MorbiNet study. Hypothyroidism comorbidity networks in the adult general population

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Abstract

Purpose: Multimorbidity impacts quality of life. We constructed hypothyroidism comorbidity networks to identify positive and negative associations with other prevalent diseases.

Methods: We analyzed data of 285,342 patients with hypothyroidism from 3,135,948 adults with multimorbidity in a population-based study in Catalonia, Spain, (period: 2006-2017). We constructed hypothyroidism comorbidity networks using logistic regression models, adjusted by age and sex, and for men and women separately. We considered relevant associations those with odds ratios (OR) >1.2 or <0.8 and p-value <1e-5 to identify coexistence greater (or smaller) than the expected by the prevalence of diseases. Multivariate models considering comorbidities were used to further adjust OR values.

Results: The conditions associated included larynx cancer (adjusted OR: 2.48); congenital anomalies (2.26); thyroid cancer (2.13); hyperthyroidism (1.66), vitamin B12/folate deficiency anemia (1.57), and goiter (1.56). The network restricted to men had more connections (mental, cardiovascular, and neurological) and stronger associations with thyroid cancer (7.26 vs 2.55), congenital anomalies (5.11 vs 2.13), hyperthyroidism (4.46 vs 1.69), larynx cancer (3.55 vs 1.67), and goiter (3.94 vs 1.64). After adjustment for comorbidities, OR values were more similar in men and women. The strongest negative associations after adjusting for comorbidities were with HIV/AIDS (OR:0.71), and tobacco abuse (0.77).

Conclusions: Networks show direct and indirect hypothyroidism multimorbidity associations. The strongest connections were thyroid and larynx cancer, congenital anomalies, hyperthyroidism, anemia, and goiter. Negative associations included HIV infection-AIDS and tobacco abuse. The network restricted to men had more and stronger associations, but not after adjusting for comorbidities suggesting important indirect interactions.

KEYWORDS: Hypothyroidism; comorbidity, chronic diseases; network analysis.

Introduction

Hypothyroidism is a common condition with an estimated prevalence of 3-5% (1, 2). It is more frequent in women and increases with age (3). Subclinical hypothyroidism was reported to affect 9% of the general population (4). The prevalence of undiagnosed hypothyroidism was estimated to be 4.11% (subclinical) and 0.65% (overt) (5). In areas without iodine deficiency, the most common cause of hypothyroidism is Hashimoto thyroiditis (6). Some chronic diseases can affect neuroendocrine systems and produce alterations in thyroid hormones, the non-thyroidal illness syndrome, with a decreased serum free triiodothyronine (T3), increased reverse T3, and unchanged or low TSH (7).

Hypothyroidism has been associated with excess mortality (8) and reduced quality of life (3), especially when there are co-morbidities (9). Patients with multimorbidity (two or more chronic conditions) have a worse quality of life, disability, more complex clinical care, and increased mortality (10). Multimorbidity can be studied with network analysis, where conditions are nodes and edges that connect nodes indicate the coexistence of disease. We aimed to construct the hypothyroidism comorbidity network in the general population and analyze both positive and negative associations, considering the temporal sequence of the diagnoses.

Materials and methods

Design and study population. We conducted a registry-based study in Catalonia, Spain, that included all the population diagnosed with at least two simultaneous chronic conditions persistent at any time during the period 2006-2017. The diseases could be diagnosed before or within the study period. We used the Information System for Research Development in

Primary Care (SIDIAP) database as a source of data. It included anonymized electronic medical files recorded by primary care professionals during routine outpatient visits for over 5.5 million people (74% of the population), users of the public primary-care health system. We analyzed 285,342 patients with hypothyroidism among a total of 3,135,948 people aged over 18 with multimorbidity (two or more coexistent chronic conditions at any time within the study period) included in the MorbiNet study (11). We used the International Classification of Primary Care, 2nd edition (ICPC-2) system (12), and followed an adaptation of chronic conditions described by O'Halloran et al. (13). Patients were included according to their diagnostic codes in the SIDIAP database. Though hypothyroidism has not been validated, the accuracy of the diagnosis should be high, as that observed in validation studies conducted with SIDIAP data in other conditions including cardiovascular risk factors, vascular diseases (14), cancer diagnoses (15) and others (16, 17). The anonymous data extraction that was provided for the MorbiNet study did not allow performing additional validation studies. We extracted the date of birth, sex, and ICPC-2 chronic disease codes for all conditions. We calculated the patients' age at the mean time between the first and last diagnoses made within 2006-2017 or in the middle of the period when no new diagnoses were made those years. We included the data until the date of death or transfer for patients who died or transferred within the study period and conditions with less than 1000 patients were excluded. A reduced number of diseases and patients were excluded for this reason and the potential impact in the models is expected to be low. The prevalence of hypothyroidism has been calculated with the total SIDIAP database as denominator (Table 1).

