Repurposing large health insurance claims data to estimate genetic and environmental contributions in 560 phenotypes

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We analysed a large health insurance dataset to assess the genetic and environmental contributions of 560 disease-related phenotypes in 56,396 twin pairs and 724,513 sibling pairs out of 44,859,462 individuals that live in the United States. We estimated the contribution of environmental risk factors (socioeconomic status (SES), air pollution and climate) in each phenotype. Mean heritability ($h^2 = 0.311$) and shared environmental variance ($c^2 = 0.088$) were higher than variance attributed to specific environmental factors such as zip-code-level SES ($\text{var}_{\text{SES}} = 0.002$), daily air quality ($\text{var}_{\text{AQI}} = 0.0004$), and average temperature ($\text{var}_{\text{temp}} = 0.001$) overall, as well as for individual phenotypes. We found significant heritability and shared environment for a number of comorbidities ($h^2 = 0.433$, $c^2 = 0.241$) and average monthly cost ($h^2 = 0.290$, $c^2 = 0.302$). All results are available using our Claims Analysis of Twin Correlation and Heritability (CaTCH) web application.

Disentangling how genetic and environmental factors contribute to many phenotypes in the same population has been largely unfeasible to date. Most study designs consider a single disease or environmental factor at a time. Administrative health data, such as insurance claims and electronic health records, may enable more comprehensive analyses of the roles of genetics and shared environment in hundreds of phenotypes. Here, we analysed a massive, individual-level claims dataset of 44,859,462 individuals to systematically partition phenotypic variance between genetic and non-genetic factors across a large US population. Documenting both the genetic and environmental contributions of phenotypic variance is instrumental for major health studies, such as the United States’ All of Us effort1. Furthermore, the use of genome sequence data in medical decisionmaking is under debate2 and estimating heritability in a ‘real-world’ setting can help to quantify the clinical utility of genome sequencing3.

In human genetics, heritability is defined as the amount of phenotype or disease variation that can be attributed to genetic factors. In family studies, other important quantities, such as ‘shared environment’ and ‘non-shared environment’, complement heritability and describe variation in phenotype resulting from non-genetic factors. Estimation of heritability and environmental components of phenotypic variation have historically used family-based studies, such as those involving twins that are concordant (and discordant) for disease. However, building twin registries can be resource-intensive in the ascertainment of both twin pairs and phenotypes. What is missing are family-based studies that measure numerous phenotypes across a large and diverse population that experience a variety of environmental exposures. First, health administration data enable such an approach because these data give a comprehensive snapshot of health (for example, thousands of disease diagnoses and laboratory reports, in addition to the cost of healthcare), and they enable family-based or twin-based studies across a large number of diseases. Although twin-based analysis in such datasets is difficult because of a lack of zygosity information, we employed methodology that utilizes sex information to differentiate between identical and non-identical twin pairs.

Second, there has also been a great deal of interest in understanding the contribution of one’s residence or ‘zip code’ in their disease state4–6. Individual-level data with geographical and temporal information (that is, patient mailing zip code and time of diagnosis) can enable an understanding of the contribution of specific geographically linked environmental factors in phenotypic variation. To our knowledge, only one study has attempted to quantify the relative contribution of local environment and genetics7. In our analysis, we quantify the relative contribution of local environment and genetics by integrating individual-level data with zip code-level information that serve as geographical indicators of the area’s SES, air pollution quality level and weather/climate.

We estimated heritability and shared environmental variance for 560 phenotypes (based on diagnostic billing codes and laboratory tests) in a cohort of 56,396 twin pairs born on or after 1985 (individuals that are on their parent’s/guardian’s insurance plan) using an individual-level claims dataset of 44,859,462 individuals from the United States. We also estimated phenotypic correlation for same sex and opposite sex siblings using a cohort of 724,513 sibling pairs (Supplementary Note). We estimated the contribution of specific environmental risk factors, such as SES, air pollution, and climate difference, to these phenotypes by linking individual claimants to external datasets via residential locations (Fig. 1d–g). In addition, we computed genetic and environmental contributions to the cost of care utilization and total comorbidities. Finally, we estimated the validity of our estimates for heritability and shared environment through systematic comparison of documented estimates in the published literature.

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Results

Data overview. We utilized de-identified member claims data from Aetna Inc., a national health insurance company, to assemble a cohort of 56,396 twin pairs and 724,513 sibling pairs (Methods and Supplementary Note) that were members for at least 3 years in the entire surveillance period between 01/01/2008 and 01/02/2016.

Fig. 1 | Geographic distribution of 56,396 twin pairs in CaTCH and an example of environmental data aggregation on a zip code basis. a, Count of twin pairs in CaTCH for each state in the United States. b, Distribution of log of population density for the entire United States (based on Census American Community Survey data) and twin pairs. c, Distribution of deprivation index for the entire United States and twin pairs. d, Time series for daily AQI for Mecklenburg county. Black lines represent the years 2008 and 2014. e, Time series for average monthly temperature for NOAA sensor closest to zip code 28210. Black lines represent the years 2008 and 2014. f, Distribution of median family income distribution among residents of zip code 28210. Black line represents the mean median income value. g, Map of county, zip code, and closest NOAA sensor for hypothetical twin pair residing in zip code 28210. Background map image from OpenStreetMap licensed under the terms of the Creative Commons Attribution-ShareAlike 2.0 license (CC BY-SA). ACS, American Community Survey; NOAA, National Oceanic and Atmospheric Administration.
The median age of twin and sibling pairs at the start of surveillance was 7 years (Table 1). The age range for twins and siblings in this cohort was between 0 and 24 years. Using the claims data, we mapped health claims codes to higher level phenotypes called \( \text{PheWAS} \) phenotypes (Supplementary Note). Among functional domains with at least five phenotypes, the prevalence of \( \text{PheWAS} \) phenotypes varied from 52.5% to 79.9% (Fig. 1). The functional domains with the highest \( c^2 \) were ophthalmological (\( c^2 = 0.183, 95\% \text{ CI: 0.147, 0.218} \)) and respiratory (\( c^2 = 0.182, 95\% \text{ CI: 0.151, 0.213} \)) phenotypes for \( \beta_{\text{sex}} \) that were significant (Methods and equation (2)).

