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Breakout sessions: Mental health & wellbeing 1

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The effects of in-utero exposure to Influenza on the mental health in childhood and longevity of British cohort

Alex Turner
2nd year PhD student
Manchester Centre for Health Economics
alexander.turner@manchester.ac.uk

Co-Authors: Matt Sutton, Eleonora Fichera

Background

- During the past decade, the effect of early-life conditions on health and non-health outcomes later in life has become a focal point of research in economics and related fields.
- The later-life effects of conditions *in-utero* have become of particular interest (Almond & Currie, 2011).
- However, a major concern is that early-life conditions and outcomes later in life, are jointly dependent on unobserved confounders.
- To identify causality, exogenous variation in early-life conditions is required.
- A large amount of studies have used temporal or geographical variation in exposure to influenza epidemics *in-utero* to identify causality.
- The idea is that being *in-utero* in an epidemic period and/or in areas where the epidemics were particularly severe, increases the likelihood of being exposed to influenza.

Influenza pandemic as natural experiments

- Most existing evidence is based on the 1918 influenza pandemic
  - Diabetes & cardiovascular disease (e.g. Almond and Mazumder, 2005)
  - Educational attainment (e.g. Neelsen and Stratmann, 2012)
  - Income & employment (e.g. Almond, 2006; Nelson, 2010)
- Kelly (2010) uses geographical variation in the 1957 Asian flu epidemic in the UK
  - Uses data from the National Child Development Study (NCDS), to study the effects of *in-utero* exposure to influenza on physical health and cognitive ability in childhood.
  - The NCDS is a British cohort dataset following a group of approximately 17,000 individuals born from 2nd -9th March 1958 from birth until present day, collecting data throughout childhood and adulthood.
  - The NCDS cohort were between 8 and 25 weeks into gestation in the epidemic period
  - The identification strategy uses exogenous geographical variation in the severity of the 1957 Asian influenza epidemic across 172 Local Authorities of Great Britain, proxied using pneumonia rates, as influenza was not a notifiable disease in 1957
  - They find that being *in-utero* in areas of higher epidemic intensity led to a reduction in cognitive ability at ages 7 and 11, and a reduction in height for children whose mothers smoked prior to pregnancy.

Gaps in the existing literature

- Lack of studies examining key health outcomes
  - Premature mortality
  - Mental health, and particularly childhood mental health (Adhvaryu et al., 2015)
    - Poor childhood mental health associated with a range of negative outcomes throughout the lifecourse.
- Previous studies don't estimate the treatment effect on the treated.
  - Exposure to an epidemic *in-utero* is not equivalent to exposure to influenza directly.
  - Therefore studies relying solely on area-level data on influenza exposure, will not estimate the effect of being exposed to an epidemic.
  - To examine this, individual-level data on influenza exposure is required.

Our study

- Use newly released data on whether mothers of NCDS cohort members contracted influenza during pregnancy.
- Use the severity of the 1957 influenza epidemic in the local authority of birth as an instrument for individual-level exposure to influenza.
  - This has the potential to recover the treatment effect on the treated.
- Study the effects of *in-utero* exposure to influenza on mental health at ages 7 and 11, and on premature mortality measured using data on stillbirths and death by ages 7, 11, 16, 23, 33, 42, 46, 50 and 55.

Mechanisms: in-utero exposure to flu and mental health

Brain development

- Development of the brain occurs between 8 and 25 weeks into gestation.
- The human brain is more susceptible to health insults in these development periods (Nyagu et al., 2002).
- 99% of the NCDS cohort were between 8 and 25 weeks into gestation in the epidemic period.

Specific mechanisms (Schlotz & Phillips, 2009)

- Under-nutrition: Influenza suppresses appetite => reduced nutritional intake for mother => reduced nutritional intake for fetus. Undernutrition *in-utero* has been linked to behavioural problems in later-life (Gale et al., 2008; Parsons et al., 2008).
- Fetal programming: Hyperactivity/inattention during childhood may be a "response ready" trait that develops as a response to a resource-depleted or fast-changing fetal environment.
- Maternal psychosocial stress: Contraction of influenza increases stress of the mother. Stress has been shown to disrupt the protective quality of the placenta and the functioning of hormone producing glands. Maternal stress during pregnancy increasing the risk that offspring develop behavioural difficulties and mental disorders (Talge, Neal, & Glover (2007))

