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Exposure to famine during gestation, size at birth, and blood pressure at age 59 y: evidence from the dutch famine

Aryeh D. Stein[1], Patricia A. Zybert[2], Karin van der Pal-de Bruin[3] and L. H. Lumey[2]
[1]*Rollins School of Public Health, Emory University, Atlanta, GA, 30322, USA;* [2]*Department of Epidemiology, Mailman School of Public Health, Columbia University, 722 West 168th St, New York, NY, 10032, USA;* [3]*TNO Quality of Life, Leiden, Netherlands*

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Abstract. We compared blood pressure of individuals (mean age 59 y) born in western Holland between January 1945 and March 1946 (mothers exposed to the Dutch Famine before or during gestation; n = 359) to blood pressure of unexposed individuals born before or conceived after the famine (n = 299) or same-sex siblings of subjects in series 1 or 2 (n = 313). Mean (SD) systolic and diastolic blood pressure were 140.3 (20.3) and 85.8 (11.0) mmHg, respectively; prevalence of hypertension (prior diagnosis of hypertension or with measured systolic/diastolic blood pressure above 140/90 mmHg) was 61.8%. Birth weight was inversely related to systolic (−4.14 mmHg per kg; 95% confidence interval (CI) −7.24, −1.03; $p < 0.01$) and diastolic (−2.09 mmHg per kg; 95% CI −3.77, −0.41; $p < 0.05$) blood pressure and to the prevalence of hypertension (odds ratio 0.67 per kg, 95% CI: 0.49, 0.93) (all age- and sex-adjusted). Any famine exposure of at least 10 weeks duration was associated with elevated systolic (2.77 mmHg; 95% CI 0.25, 5.30; $p < 0.05$) and diastolic (1.27 mmHg; 95% CI −0.13, 2.66; $p = 0.08$) blood pressure and with hypertension prevalence (odds ratio 1.44; 95% CI 1.04, 2.00; $p < 0.05$) in age- and sex-adjusted models. Exposure to famine during gestation may predispose to the development of hypertension in middle age.

Key words: Blood pressure, Cohort, Famine, Netherlands, Nutrition

Introduction

The large literature relating size at birth to later levels of blood pressure and to the prevalence of hypertension [1–4] is limited insofar as birth weight is at best a proxy for processes that occur between conception and birth [5]. Animal models suggest that specific manipulations in maternal nutrition during pregnancy, especially the administration of low-protein diets, but also global restriction of food availability, result in elevations in blood pressure [6]. Efforts to replicate these findings in humans [7–9] are limited by the challenges of measuring dietary intakes of free-living adults and the reluctance to conduct randomized trials of nutrition among pregnant women.

The Dutch Famine of 1944–1945 provides a quasi-experimental model to study the long-term consequences of maternal exposures in defined stages of gestation [10, 11]. One prior investigation, with data collected when the famine birth cohort was 50 y of age, reported no association of famine exposure with blood pressure levels [12]. The present study was conducted to replicate those findings, extend follow-up through age 59 y and provide control for family-level determinants of blood pressure through use of sibling controls.

Materials and methods

Setting

The Dutch Famine affected the western Netherlands [13–15]. Official rations, which by the end of the famine consisted almost exclusively of bread and potatoes, fell below 900 kcal per day by November 26, 1944 and were as low as 500 kcal per day by April 1945. The famine ceased immediately with liberation in May 1945. The famine affected fertility, pregnancy weight gain, maternal blood pressure, and infant birth size [16–18]. The reduction in fertility was greater among the manual compared to the non-manual occupational classes [10]. The decline in birth weight was restricted to exposure during the third trimester [19, 20].

Population source and tracing

We identified 3307 live singleton births at three institutions in famine-exposed cities (midwifery

training schools in Amsterdam and Rotterdam and the university hospital in Leiden) in 1945 and early 1946 (exposed probands, 100% sample), and in 1943 and 1947 (unexposed probands, 30 births per month, allocated across the three institutions according to their relative abundance). At the time the large majority of deliveries (70% or more) were scheduled to occur at home. The client mix at the two midwifery training schools consisted of low-risk pregnancies to women of low socioeconomic status whose home environment was unsuitable for home delivery. The client mix in Leiden also included higher risk pregnancies identified during prenatal care and emergency admissions following complications of delivery. We extracted personal identifiers including name and maternal address, birth weight and other information from the admission logs and delivery progress charts.

