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A retrospective cross-sectional study on tinnitus prevalence and disease associations in the Dutch population-based cohort Lifelines

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ABSTRACT

Tinnitus is a highly prevalent disorder with heterogenous presentation and limited treatment options. Better understanding of its prevalence and disease and lifestyle risk factor associations in the general population is necessary to identify the underlying mechanisms. To this end, we quantified the prevalence of tinnitus and identified disease and lifestyle risk factors associated with tinnitus within a general population cohort. For this study, we used the Lifelines population-based cohort study to perform a retrospective cross-sectional study. Lifelines is a large, multi-generational, prospective cohort study that includes over 167,000 participants (or 10% of the population) from the northern Netherlands. For this study, conducted between 2018 and 2021, data from the Lifelines population-based cohort study was used to perform a cross-sectional study. Adult participants (age $\geq$ 18 years) with data on tinnitus perception (collected once between 2011 and 2015) were included in this study. An elastic-net regression analysis was performed with tinnitus as the dependent variable and parameters of diseases and lifestyle risk factors (collected once between 2006 and 2014)—including hearing problems, cardiovascular disease, metabolic disorders, psychiatric disorders, thyroid disease, inflammatory disease, and functional somatic syndromes—as the independent variables. Among 124,609 participants, N = 8,011 (6.4%) reported perceiving tinnitus constantly (CT: constant tinnitus) and N = 39,625 (31.8%) reported perceiving tinnitus constantly or occasionally (AT: any tinnitus). Our analysis identified 38 parameters that were associated with AT and 48 parameters that were associated with CT. Our study identified established disease associates with tinnitus, including problems with hearing (OR 8.570 with CT), arrythmia (OR 1.742 with CT), transient ischemic attack (OR 1.284 with AT), diabetes mellitus (OR 1.014 with AT) and psychiatric disorders, including major depressive disorder (OR 1.506 with CT). Factors related to lifestyle associated with tinnitus included waist-hip ratio (OR 1.061 with CT) and smoking (OR 1.028 with AT). Novel disease associates with CT were identified for inflammatory diseases, including rheumatoid arthritis (OR 1.297) and ulcerative colitis (OR 1.588), thyroid disease (as evidenced by the use of thyroid medication) (OR 1.298), and functional somatic syndromes, including chronic fatigue syndrome (OR 1.568). In addition to validating established disease associates in a general population cohort, this study identified novel associations with tinnitus and several disease categories, including functional somatic syndromes, inflammatory diseases, and thyroid disease. Future work will be necessary to identify whether (common) mechanisms underly tinnitus and these associated disorders. Lifelines is an important new resource available for future studies investigating tinnitus in the general population.

1. Introduction

Tinnitus is a condition in which people perceive sound without an environmental stimulus. The tinnitus percept varies among individuals and for some can be intrusive, bothersome, and associated with distress and maladaptive responses, including social isolation, sleep deprivation, and mental health problems (Dalton et al.,

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2003; Henry et al., 2005; Yamasoba et al., 2013; Zeman et al., 2014). Diagnosis of tinnitus most commonly involves characterization of both the tinnitus percept (e.g. continuous versus intermittent, loudness, pitch, and lateralization) and also the (detrimental) impact on quality of life (e.g. the Tinnitus Handicap Inventory) (Tyler, 2005; van den Berge et al., 2017; Zeman et al., 2014). Estimations of the prevalence of tinnitus range between 5 and 43% (Gallus et al., 2015; McCormack et al., 2016). Prevalence increases with age and the presence of acquired hearing loss (Fredriksson et al., 2015; McCormack et al., 2016), consistent with the hypothesis that (age-related) hearing loss triggers maladaptive plasticity in the central auditory plasticity and other brain regions that gives rise to the tinnitus percept and, in turn, contribute to the response to tinnitus (Cima, 2018; Persic et al., 2020). Due to its impact on quality of life and prevalence, tinnitus imposes considerable economic burden. The estimated yearly costs per tinnitus patient are $660 (Goldstein et al., 2015) in the United States, £717 (Stockdale et al., 2017) in the United Kingdom, and €1544 (Maes et al., 2013) in the Netherlands.

Disentangling the pathophysiology underlying tinnitus from that underlying the response to tinnitus is essential not only to understand the fundamental mechanisms shaping brain plasticity but also to develop effective and reliable treatment options for tinnitus. The importance of this distinction is emphasized by recent effort to provide not only a commonly accepted and unambiguous definition of tinnitus but also to distinguish tinnitus without suffering from tinnitus with suffering as, respectively, tinnitus and tinnitus disorder (De Ridder et al., 2021). This effort should provide much needed common ground for future tinnitus research and treatments. Importantly, current treatments focus on management of the distress or maladaptive responses caused by tinnitus rather than alleviation of the pathophysiology specifically underlying generation of the tinnitus percept (Baldo et al., 2012; Fuller et al., 2020; Phillips and McFerran, 2010; Scherer and Formby, 2019).