Network analysis. The main components of networks are nodes (chronic conditions) and edges (coexistence of disease) that connect nodes in the network. We constructed multimorbidity networks with logistic regression models, adjusted by age and sex (available at www.morbinet.org) using R software (18) and for men and women separately. We considered a relevant coexistence, greater than expected by the prevalence of diseases, odds ratios (OR) >1.2 and p-value <1e-5 (Bonferroni correction to account for multiple tests). Negative associations (OR<0.8 and p-value <1e-5) were also considered. ORs were derived as the ratio between the odds of comorbidity in patients with hypothyroidism and the odds of comorbidity in patients with multimorbidity without hypothyroidism. ORs minus one can be interpreted as the excess proportion of coexistence over the expected by chance.

The hypothyroidism network (T86 code) was extracted, limited to first-degree connections of hypothyroidism and the connections among those. Node size in figures was proportional to the degree (number of connections) and edge thickness to OR values. A color code was used to show the pageRank (19) score of nodes. Nodes with higher values were darker, showing their influence based on the links they had to other nodes and the links their connections had, considering link directions and weight.

We plotted directional networks to assess temporal disease associations. We considered a temporal association when the probability that a disease was diagnosed before or after another one was below 40% or above 60%. For the rest of the situations, we assumed no temporal association, and a bidirectional arrow between the conditions was represented. We used multivariate logistic regression models penalized with the least absolute shrinkage and selection operator (LASSO) to obtain a corrected estimate of the

associations among comorbidities in the network and to filter indirect associations. The LASSO penalty parameter was estimated through cross-validation and we used the value of one standard deviation over the minimum (20). The glmnet R package was used for these calculations. We will refer to minimally adjusted OR (age-sex) as OR and adjusted OR when adjustments for additional comorbidities were applied. The LASSO models deal with collinearity, selecting only those comorbidities that retain association when adjusted for others.

Quality and sensitivity analysis. To assess the quality of data in the MorbiNet study, we compared the networks for all the patients with the subgroup with some variables correctly recorded in their electronic files. These included weight, height, and tobacco and alcohol use. The prevalence of most chronic diseases was similar in both groups, and so we used the information of all the patients to construct the networks (11).

We analyzed how the hypothyroidism networks changed when we selected different threshold OR value. As expected, the nodes and significant associations increased when the OR was lower (OR>2: 4 nodes, 4 interactions; OR>1.8: 6 nodes, 7 interactions; OR>1.5: 10 nodes, 21 interactions; OR> 1.2: 31 nodes, 216 interactions). Networks can be visualized on the website (www.morbinet.org).

Ethics. We obtained the approval from Ethics Committees (Consorci Sanitari Integral, 16/457 and IDIAP Jordi Gol, P17/207) The informed consent from patients to use their data could not be obtained because the study is retrospective observational, and population based. The analysis of the information was anonymized with no variables that might identify individual patients. We followed the Spanish law on the protection of personal data (LOPD 15/1999 of December 14).

Results

In the total SIDIAP database, the prevalence of hypothyroidism in 2017 was 5.2%. Table 1 shows the prevalence of hypothyroidism in different age and sex groups.

Undirected networks. The hypothyroidism comorbidity undirected network with OR above 1.2 had 31 nodes (21% of 148 in the global multimorbidity network) and 216 edges (7% of 3062 in the global multimorbidity network). While the average degree in the global network was 14, diseases in the hypothyroidism network were less connected with an average degree of 7. Hypothyroidism network was denser than the global multimorbidity network (0.48 vs 0.28), with higher centrality (0.54 vs 0.35) and clustering coefficient (0.70 vs 0.57). These network metrics indicate that the comorbidity associated with hypothyroidism forms a compact distinct entity when compared with other diseases.

In Table 2 we present the diseases associated with hypothyroidism in the undirected network and their degree (number of connections) both in the hypothyroidism network and the global multimorbidity network. Some nodes had many connections in the global network: unspecified anemia, 89; heart valve disease, 65; liver disease, 65; and vitamin B12/folate deficiency anemia, 64; indicating these conditions have low specificity and are associated with many diseases.

Directed networks. In Table 3 we can see the OR of conditions with strong connections with hypothyroidism in the directed network and the adjusted values obtained with multivariate models considering other comorbidities. The diseases associated with hypothyroidism with a previous diagnosis were other respiratory cancer (adjusted OR: 2.48); congenital anomalies (2.26); thyroid cancer (2.13); hyperthyroidism (1.66) and type 1 diabetes (1.50).

