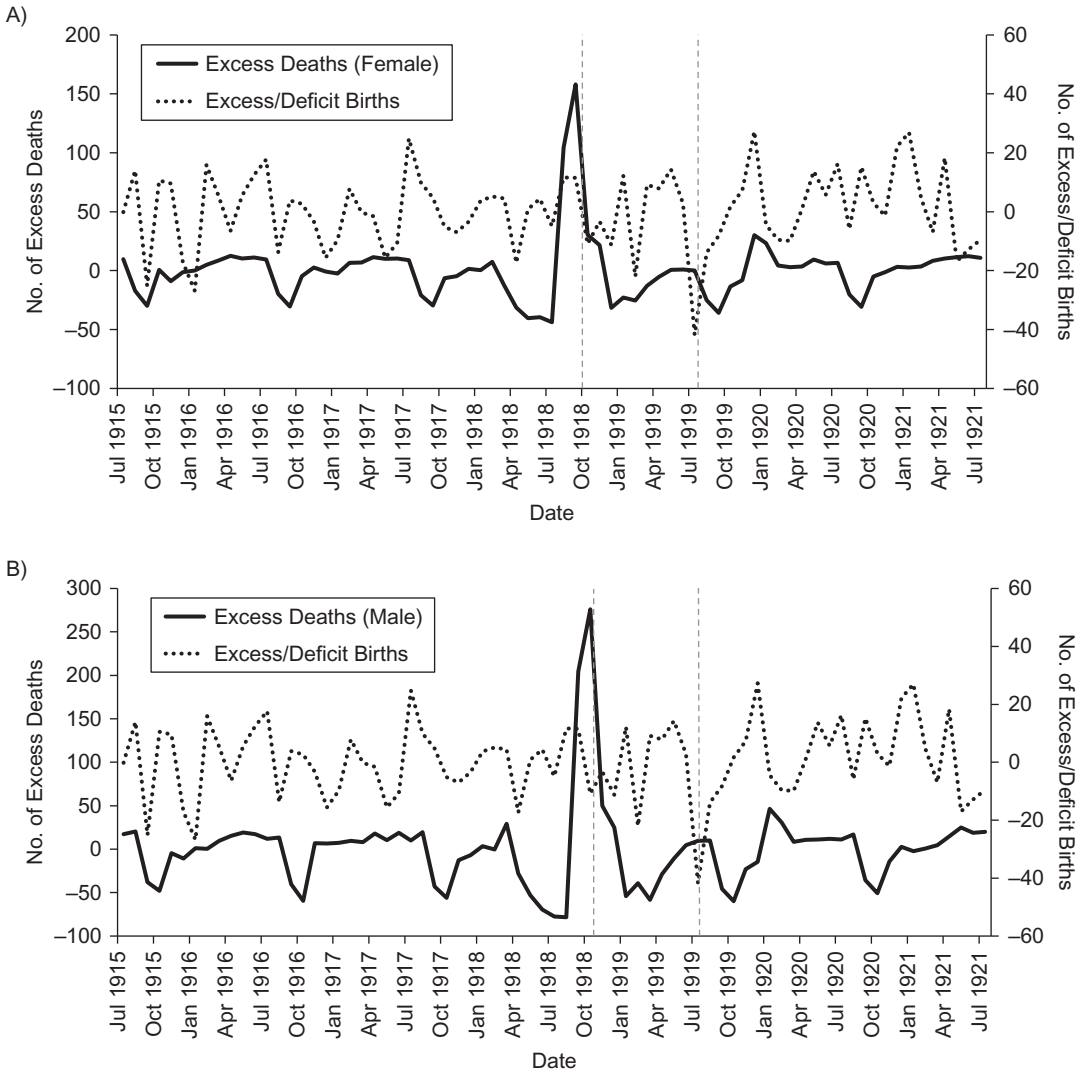

Figure 2. Excess and deficit births and excess pneumonia and influenza deaths, according to sex, Maricopa County, Arizona, 1915–1921. Time series of seasonally and trend-adjusted variance in births and excess number of pneumonia and influenza deaths is presented for female (A) and male (B) persons. The vertical dashed lines indicate the timing of peak excess deaths and deficit births, respectively.

difference in all-age or all-cause deaths (Mann-Whitney *U* test, $P > 0.05$).