### Table 1 | Characteristic of ascertained insurance claims twin and sibling cohorts

|                          | All pairs | FF pairs | MM pairs | MF pairs |
|--------------------------|-----------|----------|----------|----------|
| Number of twin pairs     | 56,396    | 17,835   | 17,919   | 20,642   |
| Number of sibling pairs  | 724,513   | 171,095  | 187,033  | 366,385  |
| Median age at start of surveillance (IQR) (twin) | 7 (2-12) | 7 (2-12) | 7 (2-12) | 7 (2-12) |
| Median age at start of surveillance (IQR) (sibling) | 60 (45-84) | 60 (45-84) | 60 (45-84) | 60 (45-84) |
| Median months of surveillance (IQR) (twin) | 61 (46-84) | 61 (46-84) | 61 (46-84) | 61 (46-84) |
| Median months of surveillance (IQR) (sibling) | 23 (12-42) | 23 (12-42) | 22 (11-41) | 23 (12-42) |
| Median number of ICD Codes (IQR) (twin) | 24 (13-42) | 24 (13-42) | 22 (11-41) | 23 (12-42) |
| Median number of ICD Codes (IQR) (sibling) | 11,666 | 7,302 | 7,235 | 7,466 |
| Distinct number of zip codes (twin) | 24,703 | 17,324 | 17,606 | 21,112 |
| Distinct number of zip codes (sibling) | 01/01/2008 – 01/02/2016 |

**FF pairs**, twin pairs where both individuals are female; **MM pairs**, twin pairs where both individuals are male; **MF pairs**, twin pairs where one individual is male and the other is female; **IQR**, interquartile range.

Estimation of \( h^2 \) and \( c^2 \). We used a twin-based method to estimate the proportion of phenotypic variance resulting from additive genetic factors (that is, the narrow-sense heritability, \( h^2 \)) and variance resulting from environmental factors shared between twins (\( c^2 \)). Given the lack of zygosity information, we estimated \( h^2 \) and \( c^2 \) using the difference in correlation between same sex (\( r_{\text{same sex}} \)) and opposite sex twin pairs (\( r_{\text{opposite sex}} \)), assuming that opposite sex pairs are dizygotic and same sex twin pairs are a mixture of monozygotic and dizygotic twin pairs (Methods). We tested the validity of the assumption that \( r_{\text{same sex}} \) is a good proxy for same sex dizygotic twin correlation (\( r_{\text{DZSS}} \)) by creating a non-twin sibling cohort and estimating the correlation between same sex dizygotic correlation (\( r_{\text{DZSS}} \)) and opposite sex dizygotic correlation (\( r_{\text{DZOS}} \)) for all 551 binary phenotypes (Supplementary Note). We found \( r_{\text{DZSS}} \) and \( r_{\text{DZOS}} \) were highly correlated \(( r = 0.978, 95\% \text{ CI: 0.974, 0.981} \)) (Supplementary Fig. 2). Also, for 95\% of phenotypes, \( r_{\text{DZSS}} = r_{\text{DZOS}} \) ranged between −0.012 and 0.051 and \( r_{\text{DZSS}} \) was, on average, 0.017 higher than \( r_{\text{DZOS}} \) (Supplementary Fig. 3), but for 23.5% of phenotypes \( r_{\text{DZSS}} = r_{\text{DZOS}} \) followed the null distribution (\( p_{\text{null}} \) statistic)\(^{11} \). We conclude that \( r_{\text{DZSS}} \) is highly correlated with \( r_{\text{DZOS}} \) for these 551 phenotypes. However, we found that \( r_{\text{DZOS}} \) is slightly lower, on average, than \( r_{\text{DZSS}} \). Therefore, the estimates of \( h^2 \) and \( c^2 \) will be slightly biased. We also found \( r_{\text{DZOS}} \) is, in general, larger than both \( r_{\text{DZSS}} \) and \( r_{\text{DZOS}} \) (Supplementary Fig. 4). Therefore, using \( r_{\text{DZSS}} \) instead of \( r_{\text{DZOS}} \) as a proxy for \( r_{\text{DZOS}} \) replaces one biased estimator for another (Supplementary Note). We also found strong evidence to the validity of our assumption of Weinberg's Rule (Supplementary Note).

Overall phenome-wide summary of \( h^2 \) and \( c^2 \). The inverse-variance weighted mean estimate among all phenotypes was 0.316 (95\% CI: 0.296, 0.335) for \( h^2 \) and 0.088 (95\% CI: 0.074, 0.102) for \( c^2 \) (Fig. 2a). In addition, among all phenotypes, the opposite and same sex correlations for twins \(( r_{\text{same sex}} = 0.307, 95\% \text{ CI: 0.297, 0.318}, r_{\text{DZSS}} = 0.240, 95\% \text{ CI: 0.229, 0.251}) \) were higher than for the siblings \(( r_{\text{DZSS}} = 0.199, 95\% \text{ CI: 0.192, 0.206}, r_{\text{DZOS}} = 0.182, 95\% \text{ CI: 0.175, 0.189}) \). The \( r_{\text{DZOS}} \) estimate was highest because same sex twin pairs are a mixture of monozygotic and dizygotic twin pairs. The higher value for \( r_{\text{DZOS}} \) compared to both \( r_{\text{DZSS}} \) and \( r_{\text{DZOS}} \) was a result of larger twin shared environment versus the sibling shared environmental effect.