Other respiratory cancer was mostly cancer of the larynx, but also the amygdala, oropharynx, nasopharynx, piriformis sinus, and hypopharynx. Some associated diseases could both precede or be diagnosed after hypothyroidism, including vitamin B12/folate deficiency anemia (adjusted OR: 1.57), goiter (1.56), and other endocrine/metabolic diseases (1.56, and includes thyroiditis). All associated diseases with diagnosis after hypothyroidism had OR values below 1.2. After adjusting for other comorbidities, some diseases lost the association, meaning they were highly correlated with other conditions associated with hypothyroidism.

Though hypothyroidism is less prevalent in men, the network (OR>1.5) restricted to men was more populated (20 nodes, 68 edges) than that of women (9 nodes, 14 edges). Figure 1 shows the network restricted to OR values over 1.5 in men and Figure 2 in women. Networks with other criteria can be visualized on the open interactive website (https://www.morbinet.org).

Minimally adjusted OR values (age adjusted) for men showed more and stronger connections as compared to women (Table 4). The network for men had more connections in mental health (psychosis, schizophrenia, obsessive-compulsive disorder, and mental retardation), cardiovascular (tachycardia, heart failure, postural hypotension), and neurological system (epilepsy, nervous system benign neoplasm) (Table 4). Some connections were stronger in men, especially thyroid cancer (OR: 7.26 in men, 2.55 in women), multiple congenital anomaly (5.11 vs 2.13), hyperthyroidism (4.46 vs 1.69), larynx cancer (3.55 vs 1.67), and goiter (3.94 vs 1.64) (Table 4). However, in the multivariate analysis, after adjustments for other comorbidities, the OR values were more similar for men and women. The main differences for the adjusted associations included neurasthenia

(OR: 1.24 in women), affective psychosis (OR: 1.26 in men), and osteoporosis (OR: 1.42 in men). The difference between minimally adjusted and adjusted for comorbidities associations suggested many of the interactions in men were indirect.

Negative associations. Some diseases were less frequently diagnosed when hypothyroidism was present (Table 5). The strongest negative associations after adjusting for comorbidities were HIV/AIDS (OR: 0.71) and tobacco abuse (OR: 0.77). The network for negative associations was more complex in women (9 nodes/8 edges, vs 4 nodes/3 edges in men). The main differences with adjusted data included chronic alcohol abuse (OR: 0.53 in women) and bronchus/lung cancer (OR: 0.73 in women).

Discussion

Hypothyroidism, a common condition especially in aged women, is frequently associated with other health problems. We studied both comorbidities and diseases with negative associations using network analysis. Comorbidities of hypothyroidism include most organ systems. Comorbidity networks showed more and stronger connections in men. As most differences disappeared when we adjusted for other comorbidities, it suggested many of the interactions for men were indirect, due to their interrelationship with other chronic conditions. Most prior studies have not analyzed hypothyroidism comorbidities separately for men and women or adjusted for other diseases.

Cardiovascular disease

Hypothyroidism was associated with heart disease, especially in men (Tables 3 and 4) but after adjusting for comorbidities most interactions disappeared or had OR below 1.2. In the myocardium and vascular tissue, there are thyroid hormone receptors and changes in

thyroid function can lead to cardiovascular dysfunction. Low thyroid function reduces heart output and increases peripheral vascular resistance (21). Also, thyroid hormones are frequently affected by heart disease. Euthyroid patients with cardiovascular disease such as acute myocardial infarction or heart failure can have abnormal thyroid hormone concentrations. As a result of low T3, diastolic dysfunction may result and is associated with poor prognosis (21) (4). In a large hypothyroid women cohort, the risk of dying from diabetes mellitus, cardiovascular, and cerebrovascular disease was higher than in women with no thyroid disease (22).

Thyroid function is essential for the normal heart electrical system (23). We found associations of atrial fibrillation/flutter with hypothyroidism (OR: 1.41, adjusted: 1.23) (Table 3). This association is controversial, some studies found no increased incidence of atrial fibrillation (24) while others reported a lower risk of atrial fibrillation in hypothyroidism (25). In contrast with these studies, we analyzed co-existence and not incident atrial fibrillation in patients with previous hypothyroidism and we did not exclude patients with thyroid replacement therapy or certain medications.

Renal

We obtained an association (OR: 1.45, adjusted: 1.17, Table 3) with hypothyroidism preceding chronic renal failure more often. Hypothyroidism has been associated with increased serum creatinine and a reduced glomerular filtration rate (26). But also thyroid dysfunction is very common in patients with chronic kidney disease (27) and low T3 levels were associated with a higher risk of cardiovascular disease and mortality (26). It has been suggested metabolic acidosis, protein loss and malnutrition, inflammation and increased

iodine levels found in kidney disease might affect thyroid hormones leading to non-thyroidal illness syndrome (7).

