An Epidemiological Human Disease Network Derived from Disease Co-occurrence in Taiwan

Yefei Jiang, Shuangge Ma, Ben-Chang Shia & Tian-Shyug Lee

In “classic” biomedical research, diseases have usually been studied individually. The pioneering human disease network (HDN) studies jointly consider a large number of diseases, analyse their interconnections, and provide a more comprehensive description of diseases. However, most of the existing HDN studies are based on molecular information and can only partially describe disease interconnections. Building on the unique Taiwan National Health Insurance Research Database (NHIRD), in this study, we construct the epidemiological HDN (eHDN), where two diseases are concluded as interconnected if their observed probability of co-occurrence deviating that expected under independence. Advancing from the existing HDN, the eHDN can also accommodate non-molecular connections and have more important practical implications. Building on the network construction, we examine important network properties such as connectivity, module, hub, and others and describe their temporal patterns. This study is among the first to systematically construct the eHDN and can have important implications for human disease research and health care and management.

In “classic” biomedical research, diseases have usually been studied individually. Accumulating evidences have shown that diseases can be interconnected. For example, epidemiological studies have suggested the correlation between asthma and certain type of cancers. Mutations in certain gene pathways, such as DNA repair and apoptosis, can lead to an elevated risk of multiple cancer types, making them “correlated”. In some early studies, a small number of pre-selected diseases were studied. A breakthrough is the pioneering human disease network (HDN) research, under which a large number of diseases are simultaneously considered, and their interconnections are modelled.

Promising findings have been made in the HDN and other pan-disease studies. Notable studies include Calvano et al., which explored the genome-wide interaction network and suggested that network analysis using comprehensive knowledge can identify new functional modules perturbed in the disease processes. Feldman et al. investigated the network properties of complex disease genes and found that network neighbours of known disease genes form an important class of candidates for identifying novel genes for the same disease. Hidalgo et al. integrated different genetic, proteomic, and metabolic datasets, proposed a Phenotypic Disease Network, and found that disease progression can be represented and studied using network methods, offering the potential to enhance our understanding of the origin and evolution of human diseases. Barabási et al. found that network medicine is essential for identifying new disease genes, for uncovering the biological significance of disease-associated mutations, and for identifying drug targets and biomarkers for complex diseases.

Many of the recent HDN and other pan-disease studies, including the aforementioned, are based on molecular information. Such studies, despite significant successes, may have limitations. Most, if not all, diseases are only partially molecular. Shared environmental exposures, socioeconomic risk factors, and others can also lead to correlations among diseases. However, such non-molecular correlations cannot be effectively reflected in the existing HDNs. Shared molecular risk factors can only suggest the potential correlation in disease occurrence. That is, two diseases sharing common molecular risk factors not necessarily have a significantly higher (or lower) probability of co-occurrence, which may make the molecular HDNs practically less relevant. In addition, searching for the molecular basis is still an ongoing effort for most diseases, which may cast concerns on the credibility of the molecular HDNs.

1Graduate Institute of Business Administration, College of Management, Fu Jen Catholic University, New Taipei City, 24205, Taiwan. 2Yale School of Public Health, New Haven, Connecticut, United States of America. 3College of Management, Taipei Medical University, Taipei, 11031, Taiwan. Correspondence and requests for materials should be addressed to S.M. (email: shuangge.ma@yale.edu) or T.-S.L. (email: 036665@mail.fju.edu.tw)
There are also a few studies that establish disease interconnections based on clinical and epidemiological data. However, with constrained data availability, they are often limited to a small number of diseases and possibly biased sample selection. The goal of this study is to construct the epidemiological HDN (eHDN), where two diseases are concluded as connected if their probability of co-occurring in clinics deviating from that expected under independence. This effort will take advantage of the unique Taiwan National Health Insurance Research Database (NHIRD; more details below). The eHDN fits the HDN analysis paradigm and will have similar important implications as the existing HDNs. On the other hand, it may advance from the existing literature in multiple aspects. Built on data observed in clinics, it can accommodate both molecular and non-molecular disease connections and hence be more comprehensive. By directly built on observed disease occurrence, it can be practically more relevant. In addition, with the huge sample size of NHIRD, the constructed network can be more reliable than some of the existing ones. Overall, this eHDN analysis may complement the existing molecular HDNs and significantly advance our understanding of disease interconnections from an epidemiological perspective. It may provide important insights for health care and management.

Methods

Database. Taiwan launched the single-payer national health insurance (NHI) programme on March 1st, 1995. By the end of 2004, about 99.9% of the Taiwan population were enrolled. With the high cost of treatments that are not insured or by commercial insurance, the dominating majority of hospital/clinic-based disease treatments go through NHI. To get insurance reimbursement, hospitals and clinics are required to provide comprehensive data on each disease treatment episode. Data are then sorted and stored in NHIRD. Compared to other databases, unique advantages of the NHIRD may include unbiasedness (virtually the whole Taiwan population are covered), comprehensiveness (comprehensive information are available on all inpatient and outpatient treatment episodes), and uniformity (all data are collected and stored under the same protocol). NHIRD has served as the basis of a large number of biomedical and public health studies (with already close to 400 publications in PubMed). We refer to Hwang et al. and the NHIRD website for more detailed information on NHIRD.