DISCUSSION

In this study, we investigated the impact of the 1918 influenza pandemic on natality fluctuations as well as on county-level mortality in the state of Arizona. We expected a natality decline in the months following peak pandemic activity, as observed in a previous study set in the United States (9). Although the time series of excess/deficit births fluctuated over time in Maricopa County, Arizona, we found a statistically significant dip of approximately 43% in births 9–11 months after peak pandemic mortality. While smaller natality drops were seen in earlier years, a drop of this magnitude was unique to the period after the pandemic, suggesting an effect of the pandemic on natality. We also found higher pandemic-related death rates in northern Arizona counties, where Native Americans were historically concentrated.

Indigenous populations have been disproportionately affected during past influenza pandemics (37, 38). For example, in New Zealand, the death rate among the Maori was at least 7.3 times higher than the corresponding death rate for the rest of the population (38). Similarly, the mortality ratios for indigenous populations relative to European populations in the continental United States and Canada were found to be 3.2 and 4.8 during the 1918 pandemic, respectively (37). Likewise, our results suggest that northern counties in Arizona with high Native American population density (e.g., Apache, Coconino, and Navajo) experienced higher excess pandemic death rates compared with other counties in the state. Anecdotal evidence recorded in the Arizona Bulletin of 1918 indicated that northern cities with a significant proportion

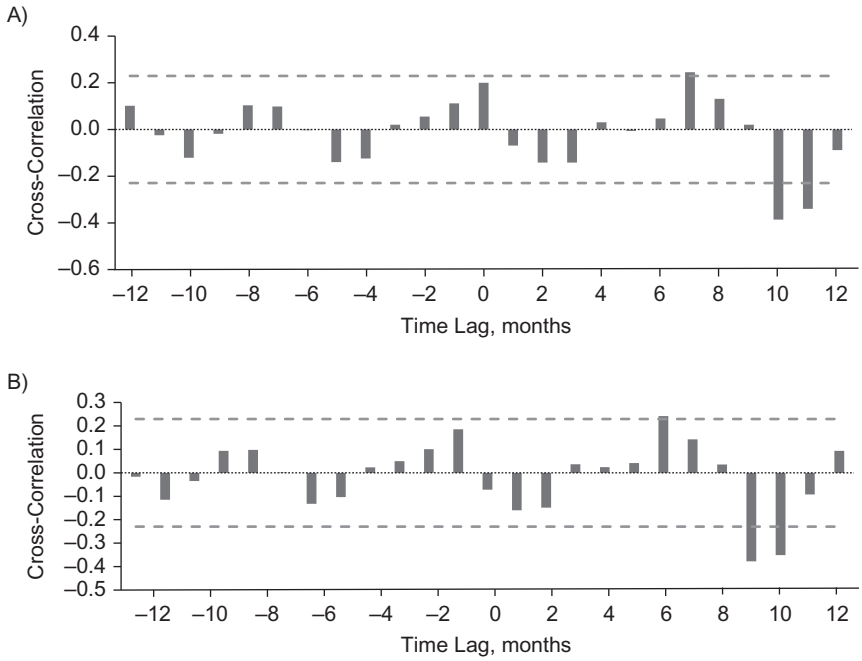

Figure 3. Cross-correlations between the excess number of pneumonia and influenza deaths and excess births, Maricopa County, Arizona, 1915–1921. Cross-correlation coefficients were calculated at each lag and lead period (−12 to +12 months); 0 indicates no lag. A) Female persons. B) Male persons. Bars represent cross-correlation coefficients between birth and death time series, and the horizontal dashed lines are the confidence interval (CI) for the null hypothesis of zero correlation between birth and death time series (upper CI = 0.23, lower CI = 0.23).

of Native Americans (27, 28) (Winslow, Holbrook, and Flagstaff) required assistance in confronting the pandemic (29). We note that quantitative data on the proportion of Native Americans by county was not available; further work should focus on exploring the association between influenza death rates and ethnicity in a more quantitative manner.