The lack of objective measures, heterogeneous presentation, and variability in response to tinnitus perception make investigation of the pathophysiology underlying tinnitus especially challenging. The lack of consensus on the criteria most relevant for the diagnosis of tinnitus or the characterization of tinnitus subtypes among a heterogeneous population complicates the design of many tinnitus studies. As a result, studies often focus on a narrow range of tinnitus phenotypes within clinical cohorts (Langguth et al., 2017; van den Berge et al., 2017). The use of clinical cohorts also complicates identification of the mechanisms underlying tinnitus from those leading to the distress in response to tinnitus. By design studies conducted with either clinical populations (Lewis et al., 2020) or clinical patients or samples (Bayraktar and Taşolar, 2017; Halford and Anderson, 1991; McKenna et al., 1991) include data only from patients with tinnitus bothersome enough to seek clinical intervention (Engdahl et al., 2012; Maes et al., 2013; Tyler, 2005). Since these patients represent a smaller subpopulation of the general tinnitus population (Bhatt et al., 2016; Cima, 2018; Dawes et al., 2020), this design introduces sample bias (McCormack et al., 2016).

In addition, most studies examining disease and lifestyle factors associated with tinnitus have been underpowered. For example, studies investigating potential biomarkers, including HDL and total cholesterol, included fewer than 200 patients (Alsalman et al., 2016; Martines et al., 2015; Sarıkaya et al., 2016). Often these studies investigated specific factors (disease associations) and, as a result, did not investigate the associations between all factors included in the study (Mahboubi et al., 2013). A few studies have utilized large population-based cohorts to investigate disease associations with tinnitus, such as the UK Biobank, KNHANES and HUNT. Although these studies have the benefit of being very large and representing the general population, they usually lack detailed tinnitus phenotyping (Dawes et al., 2020; Kim et al., 2015; Krog et al., 2010).

Both clinical studies with smaller and more narrowly defined inclusion criteria and well-powered studies investigating tinnitus phenotypes broadly using general populations are necessary to identify the mechanisms specifically underlying tinnitus. To expand the availability of large, general populations available for tinnitus investigation, we examined the Lifelines cohort study, a population-based cohort study consisting of 167,729 participants from the northern Netherlands (Scholtens et al., 2015). Due to its large size and breadth of parameters available for investigation, the Lifelines cohort study offers enormous potential for the investigation of tinnitus. In this study, we first investigated the prevalence and demographic characteristics of individuals within the Lifelines population cohort reporting the perception of tinnitus. We next investigated a wide range of disease and lifestyle factors associated with tinnitus using elastic-net regression analysis. Estimates of tinnitus prevalence within the Lifelines cohort study were consistent with previous studies. Moreover, both previously identified and novel disease and lifestyle factors were associated with tinnitus. Characterization of the tinnitus prevalence and associations within the Lifelines population cohort offer unique insights into the mechanisms underlying tinnitus broadly and not bothersome tinnitus specifically.

2. Method

2.1. Study design and participants

Lifelines is a multi-disciplinary prospective population-based cohort study examining in a unique three-generation design the health and health-related behaviors of 167,729 persons living in the northern Netherlands (Scholtens et al., 2015). It employs a broad range of investigative procedures to assess the biomedical, socio-demographic, behavioral, physical and psychological factors that contribute to the health and disease of the general population, with a special focus on multi-morbidity and complex genetics. The three-generation design, which aims to include three generations within each family, enables investigation of the genetic contributions of complex diseases. All participants provided written informed consent, and the study was approved by the medical ethical review board of the University Medical Center Groningen (UMCG). The Lifelines cohort study assesses participants using a regular schedule with five-year comprehensive visits and questionnaires in between. Between 2006 and 2014, a comprehensive visit was scheduled with questionnaires, physical measurements, interviews, and biomarker analysis. In a follow-up questionnaire (2011–2015), tinnitus was assessed. Tinnitus assessment was the only data used from this timepoint. Participants with no information on tinnitus were excluded from this study. All other data used in this study were collected during the comprehensive visit scheduled between 2006 and 2014. This study was conducted between May 2018 and January 2021. This study is, therefore, a retrospective cross-sectional study.

2.2. Demographic variables

Questionnaires were used to obtain data on sex. Age data was obtained through access to municipality records. The analyses in the current study were based on the adult (age $\geq$18 years old) Lifelines participants (N = 124,648).

2.3. Psychiatric interview

The Mini International Neuropsychiatric Interview (MINI) 5.0.0 is a brief, structured interview to diagnose psychiatric disorders

based on the DSM-IV and ICD-10 (Sheehan et al., 1998). Participants were interviewed by trained medical staff during their visits to the Lifelines facilities at baseline. Data from the interview were used to assess major depressive disorder, panic disorder, social phobia, agoraphobia, general anxiety disorder, and dysthymia.