Accounting for multiple hypotheses by controlling the false discovery rate (FDR) at 5\%, we found 326/560 (58.2\%) phenotypes had a non-zero heritability \(( h^2 > 0 \) and 180/560 (32.1\%) phenotypes had non-zero shared environmental effects \(( c^2 > 0 \)) for these phenotypes, 225/560 (40\%) \( h^2 \) estimates and 138/560 (24.6\%) \( c^2 \) estimates remained significant at a more stringent significance level by Bonferroni-adjusted \( P < 0.05 \). We show a volcano plot of both \( h^2 \) and \( c^2 \) estimates for all 560 phenotypes, where the dotted line represents the FDR threshold for each statistic (Fig. 2b,c). The majority of age \(( \beta_{\text{age}} \) and sex \(( \beta_{\text{sex}} \) fixed effects were also non-zero (Methods and equation (2)). Controlling for multiple hypotheses using an FDR threshold of 0.05 there were 487/560 (86.9\%) phenotypes for \( \beta_{\text{age}} \) and 281/560 (50.1\%) phenotypes for \( \beta_{\text{sex}} \) that were FDR significant, respectively (see URLs).

Among functional domains with at least five phenotypes, the domains with the highest \( h^2 \) were quantitative laboratory measures \(( h^2 = 0.799, 95\% \text{ CI: 0.551, 1.048}, \) seven out of seven phenotypes reached FDR threshold) and cognitive \(( h^2 = 0.594, 95\% \text{ CI: 0.355, 0.834}, \) four out of five phenotypes reached FDR threshold) (Fig. 2a). The lowest were connective tissue \(( h^2 = 0.170, 95\% \text{ CI: 0.108, 0.233}, 2 \) out of 11 phenotypes reached FDR threshold) and environment \(( h^2 = 0.211, 95\% \text{ CI: 0.161, 0.260, 24 out of 45 phenotypes reached FDR threshold}) (Fig. 2a).

The functional domains with the highest \( c^2 \) were ophthalmological \(( c^2 = 0.183, 95\% \text{ CI: 0.147, 0.218}) \) and respiratory \(( c^2 = 0.182, 95\% \text{ CI: 0.151, 0.213}, 34 \) out of 48 phenotypes reached FDR threshold) and cognitive \(( c^2 = 0.048, 95\% \text{ CI: 0.145, 0.049}, 2 \) out of five phenotypes reached FDR threshold) (Fig. 2a).

From all 560 phenotypes in this study, there were 294 phenotypes (52.5\%) in which \( c^2 \) followed the null distribution (\( p_{\text{null}} \) statistic)\(^{11} \) (Methods), consistent with a model where twin resemblance was solely a result of additive genetic variance.
Cost and comorbidities have significant $h^2$ and $c^2$. We found that average monthly cost had both significant $h^2 > 0$ and $c^2 > 0$ (Fig. 3b) in the twin pairs. Specifically, the estimate of $h^2$ was 0.290 (95% CI: 0.241, 0.339) and 0.433 (95% CI: 0.390, 0.477) for average monthly cost and number of PheWAS comorbidities, respectively. Estimates of $c^2$ were comparable; $c^2 = 0.302$, 95% CI: 0.271, 0.332 for average monthly cost and $c^2 = 0.241$, 95% CI: 0.213, 0.268 for number of PheWAS comorbidities (Fig. 3b). The same and opposite sex twin correlations ($r_{\text{twinSS}}$ and $r_{\text{twinOS}}$) for number of PheWAS comorbidities ($r_{\text{twinSS}} = 0.549$, 95% CI: 0.543, 0.556, $r_{\text{twinOS}} = 0.458$, 95% CI: 0.450, 0.465) were slightly higher than average monthly claims cost ($r_{\text{twinSS}} = 0.508$, 95% CI: 0.501, 0.515, $r_{\text{twinOS}} = 0.447$, 95% CI: 0.439, 0.455) (Fig. 3b).

Specific geocoded environmental factors. In the same model, we estimated the proportion of variance in a phenotype attributable to environmental risk factors (based on home zip code), including an SES ‘index’ (Supplementary Note) (var$_{\text{SES}}$), median air quality index exposure (var$_{\text{AQI}}$), and median monthly average temperature exposure (var$_{\text{temp}}$) in addition to $h^2$ and $c^2$. The variance components for environmental risk factors were modest compared to $h^2$ and $c^2$. For all phenotypes, var$_{\text{SES}} = 0.002$ (95% CI: 0.002, 0.002), var$_{\text{AQI}} = 0.0001$
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Comparison to published literature. We compared our estimates of \( h^2 \) and \( c^2 \) to a large meta-analysis of twin studies\textsuperscript{12} (meta-analysis of twin correlations and heritability, MaTCH) containing 9,568 phenotypes from 5,169,879 twin pairs where monozygotic heritability—published studies

![Fig. 3](https://example.com/fig3.png)

Figure 3 | Comparison of \( h^2 \) estimates in CaTCH to published literature and estimates for cost and comorbidities in CaTCH. 

**a** Scatterplot of published \( h^2 \) estimates from 56,396 twin pairs in CaTCH versus \( h^2 \) estimates from 81 published studies; vertical and horizontal error bars represent 95% CI for CaTCH and published estimates, respectively; black line is line with slope 1 and intercept 0, blue line is line of best fit and grey shaded region is 95% CI for line of best fit. 