In this study, we retrieved data collected between 2000 and 2013 from NHIRD. The initial dataset contains records on one million subjects (about 4.26% of Taiwan’s population) randomly selected from the 2005 registry for beneficiaries. In NHIRD, each subject has a unique ID, which is used to link different databases. For our analysis, we analysed both outpatient and inpatient treatments, with information in the CD (ambulatory care expenditures by visits) and DD (inpatient expenditures by admissions) files, respectively.

For disease identification, the ICD-9-CM code was used. Prior to 2005, the ICD-9-CM 1992 version was used. For consistency, it was converted to the 2001 version. With more interest on diseases, following the literature, records with the E and V codes (external causes of injury and supplemental classification), 630–679 (Pregnancy, Childbirth and Puerperium Complications), and 760–999 (Symptoms, Signs & Ill-Defined Conditions) of ICD-9-CM were removed from analysis. Limitations of the ICD-9 code have been recognised. For example, it may be biased by experts’ discrimination. In addition, the vocabulary used to describe multiple patient billing codes may actually describe the same clinical disease. To address such problems, following the literature, we adopted the electronic health record (EHR) driven Phenome-wide association studies (PheWAS) codes (PheCode), which group the ICD-9 codes into 1,723 PheWAS Codes (PheCode). To generate more reliable estimates, we focused on common diseases defined as having nonzero occurrence in each of the fourteen calendar years, leading to a total of 1,356 diseases for downstream analysis. More information on data processing is provided in Supplementary Information (SI). On the patient side, records with inconsistency (for example, conflicting sex information) were removed to ensure a high standard of analysis. The final analysed dataset contains records on 986,646 patients with 1,381,749 inpatient and 173,355,725 outpatient episodes in the study period. Among them, there are 486,992 males and 499,654 females. More information is provided in SI.
This study was exempt from full review by the Institutional Review Board of Fu Jen Catholic University, as only de-identified data are analysed for a research purpose.

Network-based Analysis. Our network analysis is based on the WGCNA (weighted gene co-expression network analysis)\[^15\], which was originally designed for the analysis of gene expression data and has demonstrated satisfactory performance in a large number of publications\[^16-19\]. A closer examination of WGCNA suggests that its applicability is not limited to gene expression data. For the completeness of this article, below the analysis steps are briefly described, and readers are referred to Horvath for more details\[^20\]. It is noted that although with some minor changes, the main advancement of this study is not on the WGCNA technique itself. Rather, this study marks a new and innovative application of the WGCNA technique. A flowchart describing the proposed analysis procedure is shown in Fig. 1. Below we provide more details on each analysis step.

Network Construction. In the eHDN analysis, a node corresponds to a disease, and two diseases are connected with an edge if their probability of co-occurrence deviating from that expected under independence. The edge information is accommodated in the adjacency matrix. Denote \(n\) as the number of diseases. For diseases \(i\) and \(j\) \((i,j \in 1, \ldots, n)\), their \(\phi\)-correlation is computed as:

\[
s_{ij} = -\frac{C_{ij}N - PP_i}{\sqrt{PP_i PP_j} (N - P_i) (N - P_j)}
\]

where, for a fixed time period, \(C_{ij}\) is the number of patients with both diseases (treated in the same or different, inpatient or outpatient, episodes), \(N\) is the total number of patients, and \(P_i\) and \(P_j\) are the number of patients with diseases \(i\) and \(j\). Denote \(S = [s_{ij}]\) as the \(n \times n\) similarity matrix with its \((i,j)\)th element being \(s_{ij}\). Then the \(n \times n\) adjacency matrix \(A\) can be defined where \((i,j)\)th element is

\[
a_{ij} = \text{adjFunc}(s_{ij}, \tau) \equiv \begin{cases} s_{ij} & \text{if } s_{ij} \geq \tau \\ 0 & \text{if } s_{ij} < \tau \end{cases}
\]

Here the threshold \(\tau\) is imposed to remove spurious small correlations, only retain the large ones, and generate a sparse and more interpretable network. Its value is chosen using the scale-free topology criterion\[^3,21\], which has been extensively adopted in the literature. In the adjacency matrix, all components take values between 0 and 1 (that is, positive and negative correlations are treated in the same manner). Two diseases are more strongly correlated (positive or negative) if their corresponding value in the adjacency matrix is bigger.

---

**Figure 2.** Top ten diseases with the highest prevalence (top) and their connectivity (bottom).
Connectivity, Module, and Hub. For node (disease) $i$, its connectivity is defined as $K_i = \sum_{j \neq i} a_{ij}$, which quantifies how strongly it is connected to the other nodes. In the literature, an alternative definition of connectivity has also been considered, where $k_i = \sum_{j \neq i} \text{TOM}_{ij}$ (the definition of TOM is provided below. More information on the two connectivity measures is provided in SI).

An important network concept is module (also referred to as “community” in some studies), which is composed of tightly connected nodes. Consider the topological overlap matrix (TOM), where its $(i, j)$th element is:

$$
\text{TOM}_{ij} = \frac{l_{ij} + a_{ij}}{\min\{k_i, k_j\} + 1 - a_{ij}}
$$

(3)

with $l_{ij} = \sum a_{u,v} a_{v,j}$. Loosely speaking, $l_{ij}$ measures how many neighbour nodes that $i$ and $j$ shared. $\text{TOM}_{ij}$ measures the distance between diseases $i$ and $j$ in a network sense. Accordingly, define $\text{dissTOM}_{ij} = 1 - \text{TOM}_{ij}$, which is non-negative and symmetric and measures the dissimilarity between any two diseases. With matrix $\text{dissTOM}$, whose $(i, j)$th element is $\text{dissTOM}_{ij}$, modules can be identified by hierarchical clustering with a dynamic tree cutting approach.