Hematological

Hypothyroidism was associated with vitamin B12/ folate deficiency anemia (OR: 1.83, adjusted OR: 1.57) and other/unspecified anemia (OR: 1.32, adjusted OR: 1.15). In hypothyroidism there is reduced erythropoiesis, nutrient deficiencies (iron, B12, and folate) and some comorbid diseases are common with anemia (28). More than half of the patients with pernicious anemia showed antithyroid autoimmunity, especially women (29).

Endocrine

Hypothyroidism had strong associations with endocrine disorders (Table 3): hyperthyroidism (OR: 1.92, adjusted: 1.66), type 1 diabetes mellitus (OR: 1.78, adjusted: 1.50), other endocrine diseases (OR: 1.77, adjusted: 1.56), goiter (OR: 1.75, adjusted: 1.56), and lipid disorder (OR: 1.27, adjusted: 1.20). Treatment of hyperthyroidism with thyroidectomy/radioiodine treatment often results in hypothyroidism and probably explains the identified association. Type 1 diabetes mellitus was associated and preceded more often hypothyroidism and may be partly due to underlying susceptibility for autoimmune conditions. We found no association above OR>1.2 with type 2 diabetes. In a large population-based retrospective cohort study, patients with type 1 diabetes mellitus had a higher incidence of thyroid autoimmune disorders (30). Patients with hypothyroidism were reported to have a higher risk of developing type 2 diabetes in a cohort study (hazard ratio: 1.19, 95% CI: 1.07-1.33) (31). Martin et al. found blood lipids to be the strongest association with hypothyroidism among cardiovascular risk factors (32).

Celiac disease

We found celiac disease to be associated with hypothyroidism (OR: 1.45, adjusted: 1.14) (Table 3). In a pooled analysis, individuals with autoimmune hypothyroidism had a high prevalence of celiac disease (33). A meta-analysis showed an increased prevalence of thyroid disease in patients with celiac disease (34).

Cancer

Some cancers were connected and preceded hypothyroidism: thyroid cancer (OR: 2.95, adjusted: 2.13), other respiratory cancers, which include larynx and pharynx, (OR: 3.00, adjusted: 2.48) and Hodgkin lymphoma (OR: 1.39, adjusted: 1.10). Patients with Hashimoto's thyroiditis had a higher risk of thyroid cancer in a cohort study in Taiwan (35). Hypothyroidism is a known complication after radiation therapy for neck and head cancer(36), with a cumulative incidence of 21% and 36% after the first and second year of therapy (37). Hypothyroidism was related to telecobalt therapy, the inclusion of the thyroid in the irradiated area (38), and higher radiation doses (36). The percentage of the thyroid receiving 25 Gy was a predictor of hypothyroidism after chemoradiation for Hodgkin lymphoma (39). A meta-analysis of trials with programmed cell death (PD-1) and programmed cell death ligand 1 (PD-L1) inhibitors as therapy for Hodgkin's lymphoma and other cancers, found hypothyroidism to be the most frequent endocrine immune adverse event (40). Non-thyroidal illness syndrome has been also documented in several types of cancer (41).

Mental Health

Mental retardation was associated, more often diagnosed before hypothyroidism (OR: 1.40; adjusted: 1.05, Table 3). Altered thyroid activity affects the development of the fetal and the mature brain. Early fetal hypothyroidism can produce an important irreversible mental retardation even if the thyroid function is normal after birth (42). Adults with intellectual disabilities had higher rates of hypothyroidism (43). A meta-analysis showed a relationship between subclinical hypothyroidism and cognitive impairment in patients aged below 75 years but not for older patients (44).

Schizophrenia was associated with hypothyroidism (OR: 1.22, adjusted: 1.03, Table 3), and affective psychosis only in men (OR: 1.43, adjusted: 1.26, Table 4), both taking place more often before thyroid disease. Patients with schizophrenia were more likely to have hypothyroidism as compared with controls (45). In a large population-based cohort study there was an increased prevalence of psychiatric diseases and use of antidepressants and anxiolytics both before and after diagnosis of hypothyroidism while treatment with antipsychotics was higher only before hypothyroidism (46). Although we did not find such association, patients with major depressive disorder were reported to have a higher incidence and prevalence of hypothyroidism than the general population (47). Hypothyroid patients often show characteristics of depression, cognitive alterations, apathy, and slow psychomotricity, while most patients with depression have normal thyroid function (48).

Neurasthenia was associated with hypothyroidism in women (OR: 1.48, adjusted: 1.24, Table 4). Neurasthenia overlaps with depression and has similarities with several diagnoses, such as chronic fatigue syndrome and fibromyalgia (49). Hypothyroidism may have some similar symptoms to fibromyalgia, including insomnia, fatigue, headache, or

arthralgia. The prevalence of fibromyalgia in patients with Hashimoto thyroiditis was 62% (50) while in the general population it was reported to be 2.4-3.4% (51).