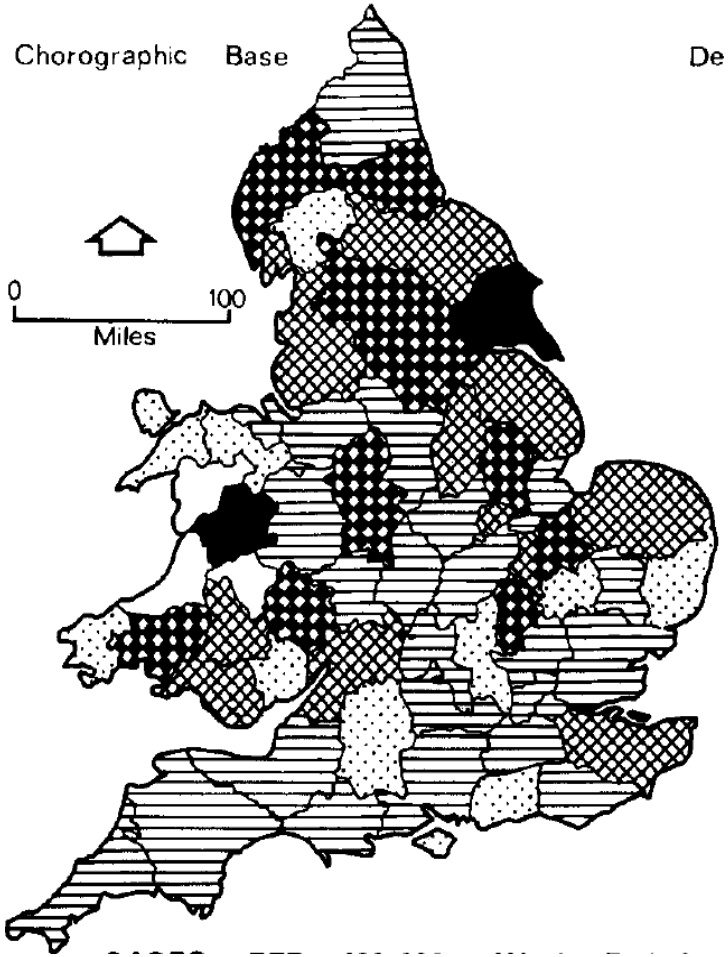
Mechanisms: in-utero exposure to flu and early death

Barker (1994) fetal origins hypothesis & it's extensions

- Original hypothesis suggested a link between fetal undernutrition and later-life disease
- Poor fetal health "reprograms" an individual's genetics, determining which parts of the genome are expressed, and therefore determining likelihood of the onset of disease in adulthood (Petronis, 2010).
- If we make the plausible assumption that those not experiencing disease have higher life expectancies, then by assumption this hypothesis also predicts that fetal health shocks will increase the likelihood of premature mortality.
- Modelling health as a dynamic process suggests that poor in-utero health could reduce health (and increase the probability of death) even in childhood (Cunha & Heckman, 2008).

The 1957 Asian Flu Epidemic

- Asian influenza hit Great Britain between June 1957 and April 1958, but cases were concentrated between September and November 1957 (the epidemic period)
- Approx. 13% of the population in England and Wales contracted influenza during the main epidemic period
- Risk was higher amongst pregnant women: ~30% of women of childbearing age were infected
- Infection rates were higher in Northern England and Scotland, but with significant within-region variation



Empirical strategy

Basic specification

$$Y_{ilra} = \alpha + \beta flu_{ilr} + \rho X_{ilr} + \gamma LA_l + \theta_r + \varepsilon_{ilra}$$

- Here Y_{ilra} represents age a outcomes (mental health, MH_{ilra}, and/or mortality, D_{ilra}) for child i born in local authority l.
- flu_{ilr}: dummy variable which equals unity if child i is exposed to maternal influenza in-utero, and zero otherwise
- X_{il}: child characteristics and family background characteristics from the NCDS birth survey
- LA_l: Local authority characteristics derived from census records
- θ_r: Region-level fixed effects: pick up effects of unobserved LA characteristics which are fixed within regions.
- Estimated using OLS with standard errors clustered at the local authority level