**b** Barplot of estimates of \( h^2 \), \( c^2 \), \( r_{\text{twinOS}} \), and \( r_{\text{twinSS}} \) for the phenotypes average monthly cost and number of PheWAS comorbidities from 56,396 twin pairs; error bars represent 95% CI.

(95% CI: 0.0003, 0.0005), and \( \text{var}_{\text{emp}} = 0.001 \) (95% CI: 0.001, 0.001) were much smaller than the mean estimates of \( h^2 \) and \( c^2 \) described earlier (Supplementary Fig. 5). Controlling for multiple hypotheses using an FDR threshold of 0.05, we found 145/560 phenotypes for \( \text{var}_{\text{emp}} \) and 117/560 phenotypes for \( \text{var}_{\text{emp}} \) that passed FDR significance. Phenotypes with the largest \( \text{var}_{\text{emp}} \) were morbid obesity (\( \text{var}_{\text{emp}} = 0.027 \), 95% CI: 0.014, 0.039) and benign neoplasm of skin (\( \text{var}_{\text{emp}} = 0.024 \), 95% CI: 0.022, 0.027). Phenotypes with the largest \( \text{var}_{\text{emp}} \) were Lyme disease (\( \text{var}_{\text{emp}} = 0.008 \), 95% CI: 0.006, 0.011) and average monthly cost (\( \text{var}_{\text{emp}} = 0.006 \), 95% CI: 0.004, 0.009). Phenotypes with the largest \( \text{var}_{\text{emp}} \) were lead poisoning (\( \text{var}_{\text{emp}} = 0.039 \), 95% CI: 0.029, 0.048) and influenza (\( \text{var}_{\text{emp}} = 0.036 \), 95% CI: 0.033, 0.039) (Fig. 2d–f).

Discussion

Here we used a large insurance claims dataset to systematically investigate the genetic and environmental contributions in phenotypic variation of 560 phenotypes, including specific environmental risk factors, such as SES, pollution exposure, and climate. Furthermore, we provide estimates of the contributions of genetics and environment in aggregate health cost and comorbidity burden, which are important for both biological research and policy implementation. We also quantified the contribution of one's genetic code and aspects of one's zip code (SES, climate, and air pollution) on the same scale of phenotypic variation for 551 disease-related phenotypes by linking to external geographic databases.

A notable strength of our study was the creation of a large twin cohort. To the best of our knowledge, we amassed the largest twin cohort in the United States that is reflective of household, geographic, and medical-service-based variation of the employed US population. The largest known US twin registries are the Mid-Atlantic Twin Registry (28,000 pairs) and Michigan State Twin Study (15,924). The largest international twin registries are from Sweden (97,000) and Denmark (85,000)\textsuperscript{13}. Our twin cohort is comparable in size to these large international twin registries. However, unlike some of these registries, we lack zygosity status for these twin pairs. Furthermore, because we are using insurance claims data, our claims datasets contained the full transactional history between all medical providers and the insurance company for a particular patient. This includes all International Classification of Disease (ICD) 9/10 billing codes sent from the medical provider to the insurance company to be reimbursed. We claim that this provides a comprehensive view into a patient's medical history. In contrast, electronic medical records, because they are a record of the medical examination process, may have deeper phenotypic information (for example, laboratory notes, radiology reports and X-ray images), but will have an incomplete medical history if the patient sees multiple medical providers.

Twin designs have lower sample size than other family-based designs, but are better powered to estimate heritability\textsuperscript{14}. However, leveraging the family-based design in a claims-based cohort is not without disadvantages. First, a common issue in insurance data includes a limited observational time window to ascertain phenotype. This can lead to ascertainment bias in phenotypes when siblings are of different ages. This is further exacerbated with analysis including parents and children where, as a result of age of onset,
the same phenotypic code may represent different disease subtypes. Second, in a family design, estimates of $h^2$ will be biased if all sources of familial environmental variation are unaccounted (for example, spousal correlation and sibling correlation). Recent family-based studies attempted to estimate some of this familial environmental variation; however, limitations remain, such as the lack of interpretability of multiple types of 'shared environment.' In contrast, twin studies have a simpler design, thereby allowing a single parameter ($c^2$) to account for all shared environment. Third, claims data do not consider that non-biological relationships can also occur when using next of kin information or subscriber relationships. There is a possibility that 'ascertained' nuclear families may contain step-children, adoptions, or half-siblings; however, this can be modeled using Census data and pedigree simulations. By using both the inferred sibling relationship and the fact that they must be born on the same day, we claim that there is a smaller chance of twins being biologically unrelated.

A major component of our analysis was the ability to compare variance components of specific environmental factors with standard measures used in family-based analysis such as heritability and shared environmental variance. We note that each twin pair has the same shared environment, but our analysis attempts to partition phenotypic variance further with several identified shared environmental factors (Methods and equation 6) that are common among groups of twin pairs. We believe partitioning the shared environment into identified environmental factors (indicators of local SES, air pollution, and climate) is akin to analysis in partitioning heritability among functional annotations. We found that variance components resulting from specific environmental factors were significantly lower than $h^2$ and $c^2$ overall and within each functional domain.
Table 2 | Quintiles for each environmental variance component

| Quintile | Deprivation index (PCI component) | Number of pairs | AQI scale | Number of pairs | Average temperature (degrees Fahrenheit) | Number of pairs |
|----------|----------------------------------|----------------|-----------|----------------|------------------------------------------|----------------|
| 1        | (−7.516, −1.12)                  | 2,652          | (10.580, 33.048) | 8,397          | (26.190, 50.879) | 7,282 |
| 2        | (−1.12, −0.21)                   | 3,892          | (33.048, 37.319) | 12,211         | (50.879, 55.241) | 12,948 |
| 3        | (−0.210, 0.666)                  | 6,098          | (37.319, 41.324) | 12,420         | (55.241, 60.517) | 10,777 |
| 4        | (0.666, 1.915)                   | 10,838         | (41.324, 45.602) | 11,525         | (60.517, 66.437) | 7,844  |
| 5        | (1.915, 9.601)                   | 24,653         | (45.602, 62.721) | 3,580          | (66.437, 81.295) | 9,282  |