The names and address at birth of all 3307 individuals were provided to the Population Register in the municipality of birth. A current address was obtained for 2300 individuals (70% of the birth cohort); 308 (9.3%) were reported to have died in the Netherlands; and 275 (8.3%) to have migrated. The Population Registry in Rotterdam declined to trace 130 individuals born out of wedlock and for 294 subjects (8.9%) a current address could not be located.

Population contact and examination

Traced individuals (n = 2300) were mailed a letter of invitation signed by the current director of the institution in which they were born, a brochure describing the study, and a response card. We mailed one reminder letter to non-responders. Initially, our study design called for the recruitment of same-sex sibling pairs, and hence lack of an available sibling was a reason for ineligibility. We received some reply to 58% of the initial letters and to 44% of the reminder letters; 347 individuals (19.6% of 1767 respondents) expressed willingness to participate together with a sibling. Among the 1415 who declined, 951 (67%) reported not having a same-sex sibling available for study. To increase the overall number of study subjects, we recontacted these 951 individuals, 375 of whom expressed willingness to participate.

We conducted a telephone interview, followed by a clinical examination at the Leiden University Medical Center. All study protocols were approved by the Human Subjects Committees of all the participating institutions. Study participants provided oral consent at the start of the telephone interview and written informed consent at the start of the clinical examination. Most clinical examinations were conducted within 6 weeks of the telephone interview.

Blood pressure was measured using an automated sphygmomanometer (Omron HEM 705-CP, Bannockburn, IL), recommended by the European Society of Hypertension Working Group on Blood Pressure Monitoring [21]. Three readings were obtained using the automatic setting from the non-dominant arm after several minutes of rest. The participant was seated and an appropriate sized cuff was used. In analyses, the mean of the two closest readings was used. Smoking status, alcohol consumption and history of physician-diagnosed hypertension were ascertained during the telephone interview. Height and waist circumference were measured using standard protocols during the clinic examination.

Statistical methods

Categorizing exposure

We used the date of last menstrual period (LMP) as noted in the original record to define the start of gestation unless it was missing or implausible (12.4%), in which case we inferred LMP from the recorded gestation and annotations on the birth record. As a final resort, we assigned LMP using cut-points from tables of gender-, parity- and birth weight-specific gestational ages from the combined birth records of the Amsterdam midwives school (1948–1957) and the University of Amsterdam Obstetrics Department (1931–1965) [22]. We characterized exposure to famine during gestation by determining the weeks post-LMP during which the mother was exposed to an official ration of <900 kcal/week (the 24 weeks included within the calendar period November 26, 1944–May 12, 1945). We considered the mother exposed in gestational weeks 1–10, 11–20, 21–30 or 31–delivery if these periods were entirely included in this time window. Thus, pregnancies with LMP between November 26, 1944 and March 4, 1945 were considered exposed in gestation weeks 1–10, those between September 18, 1944 and December 24, 1944 were considered exposed in gestation weeks 11–20, those with LMP between July 10, 1944 and October 15, 1944 were considered exposed in gestation weeks 21–30, and those with LMP between May 2, 1944 and August 24, 1944 were considered exposed in gestation weeks 31 through delivery. Individuals might be considered exposed during one or (at most) two 10-week periods. Individuals exposed in at least one of the 10-week periods were considered to have had famine exposure.

Regression models

We developed independent models for systolic and for diastolic blood pressure and for prevalent hypertension, the latter defined as presence of systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or a history of hypertension, regardless of present blood pressure level or current medication use. We used linear regression to model blood pressure level, and logistic regression to model the odds of hypertension. All analyses were implemented in Stata 8 (Stata Corp., College Station TX).