We also found high excess mortality rates in the southern mining counties of Cochise and Yuma. Cochise county was one of

Table 2. Estimates of Excess Mortality Rate per 10,000 Population and Rate Ratio Attributable to Pandemic Influenza, According to Time of Pandemic Wave and Sex, Maricopa County, Arizona, 1918–1921

Cause of Death and Pandemic Wave	Male		Female	
	Excess Death Rate per 10,000 Population	RR	Excess Death Rate per 10,000 Population	RR
P&I deaths				
Spring 1918 (April 1918)	0.23	1.26	0.25	1.22
Fall 1918 (October to December, 1918)	63.78	10.32	48.7	7.85
Winter 1919 (January to April 1919)	20.89	3.06	18.67	2.75
Winter 1920 (February 1st to April 11th, 1920)	13.42	3.13	8.26	2.53
Total pandemic period	98.32	5.07	75.88	4.12
All-cause deaths				
Spring 1918 (April 1918)	3.5	1.21	4.77	1.40
Fall 1918 (October to December 1918)	67.45	2.22	49.08	2.22
Winter 1919 (January to April 1919)	17.17	1.25	13.0	1.26
Winter 1920 (February 1st to April 11th, 1920)	13.54	1.25	13.7	1.41
Total pandemic period	101.66	1.52	80.55	1.60

Abbreviations: P&I, pneumonia and influenza; RR, rate ratio.

Table 3. Country-Specific Excess Pneumonia and Influenza and All-Cause Mortality Rates per 10,000 for Children Aged <5 Years and All Ages, Pandemic Influenza Wave, Arizona, Fall 1918

County	Excess P&I Mortality Among Ages <5 Years	Excess All-Cause Mortality Among Ages <5 Years	Excess P&I Mortality Among Total Population	Excess All-Cause Mortality Among Total Population
Apache[a]	150.30	86.00	82.92	76.05
Coconino[a]	225.80	168.20	131.68	120.20
Gila[a]	131.80	94.10	94.41	88.09
Mohave[a]	302.60	207.70	115.02	115.98
Navajo[a]	88.80	72.00	25.59	24.98
Yavapai[a]	121.60	109.50	80.46	82.36
Maricopa	64.90	54.20	56.83	58.91
Cochise[b]	111.30	110.30	68.65	69.61
Graham[b]	45.50	15.20	20.94	21.02
Pima[b]	47.50	88.10	52.99	70.88
Pinal[b]	74.30	89.30	48.05	56.91
Santa Cruz[b]	62.90	48.90	28.55	34.91
Yuma[b]	146.70	124.90	78.20	90.66

Abbreviation: P&I, pneumonia and influenza.
[a] Northern Arizona.
[b] Southern Arizona.

the counties that had operating copper mines and smelters, and Yuma county had one of the oldest silver and lead mines in the state. Mining activity could be a proxy for lower socioeconomic conditions. We cannot rule out additional within-county variability in socioeconomic factors, including, nutritional status, overall baseline health, and access to hospital care. For instance, some of the lowest pandemic mortality rates were observed in Maricopa county, within which South Phoenix was a rather stigmatized and degraded minority district (30). The study of within-county variation in pandemic mortality calls for more spatially resolved data sets.

It is important to highlight that at the time of the pandemic, the state of Arizona was characterized by significant contamination issues, lack of potable water, crowding, substandard housing, and a lack of health care for minorities (29, 30). On one hand, the state was advertised as a privileged location for health seekers due to its dry climate and pure air, but on the other hand many lived in ill-ventilated buildings and were at high risk of contracting infectious diseases (29). Many minority families in Phoenix were found to be eating and sleeping in a single room, and children were found living in the same room with persons afflicted with tuberculosis (30). Arizona had the highest infant mortality rate of all US states, particularly among minorities (30, 31). In this context, perhaps it is not surprising that the 1918 influenza pandemic disproportionately affected lower socioeconomic groups, including Native American populations geographically concentrated in northern counties.

Our study is subject to several limitations. First, due to lack of laboratory confirmation of influenza infection in the era before virology, our excess mortality approach would not have been able to distinguish elevation in mortality rates associated with noninfluenza respiratory causes and coinciding with the pandemic period. Second, we did not model other factors associated with World War I that could have influenced fertility rates (39). Third, a more refined analysis at the neighborhood level could have revealed more clearly the association of specific risk factors, including tuberculosis, income, occupation, and ethnicity (40).

In summary, we report a significant dip in excess births about 9–11 months following the peak in excess pandemic mortality. This period surpasses the expected 9 months of pregnancy and may be due to delays in reporting births or a stronger impact of influenza on pregnancy in the later part of the fall pandemic wave. Our results also show significant county-level variation in excess mortality rates during the 1918 influenza pandemic. For instance, we found that Arizona counties with relatively higher Native American population located in northern Arizona were disproportionately affected by the pandemic. Future research is needed to disentangle spatial variation in excess mortality and birth rates at finer spatial resolutions (e.g., neighborhood) in relation to demographic and socioeconomic indicators.

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