Specific environmental factors had little role in variation of most phenotypes, but we found intriguing results for a few phenotypes. The phenotype with largest socioeconomic variance component was morbid obesity (varSES = 0.027, 95% CI: 0.014, 0.039). For Lyme disease, the variance components of all three environmental risk factors passed FDR significance for the phenotype (varenv = 0.022, 95% CI: 0.015, 0.028, varAQI = 0.006, 95% CI: 0.004, 0.009, vartemp = 0.028, 95% CI: 0.023, 0.033). For lead poisoning, vartemp was FDR significant (vartemp = 0.029, 95% CI: 0.017, 0.042).

In the United States, predictors of health care cost and chronically ill patients are of particular importance. In a recent analysis of high-cost patients, the researchers emphasized that prediction of high-cost patients is important, yet current prediction methods do not include the environment. We also tested the assumption of using Weinberg’s Law, and the environment may change when assessing siblings rather than twins. We also tested the assumption of using Weinberg’s Law, and the effect of in vitro fertilization had little to no effect on h²/c² estimates (Supplementary Note).

Data on patients from health claims lack zygosity information that is typically ascertained in standard twin registries; however, by amassing a large number of non-twin sibling pairs from the same dataset, we found that the opposite sex twin correlation was close to sibling correlations. For our method to be internally valid, we make the following claims. First, we assume that phenotypic correlation of opposite sex twin pairs (rTwinSS) is equivalent to dizygotic same sex twin pairs (rTwinDZ). Second, we estimate the proportion of same sex twin pairs are monozygotic by assuming opposite sex and same sex dizygotic twin pairs are equally (Methods and equation 19). We tested the first claim by interrogating the concordance between same sex and opposite sex sibling correlations. We found that rTwinSS and rTwinDZ were highly correlated (r = 0.978, 95% CI: 0.974, 0.981), and, on average, rTwinSS was slightly higher than rTwinDZ (average rTwinSS − rTwinDZ = 0.017) for the 560 phenotypes passing our filtering criterion (Supplementary Note) and for 23.5% of phenotypes rTwinSS − rTwinDZ followed the null distribution. We conclude that, overall, rTwinDZ is a proxy for rTwinSS. We note that rTwinOS was higher than rTwinDZ, and rTwinOS for most phenotypes, suggesting increased h² and decreased c² if rTwinOS or rTwinDZ were substituted for rTwinSS for those traits. We claim that high correlation rTwinSS and rTwinDZ is primarily a result of two factors. First, our phenotypic selection procedure eliminated phenotypes with large imbalances of sex-specific prevalence. Second, we added sex as a covariate (‘fixed-effect’) to adjust for the mean differences between males and females. If rTwinOS were then for the majority of phenotypes the estimate of h² would increase and c² would decrease, raising the possibility that the contribution of the environment may change when assessing siblings rather than twins. We also tested the assumption of using Weinberg’s Law, and effect of in vitro fertilization had little to no effect on h²/c² estimates (Supplementary Note).

In our analysis, we ascertained twin pairs between the ages of 0 and 24. This selection criterion eliminated our ability to study late-onset diseases such as Parkinson’s and Alzheimer’s disease. As with any administrative dataset, there may be errors in ascertainment of phenotype; for example, doctors may not be sure whether a child has type 1 diabetes or type 2 diabetes and therefore may bill for both diseases and therefore the individual may be ascertained as having both diseases. Such bias may be reduced by applying phenotyping algorithms (for example, for diabetes) for each phenotype; however, only a limited number of such algorithms exist.

In summary, our results provide a comprehensive picture of the contribution of genetics and the environment to a large number of phenotypes. We also estimated the contribution of specific environmental risk factors in phenotype. Our estimates provide a useful baseline for determining the potential of further genetic and/or epidemiological research for a number of phenotypes of clinical relevance, applicable and complementary to precision medicine efforts, such as All of Us.

URLs. American Community Survey: https://factfinder.census.gov/; EPA AQI: https://aqi.epa.gov/aqicnweb/airdata/download_files.html#AQI; NOAA Monthly Temperature: https://www.ncdc.noaa.gov.
Online content
Any methods, additional references, Nature Research reporting summaries, source data, statements of data availability, and associated accession codes are available at https://doi.org/10.1038/s41588-018-0313-7.

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Author contributions
All authors contributed extensively to the work presented in this paper. C.M.L., P.M.V., and C.J.P. designed experiments, analysed data, and wrote the manuscript. B.T.T. developed the Shiny App for analysis. B.T.T., A.K.M., and J.Y. contributed to iterative development of the manuscript.

Competing interests
The authors declare no competing interests.

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Methods

Study population. We obtained our data from un-identifiable member claims data from Aetna Inc, a national health insurance company. The claims dataset contained the ICD 9/10 billing codes of 44,859,462 members with an Aetna Insurance plan from January 2008 to February 2016 (Supplementary Fig. 6a). This was a nationally representative dataset; 26,713 of 41,739 US mail zip codes have at least 20 members. We extracted a twin and sibling cohort to estimate genetic and environmental contribution in 560 phenotypes (Supplementary Fig. 6e–k).