With each module, connectivity can be re-computed and referred to as intramodular connectivity. Nodes (diseases) with the highest correlation with the eigen-diseases (definition below) are identified as hubs.

Remarks. The network quantities described above have important implications. Adjacency directly describes how strongly two diseases are connected to each other. Of interest are diseases that are tightly interconnected. In health care management and planning, such diseases should be considered together as opposed to individually. In network analysis, it has been suggested that more highly connected nodes play more important roles in a network. It is thus of interest to examine connectivity and identify the highly connected ones. Such nodes (diseases) may have a higher priority in disease control and prevention, as they can potentially have a higher impact on the overall health conditions. In biomedical research, clustering/classifying diseases is an important task, and the module structure provides an alternative way for disease clustering. Diseases within the same modules can potentially...
share common risk factors (and thus the analysis can have scientific value) and be treated with similar regimens (and thus the analysis can have practical value).

Temporal Trends. For all diseases, occurrence rates change over time. In addition, occurrence observed in clinics is also affected by diagnosis and other factors, which are also time-dependent. As such the eHDN and its quantities described above change over time. By conducting analysis year by year and comparing across time, we are able to obtain the temporal trends of the eHDN. This is significantly different from the molecular HDNs, which are static. For scalar quantities, variation over time can be directly assessed. For the module structure, we assess variation using the Jaccard indexes for modules obtained in consecutive years.

Visualisation. The patient-disease relationship and disease correlations can be visualised using heatmaps. The overall network structure can be visualised using the software Gephi. In such a plot, diseases that share edges are connected with lines, the size of a node is proportional to its connectivity, and different modules are represented using different colours. Construction of modules can be visualised using dendrograms and heatmaps. For scalar quantities (prevalence, connectivity, etc.), changes over time can be visualised using scatter plots (possibly with nonparametric fits). Changes of module memberships can be visualised using alluvial diagrams. Changes of modules’ mean connectivity can be visualised using radar charts. The aforementioned visualisation tools provide a more intuitive way of interpreting network structures and properties.

Results
The numbers of patients for each calendar year are shown in Table S1 in SI. In Table S2 in SI, we further present summary statistics on the numbers (proportions) of inpatient and outpatient treatment episodes, stratified by gender, age, and calendar year. Across time, an increasing trend of inpatient treatment is observed. For outpatient treatment, an increasing trend is also observed, although not as prominent as for inpatient. It is noted that the number of observations per year is large enough (larger than many of the peer studies) to make credible inference.

For a more intuitive description of the patient-disease distributions, in Fig. S2 in SI, we present the patient-disease heatmaps, where the x-axis corresponds to patients, the y-axis corresponds to diseases, and a red dot represents one disease occurrence. It is noted that with the huge sample size, plotting all patients generates plots with huge sizes. Thus, in Fig. S2, we presented results for 1% subjects randomly selected from our data in 2012 and 2013. The prevalences of diseases are computed year by year. The top ten are presented in the top panel of Fig. 2. Acute upper respiratory infections (code 465) has the highest prevalence in all years. The high prevalence of acute upper respiratory infections in Taiwan has been noted in multiple publications. Also in the top ten are gingivitis (code 523.1), acute sinusitis (code 464), and atopic/contact dermatitis (code 939) and others, all of which have been extensively examined in the literature.
Network construction and connectivity. The eHDN is constructed using the approach described above. The threshold value $\tau$ is determined as 0.03. More detailed results are provided in SI. In Fig. 3, we provide a “traditional view” of the network structure of the eHDN for the year 2013. Similar constructions/plots have also been done for other years (details omitted and available from the authors). In Fig. 3, diseases that are connected with edges are linked with lines. Extensive “activities” are observed, suggesting a high degree of interconnections among diseases. A certain number of isolated diseases not linking to other diseases are also observed.

As shown in Fig. S4 in SI, for the NHIRD data, the weighted connectivity $k_i$ and unweighted connectivity $K_i$ values are highly correlated. In the bottom panel of Fig. 2, we present the weighted connectivity values for the top ten diseases. More variations are seen in connectivity than in prevalence. For multiple diseases, bell-shaped curves are observed. Such an observation has not been made in the literature. Changing in connectivity can be caused by both intrinsic reasons (such as changing patterns in disease occurrence) as well as reasons such as diagnosis. Disease 464 (acute sinusitis) is observed to have the highest connectivity. It is a common disease and related to a large number of respiratory diseases. Significant increases in connectivity are observed for multiple diseases, especially disease 523.1 (gingivitis) and disease 939 (atopic/contact dermatitis). As a common non-destructive gum disease, gingivitis has been increasingly linked to multiple oral, digestive, and blood diseases. Also, patients with atopic/contact dermatitis and allergic rhinitis have a higher risk of asthma and many autoimmune diseases. More information on connectivity is also available in Fig. 3, where the sizes of nodes are proportional to their connectivity. The variations in connectivity across nodes are clearly observed.