Negative associations

Networks of negative associations had more nodes and connections in women. After adjusting for comorbidities, the only negative associations with OR below 0.8 were HIV-infection/AIDS and tobacco abuse, and in women also chronic alcohol abuse and bronchus/lung cancer (Table 5). In a large cohort of HIV-infected patients symptomatic hypothyroidism prevalence was low (52). However, a small study found hypothyroidism to be more common in HIV-infected patients, especially with a long infection, hepatitis B, and with highly active antiretroviral therapy (53).

Several studies found higher T3 levels in smokers (54). Smoking is associated with hyperthyroidism and negatively associated with hypothyroidism (55) and the prevalence of subclinical hypothyroidism was markedly reduced among smokers (56). No negative association of chronic alcohol abuse with hypothyroidism has been reported. Chronic alcohol exposure was found to lead to a blunted TSH response to TRH, decreased free T3, T4, and reduced thyroid volume and fibrosis (57).

We found a negative association with bronchus/lung cancer (adjusted OR: 0.73), and cancer not otherwise specified (adjusted OR: 0.89) in women (Table 5). Thyroid hormones play an important role in growth and metabolism and have been linked to the pathophysiology of certain cancers while hypothyroidism has been reported to decrease aggressiveness and delay of onset in some cases. Induced hypothyroxinemia increased the expected survival time in some advanced cancers including lung (58). An indirect negative

association between tobacco and hypothyroidism could in part support the negative associations with the cancer types mentioned.

Clinical implications

Multimorbidity affects clinical outcomes and quality of life (10). Multimorbidity can affect patient management due to drug-disease, disease-disease, and drug-drug interactions, and it can have implications for clinical care and research (59). A better knowledge of hypothyroidism comorbidities could be useful for more personalized and better attention. It could help clinicians to consider expected associated diseases. Levothyroxine treatment can interact with multiple medications and adjustments in dose could be needed with some conditions (60). So, a good knowledge of potential comorbidities and prescription is essential. Epidemiological studies like ours can guide new research and this information might also be useful for clinical guidelines which should include a comorbidity section.

Limitations and strengths

We used an electronic health record database and there might be errors in diagnosis, disease coding, or lack of registration and incorrect diagnoses and codes can be more frequent in some diseases. However, the study was large, and population based so this bias might have a limited effect and would be towards the attenuation of the association estimates. Registry data usually underestimate the prevalence of diseases. Though we could not validate the diagnosis, our estimates of prevalence were slightly higher than those observed in South Spain using thyroid hormone prescription data (61). There is no specific disease code for low T3 syndrome, and this condition was probably coded as

hypothyroidism. Subclinical and overt hypothyroidism also share the same ICPC2 disease code. So, all these different clinical situations could not be analyzed separately. We only considered coexistent diseases that were present more often than expected because of their prevalence. So, common conditions can also be in patients with hypothyroidism but no more than in other people. We studied strong associations with OR above 1.2 and that might be the reason in some cases we did not find some associations reported in other studies. Hypothyroidism usually requires regular control visits, and this increases the opportunities to diagnose other chronic conditions. However, this can also happen with most other chronic diseases. As our reference population was people with multimorbidity, we do not expect this potential bias might have a great impact. For directed networks, wrong temporal assumptions could be made in the case of delayed diagnoses.

Strengths of our study include a large population-based database in a primary care setting, and not limited to hospital files with the more seriously ill patients. The long study period allowed us to analyze the direction of temporal associations. We analyzed not only positive but negative associations as well. We have made available a freely accessible website where users can customize the networks choosing different criteria (OR, p-value, age group, network format).

In conclusion, the conditions with the strongest connections diagnosed before hypothyroidism were larynx and thyroid cancer, congenital anomalies, hyperthyroidism, and type1 diabetes. Diseases associated and diagnosed before or after hypothyroidism included vitamin B12/ folate deficiency anemia, goiter, and other endocrine diseases (as thyroiditis). Though hypothyroidism is less prevalent in men, the network restricted to men had more and stronger associations which mostly disappeared after adjusting for comorbidities and

suggested a lot of indirect interactions. The main negative associations with hypothyroidism were HIV infection-AIDS and tobacco abuse and in women also chronic alcohol abuse and bronchus/lung cancer.

Data availability

Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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Figure Legends

Figure 1. Directed hypothyroidism comorbidity network (OR >1.5) in men.

Abbreviations: Hypothyroid: hypothyroidism; resp ca: other respiratory cancer; anemia pern: anemia, vitamin B12/folate deficiency; congen anom: congenital anomaly multiple; hyperthyroid: hyperthyroidism; diabetes T1: type 1 diabetes mellitus; thyroid ca: thyroid cancer; endocr/metab dis: other endocrine/metabolic/nutrition disease. Hodg lymp: Hodgkin's disease/lymphoma; Fail: failure; chron: chronic; un: unspecified; ht: hypotension; retard: retardation; CV cong an: cardiovascular congenital anomaly; dis: disease.