For each of the three outcomes we considered a series of models. Our primary analysis focused on pooled, age- and sex-adjusted models. We first considered the dichotomy of any exposure to famine vs. no exposure, without regard to the timing of such exposure, then considered period of exposure, entering dummy variables for the four 10-week intervals as a set. We then added current smoking status, alcohol intake, height, and waist circumference to both models. Finally, we added to the models for systolic and diastolic blood pressure two dummy terms for prior diagnosis of hypertension (currently taking medication, not taking medication), both with no history as the reference. All models used the combined population of controls (unexposed births in the three hospitals and siblings of the birth series) as the reference. Analyses were run using generalized estimating equations approaches to control for clustering within families.

We examined the association between birth weight and later blood pressure in the proband series, since we did not have access to sibling birth records. The base model included birth weight, sex and age at interview; model 2 included additional terms for period of exposure to famine as described above; and models 3 and 4 included additional terms for the adult covariates as described above.

Results

Differences between traced and untraced individuals

The proportion of deceased individuals was highest among probands born in 1943 (10.4%) and lowest among probands born in 1947 (6.0%). Emigration status or other reasons why a current address was not found did not differ by year of birth or period of prenatal famine exposure. There were no clinically significant differences in mean birth weight (3350 vs. 3314 g) or length (50.4 vs. 50.2 cm), placental weight (601 vs. 592 g), maternal age at delivery (28.2 vs. 27.4 y), or birth order (2.3 vs. 2.3) comparing the birth records of study subjects traced to a current address to those who had either died, emigrated, or had not been located.

Differences between respondents and non-respondents

Among 2300 individuals who were invited to join the study, we found no significant differences in mean birth weight (3374 vs. 3339 g) or length (50.5 vs. 50.3 cm), placental weight (600 vs. 601 g), maternal age at delivery (28.6 vs. 28.1 y), or birth order (2.4 vs. 2.2), comparing those interviewed to those who were not. Response to our invitation was lower for those born in 1947 (25%) compared to all others (35%). With respect to distance between current home address and the study center, 11% of those who were interviewed lived within 5 km (3 miles) of Leiden, as compared to 10% of those who were not interviewed, and 34% of the interviewed lived more than 45 km from Leiden as compared to 29% of the non-interviewed. The median 1998 post-tax individual incomes were somewhat higher for zip-code catchments of the interviewed (Euro 23,116) vs. those of the non-interviewed (Euro 22,919).

Final sample for analysis

We obtained blood pressure data from 971 individuals: 359 exposed individuals; 299 unexposed individuals born in the study hospitals, and 313 siblings. The resulting sample sizes by (overlapping) periods of exposure are 74, 127, 145, and 133, for gestational weeks 0–10, 11–20, 21–30, and 31–delivery, respectively. There were no differences across periods of exposure in the proportion of probands who had siblings available for study. Selected characteristics of the study sample are provided in Table 1. Famine-exposed individuals had, on average, lower birth weight ($p < 0.01$), larger waist circumferences ($p < 0.01$), increased prevalence of prior diagnosis of hypertension ($p = 0.061$) and higher systolic ($p = 0.013$) and diastolic ($p = 0.067$) blood pressures, but there were no differences with respect to sex, tobacco use or alcohol consumption (all $p > 0.10$). Siblings were, on average, younger than the hospital birth series ($p < 0.001$).

Famine exposure

In age- and sex-adjusted models, systolic and diastolic blood pressure levels were 2.77 mmHg (95% confidence interval (95% CI) 0.25, 5.30; $p < 0.05$) and 1.27 (95% CI −0.13, 2.66; $p = 0.076$) higher, respectively, in those exposed to famine during gestation as compared to individuals with no famine exposure (Table 2). These estimates were attenuated slightly with adjustment for adult covariates. Estimates for men and women were of similar magnitude and were not significant in sex-stratified models (not shown).

In age- and sex-adjusted models, the odds of hypertension were elevated with exposure to famine (odds ratio 1.44; 95% CI 1.04, 2.00); this association was slightly attenuated in subsequent models. The association was somewhat stronger among men than among women, but a test for interaction was not significant ($p > 0.10$; data not shown).