In the investigation of disease connectivity, we first identify those with the highest overall connectivity across 2000 and 2013 and present the top ten diseases in the upper panel of Table 1. The list includes multiple heart diseases, type 2 diabetes, and osteoarthrosis, all of which have been suggested as connected to a large number of diseases. It is “reassuring” that our analysis coincides with “traditional wisdom”. In the lower panel of Table 1, we present the list of hub diseases for the year 2013. Their module information is also provided in the bracket. The differences between the upper and lower panels are caused by the module structure (hubs are identified within modules separately) as well as variations across years.

Figure 4. Disease module structure for the year 2013. Different modules are represented using different colours.
| Color | PheCode | Disease | Color | PheCode | Disease | Color | PheCode | Disease | Color | PheCode | Disease |
|-------|---------|---------|-------|---------|---------|-------|---------|---------|-------|---------|---------|
| pink  | 078     | Viral warts & HPV | turquoise | 624     | Symptoms involving female genital tract | red | 301     | Personality disorders | brown | 251.1   | Hypoglycemia | black | 038.2   | Gram positive septicemia |
| pink  | 110.1   | Dermatophytosis | turquoise | 625     | Pain and other symptoms associated with female genital organs | red | 301.2   | Antisocial/ borderline personality disorder | brown | 276.13  | Hypertension | black | 041.4  | E. coli |
| pink  | 110.11  | Dermatophytosis of nail | turquoise | 626     | Disorders of menstruation and other abnormal bleeding from female genital tract | red | 303.3   | Psychogenic disorder | brown | 276.41  | Acidosis | black | 270.38 | Other specified disorders of plasma protein metabolism |
| pink  | 110.12  | Athlete's foot | turquoise | 626.1   | Irregular menstrual cycle/bleeding | red | 303.4   | Somatoform disorder | brown | 276.6   | Fluid overload | black | 276.12 | Hypovolemia and/or hypotension |
| pink  | 110.13  | Dermatophytosis of the body | turquoise | 626.11  | Absent or infrequent menstruation | red | 304     | Adjustment reaction | brown | 401.2   | Hypertensive heart and/or renal disease | black | 276.14  | Hypertension |
| pink  | 216     | Benign neoplasm of skin | turquoise | 626.12  | Excessive or frequent menstruation | red | 316     | Substance addiction and disorders | brown | 401.22  | Hypertensive chronic kidney disease | black | 290  | Delirium dementia and amnestic and other cognitive disorders |
| pink  | 686     | Other local infections of skin and subcutaneous tissue | turquoise | 626.13  | Irregular menstrual cycle | red | 327     | Sleep disorders | brown | 411.1  | Unstable angina (intermediate coronary syndrome) | black | 290.1 | Dementia |
| pink  | 686.1   | Carbuncle and furuncle | turquoise | 626.14  | Irregular menstrual bleeding | red | 327.4   | Insomnia | brown | 411.2  | Myocardial infarction | black | 290.11 | Alzheimer's disease |
| pink  | 686.5   | Pyoderma | turquoise | 626.15  | Infertility, female, associated with anovulation | red | 327.41  | Organic or persistent insomnia | brown | 427.21  | Atrial fibrillation | black | 290.13 | Senile dementia |
| pink  | 689     | Disorder of skin and subcutaneous tissue NOS | turquoise | 626.2   | Dysmenorrhea | red | 333     | Extrapyramidal disease and abnormal movement disorders | brown | 428.1   | Congestive heart failure (CHF) NOS | black | 290.16 | Vascular dementia |
| pink  | 690.1   | Seborheic dermatitis | turquoise | 626.4   | Premenstrual tension syndromes | blue | 070.2   | Viral hepatitis B | brown | 428.2  | Heart failure NOS | black | 290.3 | Other persistent mental disorders due to conditions classified elsewhere |
| pink  | 695.3   | Rosacea | turquoise | 626.8   | Infertility, female | blue | 070.3   | Viral hepatitis C | brown | 433.1  | Occlusion and stenosis of precerebral arteries | black | 440  | Pneumonia |
| pink  | 695.7   | Prurigo and Lichen | turquoise | 628     | Ovarian cyst | blue | 070.4   | Chronic hepatitis | brown | 433.12  | Cerebral atherosclerosis | black | 480  | Bacterial pneumonia |
| pink  | 698     | Pruritus and related conditions | magenta | 362.21  | Macular degeneration, dry | blue | 070.9   | Hepatitis NOS | brown | 433.31  | Transient cerebral ischemia | black | 480.12 | Pseudomonal pneumonia |
| pink  | 701.1   | Keratoderma, acquired | magenta | 362.22  | Macular degeneration, wet | blue | 155.1   | Malignant neoplasm of liver, primary | brown | 503    | Pulmonary congestion and hypostasis | black | 496  | Chronic airway obstruction |
| pink  | 704.8   | Other specified diseases of hair and hair follicles | magenta | 362.23  | Cystoid macular degeneration of retina | blue | 280.2   | Iron deficiency anemia secondary to blood loss (chronic) | brown | 505    | Other pulmonary inflammation or edema | black | 496.21 | Obstructive chronic bronchitis |
| pink  | 705.1   | Dyshidrosis | magenta | 362.26  | Macular puckering of retina | blue | 285     | Other anemias | brown | 509.2   | Respiratory insufficiency | black | 501  | Pneumonitis due to inhalation of food or vomitus |
| pink  | 706.1   | Acne | magenta | 362.29  | Macular degeneration (senile) of retina NOS | blue | 317     | Alcohol-related disorders | brown | 585.1   | Acute renal failure | black | 507  | Pyelitis; pleural effusion |
| pink  | 706.2   | Sebaceous cyst | magenta | 362.4   | Retinal vascular changes and abnormalities | blue | 317.1   | Alcoholism | brown | 585.2  | Renal failure NOS | black | 509.1 | Respiratory failure |
| pink  | 706.3   | Seborrhea | magenta | 362.8   | Retinal hemorrhage/ ischemia | blue | 317.11  | Alcoholic liver damage | brown | 585.3  | Chronic renal failure (CKD) | black | 563  | Constipation |
| pink  | 939     | Atopic/contact dermatitis due to other or unspecified | magenta | 362.9   | Retinal edema | blue | 530.1   | Esophagitis, GERD and related diseases | brown | 586    | Other disorders of the kidney and ureters | black | 591  | Urinary tract infection |
| pink  | 947     | Urticaria | magenta | 366     | Cataract | blue | 530.11  | GERD | yellow | 041  | Bacterial infection NOS | black | 707.1 | Decubitus ulcer |