Empirical strategy

Instrumental variables approach

- Uses local authority epidemic severity as an instrument for individual-level in-utero exposure

$$flu_{ilr} = \delta + \pi X_{ilr} + \sigma LA_l + \varphi PreEpid_l + \tau Epid_l + \theta_r + u_{ilr}$$
$$Y_{ilra} = \alpha + \beta flu_{ilr} + \rho X_{ilr} + \gamma LA_l + \emptyset PreEpid_l + \theta_r + \varepsilon_{ilra}$$

- $Epid_l$: influenza infection rate in local authority l in the epidemic period (Sept-Nov, 1957)
  - Proxied using pneumonia infection rates per 100,000 of population, as influenza was not a notifiable disease in 1957
  - Pneumonia is an arguably good proxy for influenza as they are clinically related and trends in pneumonia rates often follow trends in influenza deaths
  - Obtained from Registrar General for England and Wales, 1957
- $PreEpid_l$: influenza infection rate in local authority l in the pre-epidemic period
  - Average influenza rates in Sept-Nov, 1956 and 1955
  - Should capture any correlation between the underlying health of the LA populations and influenza rates
- $Epid_l$ is the instrument: as is included in the outcome equation, this is interpreted as deviation of local authority influenza rates from their pre-epidemic levels

Empirical strategy

Outcomes

- Mental health at ages 7 and 11
  - Rutter behaviour scale
  - Bristol Social Adjustment Guide (BSAG)
  - Both reversed in sign (increasing in mental health) and standardised to mean of 0 and standard deviation of 1.
- Longevity
  - Dummies for still born and dead by 28 days and ages 7, 11, 16, 23, 33, 42, 46, 50, and 55

Preliminary results

Childhood mental health

Baseline specification

Table 3: Regression results from the basic specification: Childhood mental health

	Age 7						Age 11					
	Rutter behaviour index			BSAG total score			Rutter behaviour index			BSAG total score		
Fetal influenza exposure	-0.0369	-0.0402	-0.0330	-0.0213	-0.0181	0.000985	-0.0594*	-0.0593*	-0.0482	-0.0383	-0.0390	-0.00587
	(-1.34)	(-1.46)	(-1.22)	(-0.82)	(-0.69)	(0.04)	(-2.11)	(-2.11)	(-1.74)	(-1.38)	(-1.40)	(-0.22)
LA controls and region FE	No	Yes	Yes	No	Yes	Yes	No	Yes	Yes	No	Yes	Yes
Child-level controls	No	No	Yes	No	No	Yes	No	No	Yes	No	No	Yes
Observations	11980	11980	11980	12209	12209	12209	11148	11148	11148	11394	11394	11394
R-squared	0.000	0.008	0.047	0.000	0.002	0.064	0.000	0.006	0.041	0.000	0.003	0.084

* p<0.05, ** p<0.01, *** p<0.001; t-statistics in parenthesis

- Irrespective of the measure used and the age at which outcomes are recorded, being exposed to influenza *in-utero* failed to significantly reduce mental health.

Preliminary results

Childhood mental health

IV

Table 4: Regression results from the instrumental variable approach: Childhood mental health

	Age 7						Age 11					
	Rutter behaviour index			BSAG total score			Rutter behaviour index			BSAG total score		
Fetal influenza exposure	-8.737	-4.381	-6.983	3.422	12.44	9.957	1.540	12.87	9.370	-0.127	-4.776	-4.445
	(-0.76)	(-0.45)	(-0.56)	(0.47)	(0.31)	(0.36)	(0.35)	(0.49)	(0.50)	(-0.03)	(-0.30)	(-0.44)
LA controls and region FE	No	Yes	Yes	No	Yes	Yes	No	Yes	Yes	No	Yes	Yes
Child-level controls	No	No	Yes	No	No	Yes	No	No	Yes	No	No	Yes
F-statistic p-value	0.449	0.636	0.594	0.415	0.713	0.663	0.396	0.591	0.572	0.579	0.819	0.745
Durbin-Wu p-value	0.042	0.579	0.299	0.383	0.240	0.235	0.639	0.015	0.040	0.986	0.751	0.647
Observations	11980	11980	11980	12209	12209	12209	11148	11148	11148	11394	11394	11394