Figure 2. Directed hypothyroidism comorbidity network (OR >1.5) in women.

Abbreviations: Hypothyroid: hypothyroidism; resp ca: other respiratory cancer; anemia pern: anemia, vitamin B12/folate deficiency; congen anom: congenital anomaly multiple; hyperthyroid: hyperthyroidism; diabetes T1: type 1 diabetes mellitus; thyroid ca: thyroid cancer; endocr/metab dis: other endocrine/metabolic/nutrition disease.

TABLES

Table 1. Prevalence of hypothyroidism in the study population* (year 2017)

Age group	Hypothyroid Women (N)	%	Hypothyroid Men (N)	%	Hypothyroid Total (N)	%
18-49	48,250	4.0	10,389	0.8	58,639	2.4
50-69	85,112	12.1	15,344	2.3	100,456	7.3
70+	66,708	14.6	13,898	4.3	80,606	10.3
Total	200,070	8.4	39,631	1.8	239,701	5.2

*Denominators are based on the global SIDIAP database in 2017

Table 2. Nodes degree (number of significant associations) in the hypothyroidism network and in the global multimorbidity network (OR > 1.2, p<1e-5, undirected networks)

Code	Chronic disease	Degree in hypothyroidism network	Degree in global network
T86	Hypothyroidism	30	30
T99	Endocrine/metabolic/nutrition disease, other	25	58
B82	Anemia other/unspecified	22	89
K83	Heart valve disease not otherwise specified	22	65
K82	Pulmonary heart disease	21	59
U99.01	Chronic renal failure	20	62
K77	Heart failure	19	58
U88	Glomerulonephritis/nephrosis	17	46
K74	Ischemic heart disease with angina	17	62
D97	Liver disease not otherwise specified	17	65
B81	Anemia, Vitamin B12/folate deficiency	16	64
K78	Atrial fibrillation/flutter	16	47
K71	Rheumatic fever/heart disease	16	39
T92	Gout	16	46
T85	Hyperthyroidism	15	24
L99	Musculoskeletal disease, other	15	66
K79	Paroxysmal tachycardia	15	57
T81	Goiter	13	45
K73	Congenital anomaly cardiovascular	12	34
T83/82	Overweight/Obesity	12	40
A90	Congenital anomaly multiple	10	36
T93	Lipid disorder	9	29
T89	Type 1 Diabetes mellitus	9	29
D99.01	Celiac disease	8	18
T80	Congenital anomaly endocrine/metabolic	7	15
P78	Neurasthenia	7	32
B72	Hodgkin's disease/lymphoma	6	28
P85	Mental retardation	6	27
T71	Thyroid cancer	6	14
R85	Respiratory cancer, other	5	24
P72	Schizophrenia	3	27

Table 3. Direct links in hypothyroidism network truncated to strongest associations. Minimally adjusted and adjusted OR obtained with multivariate models considering comorbidities (p<1e-5)

Disease connected with hypothyroidism (T86)	OR*	A-OR**	Direction	Years To/From Hypothyroidism Mean (SD)	Comorbidity (N)
CANCER					
Thyroid cancer	**2.95**	**2.13**	To T86	2.4 (8.4)	1,849
Other respiratory cancer	**3.00**	**2.48**	To T86	4.7 (8.1)	1,333
Hodgkin's disease/lymphoma	**1.39**	1.10	To T86	4.7 (10.3)	1,332
CONGENITAL					
Congenital anomaly multiple	**2.76**	**2.26**	To T86	9.5 (17.3)	1,645
Congenital anomaly cardiovascular	**1.33**	-	To T86	6.7 (16.3)	899
Congenital endocrine/metabolic	**1.42**	1.08	Undefined		1,947
ENDOCRINE					
Hyperthyroidism	**1.92**	**1.66**	To T86	2.7 (7.6)	11,653
Goiter	**1.75**	**1.56**	Undefined		20,293
Type 1 Diabetes mellitus	**1.78**	**1.50**	To T86	5.8 (12.1)	2,800
Endocrine/metabolic/nutrition, other	**1.77**	**1.56**	Undefined		47,821
Lipid disorder	**1.27**	**1.20**	Undefined		140,914
MENTAL HEALTH					
Mental retardation	**1.40**	1.05	To T86	10.2 (18.0)	1,368
Schizophrenia	**1.22**	1.03	To T86	5.4 (10.2)	2,930
Neurasthenia	**1.52**	1.01	Undefined		444
DIGESTIVE SYSTEM					
Celiac disease	**1.45**	1.14	Undefined		1,438
BLOOD					
Anemia, Vitamin B12/folate deficiency	**1.83**	**1.57**	Undefined		5,795
Anemia other/unspecified	**1.32**	1.15	From T86	2.9 (6.6)	26,523
CARDIOVASCULAR					
Atrial fibrillation/flutter	**1.41**	**1.23**	Undefined		24,765
Paroxysmal tachycardia	**1.29**	1.06	To T86	0.2 (7.7)	4,060
Heart failure	**1.25**	-	To T86	2.2 (6.9)	13,896
Pulmonary heart disease	**1.31**	-	Undefined		1,940
Rheumatic fever/heart disease	**1.34**	-	To T86	2.7 (10.1)	3,047
Heart valve disease NOS	**1.26**	1.03	Undefined		14,552
Ischemic heart disease	**1.27**	1.03	From T86	0.3 (8.5)	6,649
RENAL					
Chronic renal failure	**1.45**	1.17	From T86	3.4 (6.8)	32,650
Glomerulonephritis/ nephrosis	**1.24**	-	Undefined		3,180