Famine exposure in specified periods of gestation

Associations of exposure to famine in specific 10-week periods during gestation with blood pressure level were not significant, with the exception of exposure in weeks 21–30 for diastolic blood pressure in the age- and sex-adjusted model (Table 3) or among men or women considered separately (not

Table 1. Selected characteristics of Dutch individuals born in one of three hospitals in 1943–1947 and their siblings and examined between 2003–2005, by sex

	Famine exposed (n = 359) Mean (SD) or %	Hospital controls (n = 299) Mean (SD) or %	Siblings (n = 313) Mean (SD) or %	p[a]
Sex (% male)	45.7	46.8	42.5	NS
Age (y)	58.7 (0.42)	58.6 (1.56)	57.2 (6.34)	<0.001
Birth weight (g)	3295 (503)	3455 (506)	–[b]	<0.001
Height (cm)	170.8 (8.9)	171.5 (9.0)	171.8 (8.9)	NS
Waist circumference (cm)	99.9 (11.5)	97.4 (11.4)	96.4 (11.2)	<0.001
Current smoker (%)	25.4	24.1	22.4	NS
Alcohol consumption (%)				NS
<1 drink per week	20.7	25.1	26.2	
1–7 drinks/week	37.3	33.4	31.0	
8–14 drinks/week	16.8	22.1	20.0	
15–21 drinks/week	15.4	12.0	12.8	
>21 drinks/week	9.8	7.4	9.9	
Blood pressure				
Previous diagnosis of hypertension (%)	39.4	34.8	30.7	0.061
Currently taking medication (%)	23.7	20.7	17.6	NS
Not taking medication (%)	15.6	14.1	13.1	NS
Systolic blood pressure (mmHg)	142.7 (20.6)	139.7 (20.5)	138.2 (19.6)	0.013
Diastolic blood pressure (mmHg)	86.7 (11.2)	85.9 (11.0)	84.7 (10.7)	0.067
Prevalent hypertension[c] (%)	67.4	60.9	56.2	0.011

[a]By analysis of variance or chi-square, as appropriate. NS $p > 0.10$.
[b]Birth weight not available for sibling controls.
[c]Systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or prior diagnosis.

shown). Famine exposure in specific periods during gestation was not significantly associated with hypertension prevalence; estimates were slightly higher for exposures late in gestation (Table 4).

Birth weight

Birth weight was inversely associated with blood pressure level and with hypertension prevalence (Table 4). The estimates for systolic and diastolic blood pressure were somewhat stronger for males (data not shown), were altered slightly by adjustment for famine exposure, and were generally attenuated with adjustment for adult covariates. The estimate for hypertension was robust to adjustment for period of exposure to famine or adult covariates.

Discussion

Using the unique circumstances of the Dutch Famine of 1944–1945, we observed that maternal exposure to acute famine was associated with increases in blood pressure level and prevalence of hypertension among

Table 2. Associations of famine exposure during gestation with later blood pressure levels[a] and prevalence of hypertension[b], Netherlands

	Systolic blood pressure		Diastolic blood pressure		Prevalent hypertension	
	mmHg[c]	95% CI	mmHg	95% CI	Odds ratio	95% CI
Age- and sex-adjusted	2.77	0.25, 5.30	1.27	−0.13, 2.66	1.44	1.04, 2.00
Additional adjustment for smoking, alcohol intake, height, waist circumference	1.95	−0.55, 4.45	0.75	−0.62, 2.11	1.32	0.94, 1.84
Additional adjustment for prevalent hypertension	1.64	−0.76, 4.05	0.59	−0.74, 1.92	–	

[a]Systolic blood pressure and diastolic blood pressure were analyzed with linear regression; regression coefficients (in mmHg) and 95% confidence intervals are presented.
[b]Hypertension (systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg or a prior diagnosis of hypertension) was analyzed using logistic regression; odds ratios and 95% confidence intervals are presented.
[c]Famine exposed n = 359; unexposed n = 612; all estimates are controlled for family clustering.