2.4. Measurements

According to the Lifelines protocol, participants are invited every five years for a physical examination and biomaterial collection (Scholtens et al., 2015). For this study, baseline measurements of anthropometry, including height, weight, body-mass index (BMI), waist and hip circumference, and blood pressure were included. More information on the cut-off values used in this study are provided in the supplementary information.

2.5. Blood biomarkers

According to the Lifelines protocol, blood is drawn every five years from all participants for direct measurements and long-term biobanking (Scholtens et al., 2015). Tubes were processed in the Lifelines laboratory, and clinical chemistry assays were performed on fresh samples in the central laboratory of the UMCG. For this study, the following biomarkers measured between 2006 and 2014 were included: cardiovascular-related (cholesterol, HDL cholesterol, LDL cholesterol, triglycerides), diabetes-related (glucose, HBA1c), and inflammation-related (leukocytes, lymphocytes, monocytes, neutrophil granulocytes and eosinophil granulocytes). More information on the cut-off values used in this study are provided in the supplementary information.

2.6. Health-related questionnaire data

Tinnitus was assessed during the first follow-up using the question, with possible answers between brackets: “Do you hear ringing or whistling in your ear(s)?” [yes, always; yes, sometimes; no, never]. Assessment of tinnitus was similar to criteria used in previous epidemiological studies (Dawes et al., 2020; Engdahl et al., 2012). Hearing-related questions include: (1) “Do you need a hearing aid?” [yes; no] and (2) “Are you limited by problems with your hearing in daily life?” [yes, severely limited; yes, somewhat limited; no, not limited at al]. General health status was assessed based on self-report of history and prevalence of diseases, disabilities, and symptoms. Health baseline questionnaire data on hearing, cardiovascular disease, metabolic disease, thyroid disease, inflammatory diseases, and functional somatic syndromes were selected for analysis. Smoking, including current and past active smoking behavior, was assessed via self-report.

2.7. Statistical analysis

Statistical analyses were performed with the R programming language and statistical environment (4.0.2) using RStudio (1.1.463). The Compare Groups package (3.4.0) was used for univariable analysis and descriptive statistics (Subirana et al., 2014). The first set of analyses compared participants reporting any tinnitus (AT; thus, answering either “Yes, sometimes” or “Yes, always” to the tinnitus questions) or no tinnitus (thus, answering “No, never” to the tinnitus question). For non-normally distributed variables, medians and interquartile ranges (IQRs) were calculated. Normally distributed variables are represented as means ± standard deviations (SD). Categorical data are represented as absolute numbers and percentages. Variables were selected based on their established relation with tinnitus (hearing, cardiovascular, metabolic and psychiatric disorders) (Nondahl et al., 2011) and relations with hearing loss (thyroid and inflammatory disease) (Kim et al., 2015; Ozbay et al., 2015; Wang et al., 2019). Because tinnitus meets the criteria for functional syndromes (Wessely et al., 1999), this disease category was also taken into account. Overall, these categories yielded 51 parameters of interest.

To identify parameters associated with tinnitus, an elastic-net regression was performed utilizing the glmnet package (Version 4.1-1). Since these statistical models cannot work with missing data, 43 cases had to be excluded because data was still missing, including 1 case reporting “yes, always” tinnitus (leaving a final $N = 124{,}609$). This had no major effect on tinnitus prevalence. All other data were imputed using the Mice package (3.7.0). The amount of missing data was small and varied between 0%, in the case of the variables sex, age and multiple sclerosis, and 17.4%, in the case of biomarker levels of Hba1c. Data for the biomarker levels of Hba1c had the most missing values followed by the data for dysthymia, in which 3.0% of the values were missing. The median number of all missing values per parameter was 0.85% [0.00; 1.05 IQR]. Again, data on tinnitus was not imputed.

The dataset was then split randomly into a training dataset (80% of the complete cases; $N = 99{,}686$) to train the model and a testing dataset (20% of the complete cases; $N = 24{,}922$) to test the predictive accuracy of the model. A 10-fold cross-validation was used to identify the optimal regularization parameter (λ). The best λ value, according to the algorithm, corresponded to the best fitting model. Next the optimal elastic-net mixing parameter ($\boldsymbol{\alpha}$) was identified using a series of regression models while changing $\boldsymbol{\alpha}$ between the following range: $0.1 \leq \boldsymbol{\alpha} \leq 1$. This yielded an optimal regularization parameter of 0.9. An elastic-net regression was run using both alpha and lambda, which identified the parameters associated with tinnitus.