T86 code: Hypothyroidism. NOS: Not otherwise specified.

*Minimally adjusted OR (age and sex).

**OR Adjusted also for other comorbidities in the network using LASSO multivariate models

Table 4. Minimally adjusted and adjusted OR (considering comorbidities) for hypothyroidism direct links (strongest associations) in the hypothyroidism directed network for men and women (p<1e-5)

Group	Disease connected with hypothyroidism	OR* men	OR* women	A-OR** men	A-OR** women
Cancer	Thyroid cancer	**7.26**	**2.55**	**2.27**	**2.36**
	Other respiratory cancer	**3.55**	**1.67**	**1.20**	**1.40**
	Hodgkin's disease/lymphoma	**1.94**	**1.22**	-	-
Congenital	Congenital anomaly multiple	**5.11**	**2.13**	**2.02**	**2.09**
	Congenital anomaly cardiovascular	**1.66**	**1.24**	-	-
	Congenital anomaly endocrine/metabolic	**1.42**	**1.42**	-	-
Endocrine	Hyperthyroidism	**4.46**	**1.69**	**1.91**	**1.96**
	Goiter	**3.94**	**1.64**	**2.01**	**2.06**
	Type 1 Diabetes mellitus	**1.89**	**1.74**	**1.23**	**1.26**
	Endocrine/metabolic/nutrition, other	**1.75**	**1.79**	**1.51**	**1.51**
	Lipid disorder	**1.33**	**1.27**	1.17	1.18
Mental	Mental retardation	**2.07**	-	-	-
health	Schizophrenia	**1.53**	-	-	-
	obsessive compulsive disorder	**1.49**	-	-	-
	Neurasthenia	**-**	**1.48**	-	**1.24**
	Affective psychosis	**1.43**	-	**1.26**	-
Blood	Anemia, Vitamin B12/folate deficiency	**2.01**	**1.77**	**1.51**	**1.58**
	Anemia other/unspecified	**1.69**	**1.25**	**1.21**	**1.24**
	Purpura/coagulation defect	**1.33**	-	-	-
Cardio	Atrial fibrillation/flutter	**1.77**	**1.32**	1.12	1.11
vascular	Paroxysmal tachycardia	**1.76**	-	1.07	-
	Heart failure	**1.58**	-	-	-
	Postural hypotension	**1.52**	-	-	-
	Pulmonary heart disease	**1.49**	**1.27**	-	-
	Rheumatic fever/heart disease	**1.48**	**1.32**	1.08	1.12
	Heart valve disease NOS	**1.44**	**1.22**	1.03	1.05
	Ischemic heart disease	**1.31**	**1.28**	-	-
Renal	Chronic renal failure	**1.65**	**1.40**	1.16	1.14
	Glomerulonephritis/ nephrosis	**1.32**	**1.22**	-	-
Nervous	Benign neoplasm nervous system	**1.41**	-	-	-
System	Epilepsy	**1.35**	-	-	-
Other	Celiac disease	**2.03**	**1.39**	**1.23**	**1.34**
	Weakness/tiredness general	**1.36**	-	1.18	-
	Osteoporosis	**1.25**	-	**1.42**	-

NOS: Not otherwise specified

*Minimally adjusted OR (age).

**Adjusted also for other comorbidities in the network using LASSO multivariate models.

Table 5. Negative associations with hypothyroidism (p<1e-5 and OR<0.8).