Twin and sibling cohort creation. We created the twin cohort by extracting primary subscribers and their dependents. Specifically, a primary subscriber would add ‘dependents’ to his/her policy (approximately 26.1% are sole subscribers) and dependent individuals were coded as ‘child’, ‘grandchild’, ‘spouse’, ‘domestic partner’, ‘legal dependent’, and ‘student’. We ascertained family structure in this dataset using the relationship between the primary subscriber and child dependents (Supplementary Fig. 6f). We restricted family size to, at most, 15 members living together (average family size is 3.98) (Supplementary Fig. 6e). Once family units were created, we further extracted twins by comparing the birthdate of child subscribers that are linked to the same primary subscriber. We selected families were created, we further extracted twins by comparing the birthdate of child subscribers and environmental contribution in 560 phenotypes (Supplementary Fig. 6f). We restricted family size to, at most, 15 members living together (average family size is 3.98) (Supplementary Fig. 6e). Once family units were created, we further extracted twins by comparing the birthdate of child subscribers that are linked to the same primary subscriber. We selected families where there is only one twin pair and eliminated children that are part of a triplet or greater because the assumption of $h^2$ and $c^2$ assumed twin pairs are independent and not part of an extended pedigree (Supplementary Fig. 6g).

We created a sibling cohort as a basis for comparison to our twin cohort. Like the twin cohort, the sibling cohort utilized dependent information from the primary subscriber in order to determine sibling pairs (Supplementary Fig. 6j). The sibling cohort also included families where there were at most 15 members. Individuals must be born on or before 1985, individuals were enrolled as members for at least 36 months, and each individual had at least one ICD9/10 code (Supplementary Fig. 6b–d). The age difference between sibling pairs had to be at least 11 months and no more than 36 months (Supplementary Fig. 6k). Also, for each family, a single sibling pair that meet these conditions was selected at random (Supplementary Fig. 6k).

Comparison of twin cohort to national population. We compare our twin cohort to the general population using American Community Survey (ACS) Census data. In particular, we ascertained all twins that were members, for at least one year between 2009–2013 and compared with the 2009–2013 ACS estimates. Using Census data, we estimated a measure for SES for each zip code called the deprivation index, a measure used in epidemiological literature[25] (Supplementary Note). The deprivation index is a measure of SES for a zip code based on seven Census variables that were extracted from the 2009–2013 ACS (see URLs). High deprivation index values correspond to higher SES status and vice versa. For all individuals in the 2009–2013 ACS, we estimated the population density (transform of number of people per square mile) and deprivation index based on their home zip code and compare to the population density and deprivation index of all twins, enrolled between 2009–2013, based on their home zip code. We observed that more twin pairs live in high population density areas compared to the general population (Fig. 1h). The SES status of twin pairs, based on their home zip code, is slightly higher than the general US population (Fig. 1c).

Phenotype ascertainment. The claims dataset contained all ICD version 9/10 (hereafter ICD9/10, respectively) billing and diagnostic codes provided by the healthcare provider to the insurance company (Aetna, Inc.) for transactional purposes while the individual was a subscriber to the health plan. In practice, many ICD9/10 codes may represent the same overarching phenotype, for example, ICD 250.00 represents type 2 diabetes that is controlled, while 250.02 is type 2 diabetes that is uncontrolled. Thus, we used PheWAS code groupings[25]. PheWAS codes are a way of combining ICD9 codes, used for phenotype-wide association studies[25]. Multiple ICD9/10 codes are combined into a single ‘phenotype’. Specifically, an individual was identified as positively having a PheWAS phenotype if they had at least one ICD 9/10 code from the PheWAS code grouping, for example, ICD 9 codes 250.00 and 250.02 both mapped to PheWAS code 250.2 type 2 diabetes. For rarer phenotypes, we utilized the groupings found in Blair, Rzehkowsky et al.[25] (we will collectively refer to these phenotypes as PheWAS codes). In total, we mapped Aetna subscriber ICD9/10 diagnostic codes to 1,900 PheWAS codes (Supplementary Fig. 6c). PheWAS mappings were originally constructed using ICD9 codes, but the surveillance period for the insurance data spanned the transition from ICD9 to ICD10. In order to accommodate ICD10 codes, we utilized the United States Center for Disease Control and Prevention 2016 General Equivalency Mapping of ICD10 (see URLs) codes to ICD9 and subsequently to PheWAS codes.

For a subset of individuals, the claims dataset provided results of diagnostic clinical laboratory tests (hereafter called ‘lab test’) conducted during the individual’s medical care (Supplementary Fig. 6c). Each lab test was identified by a logical observation identifier name and code[25]. For only the twin cohort, we ascended all lab tests where twin pairs were measured on the same day. In our analysis we included all laboratory tests where there were at least two lab tests that match our criterion. The phenotypes we analysed include common laboratory tests such as low density lipoprotein cholesterol, high density lipoprotein cholesterol, triglycerides, leukocyte counts and hemoglobin counts. If a twin pair had multiple lab tests, then we randomly sampled a single lab test event for analysis.

Out of a total of 1,900 binary phenotypes, we removed phenotypes with low prevalence or where disparity in male and female prevalence was high (Supplementary Fig. 6d) among twin pairs. In particular, for each phenotype, we imposed a filtering criterion where the ratio of male prevalence to female prevalence (or female to male prevalence) among twin pairs must be less than five (Supplementary Fig. 6d). In addition, only phenotypes with a prevalence of at least 0.3% were kept, resulting in phenotypes where at least 338 cases were expected and at least one concordant same sex and opposite sex pair allowing for stable estimation of $h^2$ and $c^2$, resulting in 551 binary phenotypes. In the case of the quantitative phenotypes, we analysed laboratory values that had at least 2,000 twin pairs (Supplementary Fig. 6d). For the sibling pairs, we ascertainment only the 551 binary phenotypes.