* p<0.05, ** p<0.01, *** p<0.001; t-statistics in parenthesis

- Puzzling results. Estimates of *in-utero* influenza's impact vary widely dependent on the measure used and the age at which outcomes are recorded, with many effects of opposite sign and or large magnitudes.
- However, due to considerably large standard errors, these large magnitudes do not translate into statistical significance.
- Weak instrument problem: first stage F-statistic is highly insignificant indicating that a higher intensity in the epidemic in cohort members' local authority of birth does not increase the probability of in-utero exposure to influenza.
- Durbin-Wu tests indicate that flu is exogenous! – but test is highly sensitive to weak instruments

Preliminary results

Longevity

Baseline specification

Table 5: Regression results from the basic specification: longevity outcomes

	Stillbirth	28 days	Age 7	Age 11	Age 16	Age23	Age 33	Age 42	Age 46	Age 50	Age 55
Fetal influenza exposure	0.0108**	0.0122**	0.00979*	0.00984*	0.00883	0.0112*	0.0134*	0.0140*	0.0129*	0.0111	0.0108
	(2.87)	(2.74)	(2.08)	(2.06)	(1.82)	(2.16)	(2.46)	(2.40)	(2.12)	(1.74)	(1.65)
LA controls and region FE	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Child-level controls	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Observations	14603	14603	14603	14603	14603	14603	14603	14603	14603	14603	14603
R-squared	0.086	0.143	0.176	0.173	0.168	0.152	0.145	0.126	0.113	0.104	0.098

* p<0.05, ** p<0.01, *** p<0.001; t-statistics in parenthesis

- In-utero exposure to influenza significantly reduces age of death
- A strong effect is found at birth, where fetal exposure to influenza increases the probability of being stillborn or dying in a neonatal unit by just over one percentage point
- The magnitude of this effect remains around one percentage point across the life-course, and maintains statistical significance at 28 days and at ages 7, 11, 23, 33, 42, and 46

Preliminary results

Longevity

IV

Table 6: Regression results from the instrumental variable approach: longevity outcomes

	Stillbirth	28 days	Age 7	Age 11	Age 16	Age23	Age 33	Age 42	Age 46	Age 50	Age 55
Fetal influenza exposure	-1.035	-2.600	-1.158	-1.009	-0.517	-0.847	-1.095	-1.636	-1.965	-1.787	-1.101
	(-0.29)	(-0.28)	(-0.26)	(-0.26)	(-0.21)	(-0.25)	(-0.28)	(-0.30)	(-0.30)	(-0.31)	(-0.30)
LA controls and region FE	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Child-level controls	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
F-statistic p-value	0.7772	0.7772	0.7772	0.7772	0.7772	0.7772	0.7772	0.7772	0.7772	0.7772	0.7772
Durbin-Wu p-value	0.4163	0.039	0.371	0.4348	0.6831	0.5259	0.4067	0.3201	0.2798	0.3972	0.5957
Observations	14603	14603	14603	14603	14603	14603	14603	14603	14603	14603	14603

* p<0.05, ** p<0.01, *** p<0.001; t-statistics in parenthesis

- Puzzling results again.
- Implausible coefficients - The models predict that exposure to influenza in-utero reduces the probability of death by over 100% at some ages.
- However, these are again insignificant – driven again by the weak instrument problem

Discussion

- Preferred specification is one where exposure to influenza in-utero is exogenous.
- We find that in-utero exposure to influenza had no impact on mental health at either age 7 or age 11. Surprising, given the multiple possible mechanisms.
- Substantial impact of fetal exposure on the probability of stillbirths, and the differential in death rates remain constant over the lifecourse.
- However, the degree to which these results can be trusted is limited, given the weak instrument problem.

Discussion

- Failure of geographical fluctuations in epidemic intensity to predict individual-level exposure
  - Concerning given that many studies examining the causal effect of early-life conditions use geographical variation in in-utero exposure to adverse health conditions to identify its effects, so the assumption that area-level exposure predicts individual-level exposure is therefore key.
  - Later studies should examine this link more carefully.
- Reasons for the failure of the instrument:
  - Pneumonia rates a poor proxy for influenza rates
  - Errors in newly-released data on influenza exposure
  - Non-random selection into the NCDS sample – those who contract influenza may be less likely to complete the birth survey
- Further limitations:
  - Unobserved LA characteristics which vary within region and over time e.g. quality of healthcare services
  - Maternal mental health problems
  - Quality of deaths data – lower death rates for those that migrate
  - Migration in response to the epidemic
  - Mortality selection

Thank you!

alexander.turner@manchester.ac.uk

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Tea/coffee break and poster session

15:20-15:50

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