Table 3. Association of famine exposure during 10-week periods of gestation with later blood pressure[a] and prevalent hypertension[b], Netherlands

	Age- and sex-adjusted		Additional adjustment for smoking, alcohol, height and waist circumference		Additional adjustment for prevalent hypertension	
Systolic blood pressure (mmHg; 95% confidence interval)						
Gestational weeks 1–10[c]	1.52	−3.30, 6.33	1.03	−3.64, 5.71	1.20	−3.28, 5.69
Gestational weeks 11–20	−1.02	−5.00, 2.96	−1.34	−5.23, 2.56	−1.18	−4.92, 2.55
Gestational weeks 21–30	3.02	−0.78, 6.82	1.57	−2.15, 5.30	1.33	−2.24, 4.90
Gestational weeks 31–delivery	2.49	−1.29, 6.27	2.34	−1.36, 6.05	2.02	−1.53, 5.57
Diastolic blood pressure (mmHg; 95% confidence interval)						
Gestational weeks 1–10	1.42	−1.22, 4.06	1.05	−1.49, 3.59	1.10	−1.36, 3.57
Gestational weeks 11–20	−1.12	−3.31, 1.07	−1.32	−3.44, 0.79	−1.26	−3.32, 0.80
Gestational weeks 21–30	2.15	0.06, 4.24	1.30	−0.73, 3.32	1.19	−0.78, 3.15
Gestational weeks 31–delivery	1.01	−1.07, 3.08	0.89	−1.12, 2.90	0.71	−1.24, 2.66
Prevalent hypertension (odds ratio; 95% confidence interval)						
Gestational weeks 1–10	1.24	0.68, 2.28	1.14	0.62, 2.11	–	
Gestational weeks 11–20	1.03	0.62, 1.70	0.98	0.59, 1.65	–	
Gestational weeks 21–30	1.42	0.87, 2.33	1.23	0.74, 1.05	–	
Gestational weeks 31–delivery	1.43	0.88, 2.32	1.42	0.86, 2.35	–	

[a]Systolic and diastolic blood pressures were analyzed with linear regression; regression coefficients (in mmHg) and 95% confidence intervals are presented.
[b]Hypertension (systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg or a prior diagnosis of hypertension) was analyzed using logistic regression; odds ratios and 95% confidence intervals are presented.
[c]Sample sizes are n = 74, 128, 145, 133 for exposure in gestation weeks 1–10, 11–20, 21–30, and 31 through delivery, respectively, and n = 612 unexposed. Exposure in specific 10-week periods implies exposure for the whole of the 10-week interval, and is adjusted for overlapping exposure periods. All estimates are controlled for family clustering.

the offspring at age 59 y. We were unable to demonstrate clear associations between exposure in specific periods of gestation and blood pressure level, likely due to small sample sizes.

In a similar population examined 9 y previously [12], the mean systolic blood pressure in those exposed in late, mid, and early gestation, and adjusted for sex and age, was 1.3 mmHg higher (95% CI: −1.9, 4.4), 0.6 mmHg (95% CI: −3.9, 2.7) lower, and 1.7 mmHg (95% CI: −5.6, 2.2) lower, respectively, than in an unexposed group, estimates that are consistent with our observations. In the one other study of adults exposed to famine during gestation, conducted among survivors of the siege of Leningrad (now St. Petersburg) Russia, no association was observed between famine exposure and blood pressure levels at age 40 y [23]. As the siege lasted over 2 y, it is not possible to distinguish among exposures at different stages of gestation, and as the population denominators are not known with certainly, the extent of loss to follow-up cannot be determined.

Our study adds to the literature of the Dutch Famine in two ways. We have traced and studied individuals from institutions not previously studied,

Table 4. Association of birth weight with later blood pressure[a] and prevalent hypertension[b] among 657 individuals born in three hospitals in Holland 1943–1947 and studied in 2003–2005

	Age- and sex-adjusted		Additional adjustment for exposure to famine		Additional adjustment for smoking, alcohol, height and waist circumference		Additional adjustment for prevalent hypertension	
Systolic blood pressure (mmHg: 95% confidence interval)	−4.14	−7.24, −1.03	−3.76	−6.91, −0.62	−3.75	−6.91, −0.59	−2.71	−5.76, 0.34
Diastolic blood pressure (mmHg; 95% confidence interval)	−2.09	−3.77, −0.41	−2.01	−3.71, −0.31	−1.93	−3.62, −0.24	−1.46	−3.11, 0.19
Hypertension (odds ratio; 95% confidence interval)	0.67	0.49, 0.93	0.69	0.50, 0.96	0.68	0.48, 0.97	–	