Continued
| Color | PheCode | Disease                                      | Color | PheCode | Disease                                      | Color | PheCode | Disease                                      | Color | PheCode | Disease                                      |
|-------|---------|----------------------------------------------|-------|---------|----------------------------------------------|-------|---------|----------------------------------------------|-------|---------|----------------------------------------------|
| turquoise | 112 | Candidiasis                                  | magenta | 366.2 | Senile cataract                              | blue  | 530.12 | Ulcer of esophagus                          | yellow | 250.2 | Type 2 diabetes                             |
| turquoise | 131 | Protozoan infection                         | magenta | 367.4 | Presbyopia                                   | blue  | 530.14 | Reflux esophagitis                          | yellow | 272.1 | Hyperlipidemia                               |
| turquoise | 218.1 | Uterine leiomyoma                           | magenta | 368.9 | Subjective visual disturbances               | blue  | 530.2 | Esophageal bleeding (varices/ hemorrhage)   | yellow | 272.11 | Hypercholesterolemia                         |
| turquoise | 218.2 | Other benign neoplasm of uterus             | magenta | 369.5 | Concomitants, infectious                     | blue  | 530.7 | Gastroesophageal ulceration- hemorrhage syndrome | yellow | 272.12 | Hyperglyceridemia                            |
| turquoise | 220  | Benign neoplasm of ovary                    | magenta | 370.2 | Superficial keratitis                        | blue  | 531.1 | Hemorrhage from gastrointestinal ulcer      | yellow | 272.13 | Mixed hyperlipidemia                         |
| turquoise | 220  | Endometriosis                               | red    | 370.3 | Other unspecified disorders                  | blue  | 531.2 | Gastric ulcer                               | yellow | 274.1 | Gout                                         |
| turquoise | 253  | Disorders of the pitutary gland and its hypothalamic control | magenta | 370.31 | Keratoconjunctivitis sicca                   | blue  | 531.2 | Gastric ulcer                               | green  | 721.1 | Spondylolisthesis without myelopathy        |
| turquoise | 253.1 | Pituitary hyperfunction                      | magenta | 371.2 | Concomitants, noninfectious                  | blue  | 531.3 | Duodenal ulcer                              | yellow | 274.11 | Gouty arthropy                               |
| turquoise | 256  | Ovarian dysfunction                         | magenta | 371.21 | Allergic conjunctivists                      | blue  | 531.4 | Peptic ulcer, site unspecified              | yellow | 276.11 | Hyperosmolality and/or hypernatremia         |
| turquoise | 256.4 | Polycystic ovaries                          | magenta | 371.3 | Inflammation of eyelids                      | blue  | 535.8 | Other specified gastritis                    | yellow | 332   | Parkinson's disease                          |
| turquoise | 261  | Inflammatory diseases of female pelvic organs | magenta | 372   | Disorders of conjunctiva                     | blue  | 535.9 | Gastritis and duodenitis, NOS               | yellow | 342   | Hemiplegia                                   |
| turquoise | 264.1 | Pelvic peritoneal adhesions, female (postoperative) (postinfection) | magenta | 374.1 | Ectropion or entropion                       | blue  | 536.8 | Dyspepsia and other specified disorders of function of stomach | yellow | 349   | Other and unspecified disorders of the nervous system |
| turquoise | 264.3 | Pelvic inflammatory disease (PID)            | magenta | 375.1 | Dry eyes                                     | blue  | 564   | Functional digestive disorders              | yellow | 401.1 | Essential hypertension                     |
| turquoise | 264.31 | Acute inflammatory pelvic disease           | red    | 295   | Schizophrenia and other psychotic disorders | blue  | 564.1 | Irritable bowel Syndrome                    | yellow | 401.21 | Hypertensive heart disease                  |
| turquoise | 264.32 | Chronic inflammatory pelvic disease         | red    | 295.1 | Schizophrenia                                | blue  | 571.5 | Other chronic nonalcoholic liver disease    | yellow | 411.3 | Angina pectoris                              |
| turquoise | 264.33 | Pelvic inflammatory disease, NOS             | red    | 295.2 | Paranoid disorders                           | blue  | 571.51 | Cirrhosis of liver without mention of alcohol | yellow | 411.4 | Coronary atherosclerosis                    |
| turquoise | 264.4 | Infectious diseases of uterus, except cervix | red    | 295.3 | Psychosis                                    | blue  | 571.8 | Liver abscess and sequelae of chronic liver disease | yellow | 411.8 | Other chronic ischemic heart disease, unspecified |
| turquoise | 264.5 | Infectious disease of cervix, vagina, and vulva | red    | 296   | Mood disorders                               | blue  | 571.81 | Portal hypertension                        | yellow | 430.2 | Intracerebral hemorrhage                    |
| turquoise | 264.51 | Cervicitis and endocervicitis               | red    | 296.1 | Bipolar                                      | blue  | 573   | Other disorders of liver                    | yellow | 433   | Cerebrovascular disease                     |
| turquoise | 264.52 | Vaginitis and vulvovaginitis                | red    | 296.2 | Depression                                   | blue  | 578.1 | Hematemia                                   | yellow | 433.2 | Occlusion of cerebral arteries               |
| turquoise | 265   | Endometriosis                               | red    | 296.22 | Major depressive disorder                    | blue  | 578.9 | Hemorrhage of gastrointestinal tract        | yellow | 433.21 | Cerebral artery occlusion, with cerebral infarction |
| turquoise | 269   | Noninflammatory female genital disorders     | red    | 300   | Anxiety, phobic and dissociative disorders  | brown | 250.22 | Type 2 diabetes with renal manifestations   | yellow | 433.6 | Acute, but ill-defined cerebrovascular disease |
| turquoise | 269.1 | Noninflammatory disorders of ovary, fallopian tube, and broad ligament | red    | 300.1 | Anxiety disorder                             | brown | 250.23 | Type 2 diabetes with ophthalmic manifestations | yellow | 433.8 | Late effects of cerebrovascular disease     |
| turquoise | 269.3 | Noninflammatory disorders of cervix         | red    | 300.11 | Generalized anxiety disorder                 | brown | 250.24 | Type 2 diabetes with neurological manifestations | yellow | 588   | Disorders resulting from injured renal function |