For the twin cohort, in the claims dataset, we utilized an opportunity to derive phenotypes based on aggregate claims, including the total number of PheWAS codes per individual (or comborbidities) and the average monthly cost incurred per individual (hereafter called ‘average monthly cost’). The number of PheWAS codes was calculated from distinct PheWAS codes ascertained for a patient (or individual) during the time of surveillance (at least 36 months) and can be thought of as the total number of ‘comorbidities’ coded for each individual. Average monthly cost was the total claim costs divided by the months that the individual was a member of this insurance company when the costs were incurred.

Specific environmental risk factors. For each twin pair we ascertained their home zip code and linked to Census data deprivation index, daily air quality index data, and monthly average temperature data. The deprivation index is a composite score of SES for a zip code based on seven variables from the 2009–2013 ACS (Supplementary Note). The Environmental Protection Agency used the air quality index (AQI) to summarize air pollution level in a particular location. The AQI has a range between 0 and 500. An AQI value between 50–100 is moderate air quality, 50–100 is considered unhealthy air quality. We downloaded all daily county-level AQI data provided by the EPA (see URLs) and estimated the median AQI level exposure for each twin pair based on the twin pairs dates of enrollment and closest county to their zip code (maximum distance of 30km) (Fig. 1d). We also ascertained all monthly average temperature data from sensors located throughout the United States from the National Atmospheric and Oceanic Administration (NOAA) (see URLs). For each twin pair, we found the closest NOAA sensor to their home zip code and extracted all monthly average temperature data based on their months of enrollment within the insurance claims dataset, then estimated the median monthly average temperature based on those values (Fig. 1e). This linkage provided, for each twin pair, a quantitative measurement for median family income, median AQI and median monthly average temperature based on their home zip code. The quantitative value for each environmental risk factor was binned into quintiles based on the distribution of the quantitative value among the general US population (see Table 2 for the ranges and number of twin pairs in each quintile).
pairs but different for opposite sex pairs, thus the covariance between individuals $i$ and $j$ in a pair is $cov(y_i, y_j) = V_{pair} + V_{extraSS}$ for opposite sex pairs and $cov(y_i, y_j) = V_{pair} + V_{extROS}$ for same sex pairs. Same sex and opposite sex variance components were estimated as follows:

$$V_{twinSS} = V_{pair} + V_{extraSS}$$

(3)

$$V_{twinOS} = V_{pair}$$

(4)

$$V_{ext} = V_{pair} + V_{extraSS} + V_{res}$$

(5)

This model was extended to include environmental risk random effects $u_{env}$ and $u_{temp}$ based on the quintiles (Table 2) for each environmental risk factor, written as follows:

$$y = X\beta + u_{pair} + u_{extraSS} + u_{SS} + u_{DZ} + u_{temp} + \epsilon$$

(6)

The random effects $u_{pair}$ and $u_{extraSS}$ are the same as in equation (2), while the random effects $u_{SS}$, $u_{DZ}$ and $u_{temp}$ will be common to all individuals belonging to the same deprivation index, AQI or temperature quintile bin, respectively.

Estimation of twin same sex and opposite sex correlation. We used variance components $V_{extraSS}$ and $V_{extROS}$ to estimate $h^2$ and $c^2$ by first transforming them into correlation on the observed scale:

$$r_{twinSS01} = \frac{V_{twinSS}}{V_{ext}}$$

(7)

$$r_{twinOS01} = \frac{V_{twinOS}}{V_{ext}}$$

(8)

Conversion of binary phenotypes to liability scale. In the case of quantitative (real-valued) phenotypes, we used correlations $r_{twinSS}$ and $r_{twinOS}$ on the observed scale to estimate $h^2$ and $c^2$, but in the case of binary phenotypes we transformed these correlations onto the liability scale. The transformation of correlation from the observed scale to the liability scale was estimated as follows (opposite sex formulas are same as same sex) :

$$T = \Phi^{-1}(1-K)$$

(9)

$$z = \Phi(T)$$

(10)

$$i = \frac{z}{K}$$

(11)

$$E^h_{twinSS} = K + \frac{V_{twinSS}}{K}$$

(12)

$$T_{twinSS} = \Phi^{-1}(1-E^h_{twinSS})$$

(13)

$$r_{twinSS} = \frac{(T-T_{twinSS})}{\sqrt{1-(T^2-T_{twinSS}^2)(1-T)}}$$

(14)

Estimation of heritability and shared environmental variance. In traditional twin studies, where zygosity of twins were known, the $h^2$ and $c^2$ of a phenotype were calculated using the monozygotic (MZ) twin correlation $r_{twinMZ}$ and dizygotic (DZ) same sex twin correlation $r_{twinDZSS}$ as follows:

$$h^2 = 2(r_{twinMZ} - r_{twinDZSS})$$

(18)

$$c^2 = 2r_{twinDZSS} - r_{twinMZ}$$

(19)