[a]Estimates for systolic and diastolic blood pressure are linear regression coefficients, expressed as mmHg per kg.
[b]Estimates for prevalent hypertension (systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg or a prior diagnosis of hypertension) are odds ratios per kg.

ensuring an independent replication of earlier observations and increasing the overall size of the population now recruited for study. This is of importance for future research as both our study and the prior investigation have limited power to detect gestation-specific effects, which may explain the generally null period-specific findings. Our use of sibling controls reduces the potential bias related to family-level factors that might predict inter-individual variation in blood pressure. A strong association between family socioeconomic status, measured as paternal occupational class, and fertility during the famine, with fertility declining most sharply among lower social class sectors, has been previously reported [10]. Our estimates were attenuated with adjustment for several adult covariates (most notably waist circumference), suggesting that these may be, at least in part, mediators of any association. Elsewhere we have reported on marked increases in several measures of body mass in women following famine exposure [24]; in the present analysis we controlled for waist circumference as an exemplar of these. Control for behavioral predictors of blood pressure, namely tobacco and alcohol, did not affect our estimates, as these behaviors did not vary across exposure groups. Control for prevalent hypertension may reflect selection on a common effect that may induce bias [25]; we observed that estimates were attenuated with this additional adjustment, and in some cases statistical significance dropped below the traditional value of 0.05. We note that our estimates for prevalent hypertension are not subject to this caveat as this effect is in fact the endpoint of interest.

We assigned exposure based on LMP. In contrast, previous investigations of the consequences of exposure to the Dutch Famine have characterized exposure based on date of birth, and necessarily incorporated an assumption of a constant 9 months gestation at delivery. It has been suggested in other settings that duration of gestation is affected by maternal nutritional status at birth and during gestation [26]. The LMP-based approach may better identify periods of exposure critical to early fetal development, while circumstances surrounding the delivery process that may not reflect processes that occurred earlier in gestation may be better captured using assignments based on date of birth.

The underlying physiological changes induced by exposure to famine during gestation are as yet unknown. Development of total nephron number, itself implicated in the development of hypertension, is most rapid in the third trimester and is complete in humans by gestational week 36 [27]. Animal data suggest that nephron number can be manipulated through maternal food restriction at various stages of gestation [28, 29], and nephron number and structure has been associated with birth size in humans [30] but to date no study has demonstrated a relationship of nephron number to maternal nutrition in humans, and this potential mechanism must remain speculative. Recently, it has been demonstrated that the blood pressure response to psychological stressors differs according to exposure to the famine [31]; this may reflect an additional mechanism.

Our results must be considered in the light of the considerable attrition that we experienced, and hence participation bias is possible. Failure to identify a current address, whether due to mortality, migration, or loss to follow-up, was not differential by famine exposure status. The Famine remains a highly salient event in Dutch society. Among traced individuals, participation rates were slightly lower among individuals born after the famine ended, but was not differential by distance from the clinical center. Blood pressure levels and prevalence of hypertension increase with age, and we adjusted for age in our models. However, we cannot assess whether blood pressure levels differ systematically among individuals not studied.

The circumstances of the Dutch famine provide an opportunity to distinguish between causal effects of famine on birth weight and statistical associations of birth weight with later blood pressure [5]. The association between birth weight and blood pressure in our data and in the previous report [21] is somewhat stronger than others have observed [2]. While we use caloric rations to define the onset and end of the famine, exposure to famine involves not just reduction in food intakes, but also increases in stress, infections, and other factors that may impact on later health. Nevertheless, the famine was clearly a cause of the change in birth weight among those exposed in later gestation [32], a period itself most consistently linked to elevated blood pressure in our data.

Our data are suggestive that the observed associations between birth weight and later blood pressure may reflect an underlying role of maternal nutrition, at least in extreme circumstances. While the generalizability of these findings to present western populations is likely to be limited, severe periodic food restriction was widespread until recently in many regions globally, and birth weights are depressed relative to western references in much of the developing world.

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Address for correspondence: L. H. Lumey, Department of Epidemiology, Mailman School of Public Health, Columbia University, 722 West 168th St, New York, NY, 10032, USA;
Phone: +1-212-305-9222; Fax: +1-212-342-5169;
E-mail: lumey@columbia.edu