Continued
Disease module structure for the year 2013. Different modules are represented using different colours.

Table 2. Disease module structure for the year 2013. Different modules are represented using different colours.

Table 3. Jaccard similarity index between modules in the year 2012 and 2013.

Module identification and properties. Construction of the module structure first involves constructing the dendrogram. In the left panel of Fig. S6 in SI, we show the dendrogram for the year 2013 as well as the identified modules. Different colours represent different modules, and the grey colour represents diseases not classified in the identified modules. Different modules are also represented using different colours in Fig. 3. In Fig. 4, we show the heatmap of the diseases and mark different modules using black boundaries. The “clustering structure” along the diagonal is clearly seen, which suggests the distinct differences across modules. For the year 2012, we show the corresponding plots in Fig. S9 in SI. A careful comparison of the plots suggests variation across time (more definitive results below). For the other years, similar plots can be generated (omitted here, available from the authors).

Different modules differ in multiple aspects. First, they have different sizes. The nine modules have sizes 22 (pink), 39 (turquoise), 21 (magenta), 24 (red), 32 (blue), 27 (brown), 25 (yellow), 24 (black), and 25 (green), respectively. Also, as can be seen from Fig. 4, the levels of connections within modules also vary. For example, there are tighter connections within the green module than others. Diseases in different modules also have different levels of connectivity. More detailed statistics on connectivity are provided in Fig. S5 in SI. From a biomedical perspective, it is of interest to examine the “meanings” of the modules. In Table 2, we provide the detailed list of diseases in the nine modules. As suggested in the published HDN studies, the modules provide an alternative way of defining disease classifications. More specifically, our classification, as shown in Table 2, is based on whether diseases co-occur on the same patients. An enrichment analysis is conducted to examine the representative diseases of different modules. It is found that the nine modules are enriched with the following diseases: mycoses and bacterial of skin and subcutaneous tissue disorders (pink); gynaecological disorders (turquoise); ophthamological disorders (magenta); neurotic personality and other nonpsychotic mental disorders (red); circulatory and digestive system disorders (blue); comorbidity of endocrine and cardiovascular disorders (brown); endocrine and cardiovascular disorders (yellow); degenerative disorders (black) and arthropathies and related disorders (green), respectively. It is noted that some disease clustering/classification structures in the literature are based on, for example, biology and are defined for the whole population. In contrast, our network and module structure, based on the NHIRD, are tailored to the Taiwan population. The Taiwan population are dominatingly Asian, which may have disease risk and characteristics different from other populations. In addition, disease occurrence highly depends on environmental, socioeconomic, and other factors, which vary significantly across regions/countries. As such, for the Taiwan population and their health care and management, our constructed module structure/disease classification can be more sensible.

Modules can describe the interconnections among diseases, with those in the same module more tightly connected. In a further step of analysis, it is of interest to examine the interconnections among modules. The eigen-disease of each module is extracted for this purpose. Eigen-diseases are defined as the first principal components of the modules. Literature suggests that, under certain conditions, they have the highest connectivity and can best represent the corresponding modules. The hierarchical clustering of the nine eigen-diseases is shown in the right panel of Fig. S9 in SI. The brown and yellow eigen-diseases are clustered the first. Figure 4 suggests that...
this result is sensible as both modules are enriched with diseases related to endocrine and cardiovascular disorders. These two modules are then clustered with the black module, which is enriched with degenerative disorders. This connection has not been carefully examined for the Taiwan population in the literature and demands more attention.