In a health administration dataset, the zygosity status of twins is not known. However, opposite sex twin pairs are dizygotic and same sex twin pairs are a mixture of monozygotic and dizygotic pairs. Assuming the probability of a dizygotic twin pair being same sex is 50% (Weinberg’s Rule29), we estimated the probability $p$ of a pair being monozygotic given they are same sex is calculated as follows6,30,31:

$$p(MZ) = 1 - 2p(OS) = 1 - 2 \frac{N_{SS}}{N_{SS} + N_{DZ}}$$

(19)

$$p(SS) = \frac{N_{SS}}{N_{SS} + N_{DZ}}$$

(20)

$$p = p(MZ|SS) = p(MZ)$$

(21)

where $N_{SS}$ was the total number of twin pairs, $N_{DZ}$ was the number of opposite sex pairs and $N_{SS}$ was the number of same sex pairs. Assuming $r_{twinOS}$ was equal to $r_{twinDZSS}$ and $r_{twinSS}$ was a mixture of $r_{twinDZSS}$ and $r_{twinSS}$ then $h^2$ and $c^2$ were estimated as follows:

$$r_{twinOS} = \frac{r_{twinSS} + (1-p)r_{twinDZSS}}{p}$$

(22)

$$r_{twinSS} = p r_{twinMZ} + (1-p) r_{twinDZSS}$$

(23)

$$h^2 = \frac{2}{p}(r_{twinSS} - r_{twinOS})$$

(24)

$$c^2 = \frac{(p + 1)r_{twinOS} - r_{twinSS}}{p}$$

(25)

We estimated standard errors for $r_{twinSS}$, $r_{twinOS}$, $h^2$, $c^2$, var$SS$, varDZ, varAQI and vartemp via bootstrap resampling (500 samples). In the analysis of binary phenotypes and derived quantitative phenotypes, which use the full twin cohort, the parameter $p$ was 0.42. We estimated the parameter $p$ for quantitative phenotypes, using equation (21), based on the subset of twins that had that particular quantitative phenotype (Supplementary Note). The $p$ estimates for quantitative phenotypes ranged from 0.513 to 0.572.

Multiple comparisons. For all statistics (variance components $h^2$, $c^2$, var$SS$, var$DZ$, var$AQI$ and var$temp$) we estimated $P$ values using a two-tail z-test statistic and we accounted for multiple hypothesis testing by controlling by estimating the FDR. In particular, we used the Benjamini–Yekutieli32 method to estimate the FDR rate that assumes dependencies between phenotypes. We estimated FDR adjusted $P$ values for all statistics and report the number of phenotypes, for each statistic, which achieved FDR < 5%

We fit all random effects models with the 'lmer' package in R.33 We wrote our own bootstrapping procedure in order to estimate standard errors for all statistics presented in this paper. We used the pdmultinom function in the base stats R package for FDR correction.

Matching of PheWAS codes to functional domains from MatTCH. We sought to compare how $h^2$ and $c^2$ estimates compared to the published literature. To enhance comparison, we downloaded $h^2$ and $c^2$ estimates from a large and recent meta-analysis of twin studies11. We mapped PheWAS codes into functional domains as published by the International Classification of Functioning, Disability and Health or International Statistical Classification of Diseases and Related Health Problems (ICD-10). In the claims dataset, we mapped each PheWAS code to their constituent ICD9 code and then mapped again to the corresponding ICD10 chapters and subchapters. If the associated chapter or subchapter from a PheWAS code overlapped with a functional domain then we considered it part of the domain. We estimated the mean $h^2$ and $c^2$ for each domain with an inverse-variance weighting estimate. We also estimated the number of
phenotypes that follow a model due to additive genetic variance and not non-additive genetics (including dominance) or shared environmental variance, which was estimated by the number of phenotypes that follow $2 \tau_{\text{model}} = \tau_{\text{null}}$. This was equivalent to the number of phenotypes that follow the null hypothesis ($\pi_0$ statistic) $c^2 = 0$, which was directly estimated in our study.

Overall and functional domain values of $h^2$ and $c^2$ were calculated with the ‘metafor’ R package by using the DerSimonian–Laird estimator to calculate estimates and standard errors. The $\pi_0$ statistic was estimated using the ‘qvalue’ R package.

Comparison of $h^2$ estimates to published literature. In our analysis, we compared $h^2$ estimates from the published literature to $h^2$ estimates from CaTCH (Supplementary Note). The correlation between CaTCH $h^2$ estimates and published $h^2$ estimates used a correlation estimator that also incorporated standard errors. We used jackknife resampling in order to estimate the standard error for this estimator, as suggested by the authors of this method.

Reporting Summary. Further information on research design is available in the Nature Research Reporting Summary linked to this article.

Data Availability
The data that support the findings of this study are available from Aetna Insurance, but restrictions apply to the availability of these data, which were used under licence for the current study, and so are not publicly available. Please contact N. Palmer (nathan_palmer@hms.harvard.edu) for inquiries about the Aetna dataset. Summary data are, however, available from the authors upon reasonable request and with permission of Aetna Insurance. Code for analysis, generation of figures and figure files is available at https://github.com/cmlakhan/twinInsurance.

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Software and code

Policy information about availability of computer code

| Data collection | All claims data was stored in a Microsoft SQL Server 2014 database. We wrote scripts consisting of SQL queries to extract data from raw insurance data into a form suitable for analysis. SQL scripts are not publicly available due to sensitivity in exposing proprietary insurance information, but can be made available to reviewers upon request. |
| --- | --- |
| Data analysis | We performed all data analysis using R version 3.3.2 and libraries therein. In particular data processing used tools from the tidyverse (1.1.1) library and random effects modeling used the lme4 library (version 1.1-14). R scripts used to perform our analysis can be found in our github repo (https://github.com/cmlakhan/twinInsurance). |

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Life sciences study design

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| Sample size | We are repurposing an existing dataset therefore our sample size was determined based on all individuals that fit our filtering criterion. Our filtering criterion is described in the Online Methods section of our manuscript. |
| Data exclusions | We repurposed an existing dataset which was not meant for twin studies. Therefore, we applied multiple filtering criterion in order to best ascertain twin pairs with a long surveillance period in order to ascertain phenotypes. We describe our filtering process in detail in the online methods section. |
| Replication | N/A |
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