Disease	OR* all	A-OR** all	OR* men	OR* women	A-OR** men	A-OR** women
HIV-infection/AIDS	**0.39**	**0.71**	**0.48**	**0.32**	**0.54**	**0.52**
Drug abuse	**0.57**	-	**0.54**	**0.60**	0.90	0.98
Tobacco abuse	**0.71**	**0.77**	**0.65**	**0.73**	**0.64**	**0.65**
Pancreas Cancer	**0.76**	-	-	**0.78**	-	-
Chronic enteritis/ulcerative colitis	**0.77**	0.96	-	**0.76**	-	0.92
Ankylosing spondylitis	**0.78**	-	-	-	-	-
Chronic alcohol abuse	**0.78**	0.87	-	**0.76**	-	**0.53**
Bronchus/lung cancer	**0.79**	-	-	**0.72**	-	**0.73**
Cancer not otherwise specified	**0.80**	0.95	-	**0.75**	-	0.89

*Minimally adjusted OR (age and sex).

**OR Adjusted also for other comorbidities in the network using LASSO multivariate models

Figure 1

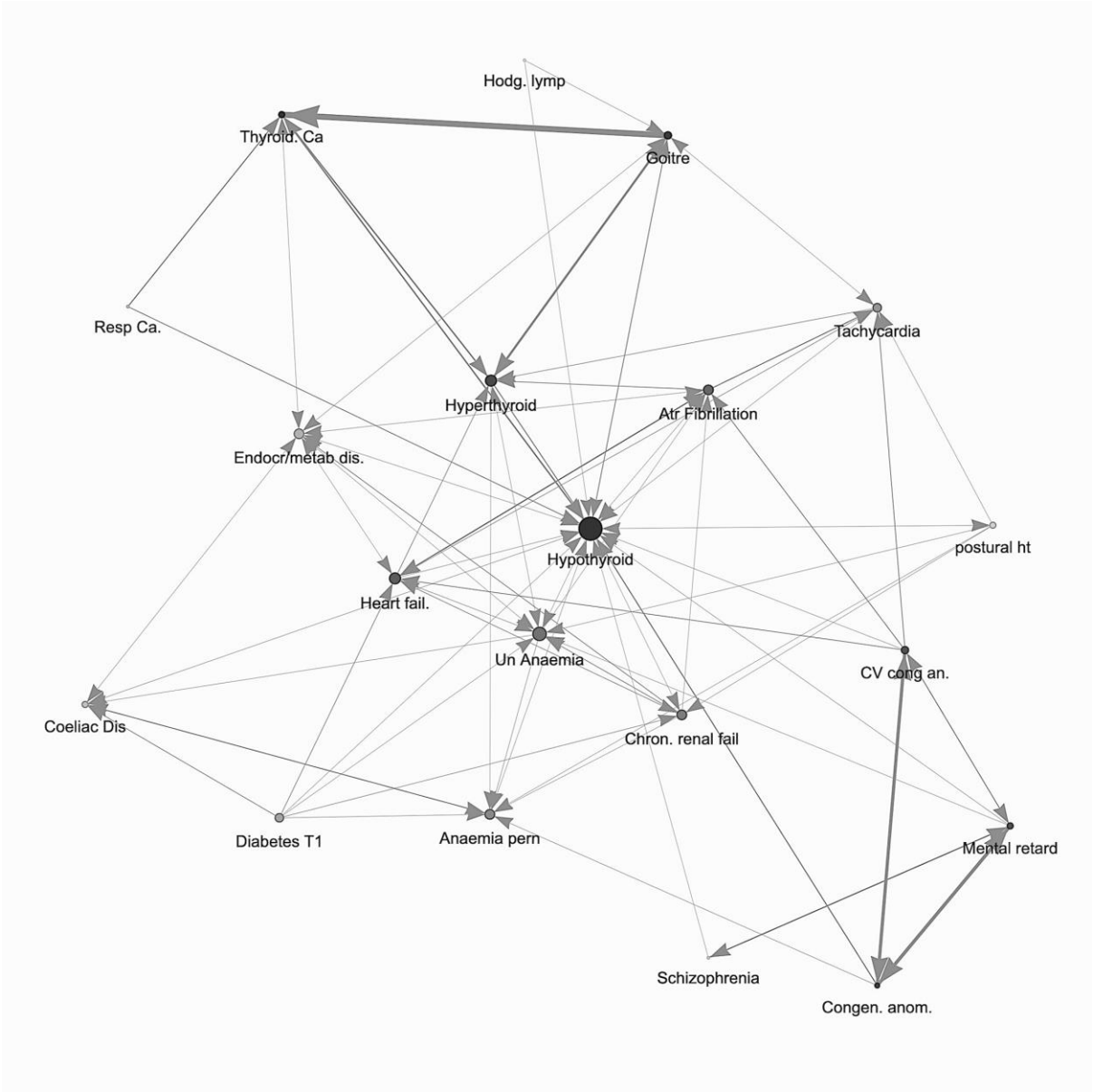

Figure 2