Temporal trends. As discussed above, a significant advantage of the eHDN is that temporal variations can be observed. For the studied diseases, their prevalence varies across time, as shown in the upper panel of Fig. 2. More importantly, their network structures, connectivity (bottom panel of Fig. 2), module structure (Figs 4 and S9), and hub structure (Table 1) all vary across time. For the module structure, which defines disease clustering/classification, we show detailed changes between consecutive years in Tables 3 and S4–S15 in SI. Take year 2012 and 2013 as an example (patterns for other years are similar). Most of the modules in 2012 have corresponding modules in 2013 with the Jaccard similarity indexes larger than 0.5 (which suggests a correspondence), except for the red module in 2012, which has Jaccard index 0.36 with the magenta module in 2013. Overall it is observed that the module structures vary significantly between 2001 and 2005, become “stable” around 2005, and then fluctuate again between 2007 and 2011. Modules with “more unique” diseases, for example the modules enriched with gynaecological disorders (which have unique etiological pathways), tend to be more stable throughout the years. As an alternative way of visualising changes of module structures over time, the alluvial diagrams are shown in Figs S10–S22 in SI. It is noted that such plots provide similar information as in Tables S4–S15 in eSI, however, in a more intuitive way and can be preferred by some practitioners.

For the modules, we also summarise their connectivity and examine changes over time. The results are presented in the radar charts in Figs S10–S22. Again, significant across-module differences are observed. For some modules, for example the one enriched with respiratory failure related diseases, significant temporal variations are observed. For disease 509.1 (respiratory failure), we present the temporal trends of connectivity and in模ularity connectivity in the upper panel of Fig. 5. For a better visualisation, the nonparametric smooth fits are also added. The observed trends are similar to those reported in the literature27. A representative of “the opposite”
is disease 411.4 (coronary atherosclerosis), which is shown in the bottom panel of Fig. 5 and has a much more stable connectivity. This observation is similar to that in Tseng et al.\textsuperscript{26}.

**Discussion**

HDN and other pan-disease research has drawn significant attention in recent literature and has brought significant insights beyond single-disease studies. Significantly different from the existing studies that are based on molecular information, in this study, we have taken advantage of the unique NHIRD, constructed the eHDN co-occurrence network, and studied its properties. This study has several contributions. The constructed eHDN provides a way of describing disease interconnections in a “global” manner. The adjacency measure establishes disease connections from an epidemiological perspective. The constructed modules provide an alternative way of disease clustering/classification. A closer examination of the analysis results suggest that the identified highly connected diseases and modules have sound biological interpretations, which provide support to the validity of the proposed analysis. This study also establishes a new way for analysing disease epidemiological data. The adopted technique is heavily based on the WGCNA studies. This study demonstrates the effectiveness of this technique for epidemiological data. In addition, this study also demonstrates various effective way of visualising the analysis results, which provides a more intuitive way of understanding disease epidemiological data. This study also provides an alternative analysis of NHIRD - in the literature, analysis has usually been focused on individual diseases.

Despite significant advancements, this study inevitably has limitations. The Taiwan population is dominantly Asian. Thus, extending the findings to other races should be done with cautious. In our analysis, to describe the “big picture”, we conduct analysis on the whole selected cohort. The occurrence of most diseases depends on age, gender, and other factors. It will be of interest to conduct stratified analysis. Information is only available for the year 2000–2013. Without information on diagnosis prior to 2000, our analysis only captures disease occurrence within this time period. The WGCNA-based technique, although successful and popular, also has limitations. The network generated is undirected and hence cannot reflect the “order” of diseases. In this study, we have only analysed the most important network properties (connectivity, hub, module, etc.). Other, more subtle network properties may also be of interest. In addition, we have focused on the application of the WGCNA technique. Its theoretical validity for the NHIRD data has not been examined. However, the sensible analysis results provide some support to the validity of the analysis technique. There are other statistical techniques for network construction and analysis. It will be of interest, however beyond the scope of this study, to compare different network constructions for the NHIRD data.

The merit of HDN analysis has been well established in the literature. Results obtained in this study can be valuable for basic and clinical science researchers as well as health care providers and policymakers. This study focuses on disease connection from an epidemiological perspective and may well complement the existing HDN studies. Specifically, comparing the eHDN with molecular HDNs may suggest which disease connection are attributable to molecular and non-molecular causes. However, in the literature, there is a lack of molecular HDN specific to the Asian population (it is noted that molecular risk factors of many diseases are race-specific).

In addition, the existing molecular HDNs have been constructed based on techniques other than the WGCNA. With these considerations, we postpone the joint analysis of eHDN and molecular HDNs to future studies.

**References**

1. Vesterinen, E., Pukkala, E., Timonen, T. & Aromaa, A. Cancer incidence among 78000 asthmatic patients. *International journal of epidemiology* **22**, 976–982 (1993).
2. Goh, K.-I. et al. The human disease network. *Proceedings of the National Academy of Sciences* **104**, 8685–8690 (2007).
3. Hidalgo, C. A., Blumm, N., Barabási, A.-L. & Christakis, N. A. A dynamic network approach for the study of human phenotypes. *PLoS computational biology* **5**, e1000353 (2009).
4. Barabási, A.-L., Oltvai, Z. N. Theome of networks. *Science* **298**, 526–534 (2002).
5. Vidal, M., Sierk, M. E. & Barabási, A.-L. Interactome networks and human disease. *Cell* **144**, 986–998 (2011).
6. Zhou, X., Menche, J., Barabási, A.-L. & Sharma, A. Human symptoms–disease network. *Nature communications* **5** (2014).
7. Calvano, S. E. et al. A network-based analysis of systemic inflammation in humans. *Nature* **437**, 1032–1037 (2005).
8. Feldman, I., Rehtsly, A. & Vitkup, D. Network properties of genes harboring inherited disease mutations. *Proceedings of the National Academy of Sciences* **105**, 4323–4328 (2008).
9. Barabási, A.-L., Gulbahce, N. & Loscalzo, J. Network medicine: a network-based approach to human disease. *Nature Reviews Genetics* **12**, 56–68 (2011).
10. Chen, L., Blumm, N., Christakis, N., Barabási, A. & Deisboeck, T. S. Cancer metastasis networks and the prediction of progression patterns. *British journal of cancer* **101**, 749–758 (2009).
11. National Health Research Institutes. National health insurance research database (NHIRD). http://nhird.nhri.org.tw/ (Online; accessed 19 April 2017).
12. Peng, Y.-H. et al. Risk of migraine in patients with asthma: a nationwide cohort study. *Medicine* **95** (2016).
13. Hwang, C.-Y. et al. Prevalence of atopic dermatitis, allergic rhinitis and asthma in taiwan: a national study 2000 to 2007. *Acta dermatovenerologica* **90**, 589–594 (2010).
14. Denny, J. C. et al. Phewas: demonstrating the feasibility of a phenome-wide scan to discover gene–disease associations. *Bioinformatics* **26**, 1205–1210 (2010).
15. Zhang, B. & Horvath, S. et al. A general framework for weighted gene co-expression network analysis. *Statistical applications in genetics and molecular biology* **4**, 1128 (2005).
16. Horvath, S. et al. Analysis of oncogenic signaling networks in glioblastoma identifies asp3 as a molecular target. *Proceedings of the National Academy of Sciences* **103**, 17402–17407 (2006).
17. Weiss, J. N. et al. good enough solutions? and the genetics of complex diseases. *Circulation research* **111**, 493–504 (2012).
18. Hawrylycz, M. J. et al. An anatomically comprehensive atlas of the adult human brain transcriptome. *Nature* **489**, 391–399 (2012).
19. Luo, Y. et al. Single-cell transcriptome analyses reveal signals to activate dormant neural stem cells. *Cell* **161**, 1175–1186 (2015).
20. Horvath, S. Weighted network analytic applications in genomics and systems biology (Springer Science & Business Media, 2011).
21. Dong, J. & Horvath, S. Understanding network concepts in modules. *BMC systems biology* **1**, 24 (2007).
22. Horvath, S., Dong, J. & Yip, A. Using the factorizability decomposition to understand connectivity in modular gene co-expression networks. Tech. Rep., UCLA Technical Report. www.genetics.ucla.edu/labs/horvath/ModuleConformity (2005).
23. Ravasz, E., Somera, A. L., Mongru, D. A., Oliva, Z. N. & Barabási, A.-L. Hierarchical organization of modularity in metabolic networks. *Science* **297**, 1551–1555 (2002).
24. Bastian, M., Heymann, S. & Jacomy, M. *et al.* Gephi: an open source software for exploring and manipulating networks. *ICWSM* **8**, 361–362 (2009).
25. Pillai, D. P. *Clinical trend discovery and analysis of Taiwanese health insurance claims data*. Ph.D. thesis (Massachusetts Institute of Technology, USA 2016).
26. Tseng, L.-N. *et al.* Prevalence of hypertension and dyslipidemia and their associations with micro-and macrovascular diseases in patients with diabetes in taiwan: an analysis of nationwide data for 2000–2009. *Journal of the Formosan Medical Association* **111**, 625–636 (2012).
27. Chen, W. *et al.* Incidence and outcomes of acute respiratory distress syndrome: a nationwide registry-based study in taiwan, 1997 to 2011. *Medicine* **94** (2015).
28. Wu, L.-C. *et al.* Autoimmune disease comorbidities in patients with atopic dermatitis: a nationwide case–control study in taiwan. *Pediatric Allergy and Immunology* **25**, 586–592 (2014).

**Acknowledgements**

We thank the reviewers for their careful review and insightful comments, which have led to a significant improvement of the article. We would like to acknowledge Mingchih Chen and Ariana Chang for their support, and thoughtful comments on the manuscript. This research was supported by Fu Jen Catholic University of Taiwan under the Grant No. 300394 and the Ministry of Science and Technology under Grant Nos MOST106-2221-E030-011-MY2, MOST106-2221-E030-012 and MOST106-3011-F038-004.

**Author Contributions**

Conceived and designed the research process: T.S. Lee, S.G. Ma. Performed lecture review: S.G. Ma, Y.F. Jiang. Analysed data: T.S. Lee, B.C. Shia. Contributed reagents/materials/analysis tools: T.S. Lee, B.C. Shia, Y.F. Jiang. Wrote paper: Y.F. Jiang, S.G. Ma, T.S. Lee.

**Additional Information**

Supplementary information accompanies this paper at https://doi.org/10.1038/s41598-018-21779-y.

**Competing Interests:** The authors declare no competing interests.

**Publisher’s note:** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

© The Author(s) 2018