A second set of analyses examined a subset of the data above and compared participants reporting constant tinnitus (CT; thus, answering “Yes, always” to the tinnitus questions) or no tinnitus (thus, answering “No, never” to the tinnitus question). This analysis yielded a final $N = 93{,}040$ participants. This dataset was also split into a training dataset (80% of the complete cases; $N = 74{,}432$) and a testing dataset (20% of the complete cases; $N = 18{,}608$), which was then used for 10-fold cross-validation and regularization optimalization which yielded a regularization parameter of 0.3. Results are presented as odds ratios (ORs), ORs >1.000 (positive or direct association, so more associated with tinnitus) or <1.000 (negative or inverse association, so more associated with not having tinnitus) are considered significant.

In these analyses we use elastic net regression, which is a penalized regression method that combines the benefits of both Lasso and Ridge regression. Penalized regression outperforms linear and logistic regression in the presence of multicollinearity, an issue complicating tinnitus predictors. Moreover, penalized regression tries to equalize the weight of the predictors, which allows to include a higher number of predictors without the model putting a large weight on only a few predictors. This method has been used previously (Simoes et al., 2019). In penalized regression models, variance is reduced by introducing substantial bias, which makes error estimations uninformative (Goeman et al., 2014). Thus, standard errors or confidence intervals are generally not reported when using penalized estimation methods (Goeman et al., 2014). For this reason, confidence intervals are not reported in this study.

3. Results

3.1. Prevalence of tinnitus increases with age in the Lifelines cohort

Following data imputation, 85,026 (68.2%) participants reported never perceiving tinnitus, whereas 31,611 (25.4%) participants reported perceiving tinnitus sometimes and 8,011 (6.4%) participants reported perceiving tinnitus constantly (constant tinnitus: CT). Par-

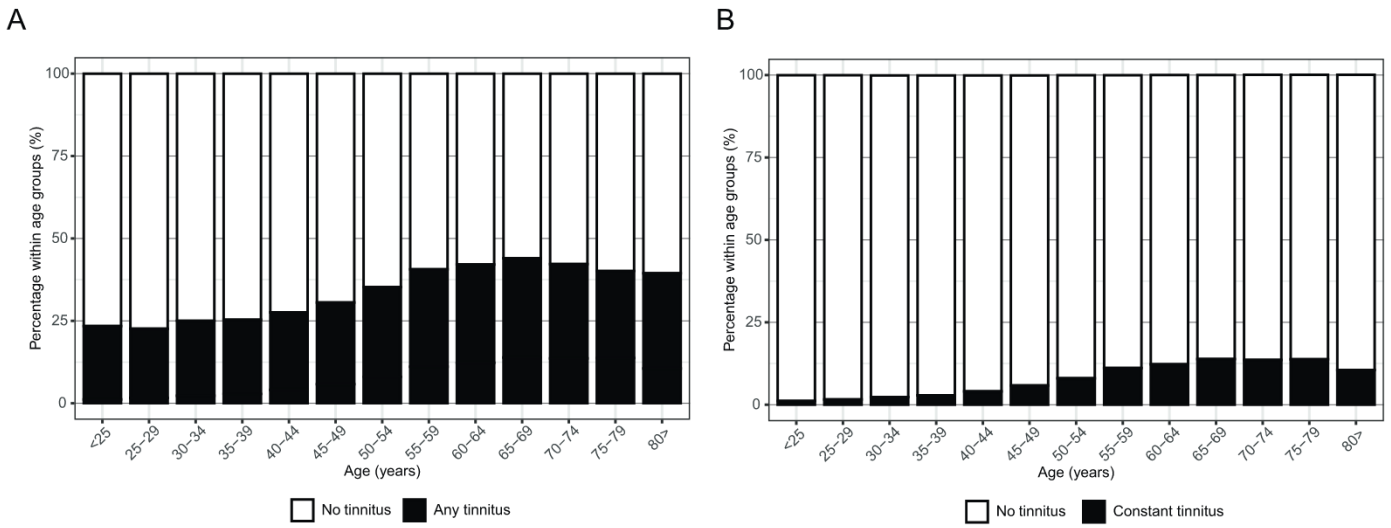

Fig. 1. Tinnitus prevalence in the Lifelines cohort study (total $N = 124{,}648$) by age group shows the highest prevalence within the individuals between 55 and 75 years old. Data presented as percentages of tinnitus type per age group, and age is in years. White: no tinnitus; Black: (A) any tinnitus (AT), (B) constant tinnitus (CT).

Table 1
Prevalence number for tinnitus in the Lifelines cohort study.

	No tinnitus $N = 85026$	Occasional tinnitus $N = 31611$	Constant tinnitus $N = 8014$
Age groups:			
<25	4635 (5.45%)	1346 (4.26%)	70 (0.87%)
25–29	6087 (7.16%)	1653 (5.23%)	127 (1.58%)
30–34	7465 (8.78%)	2264 (7.16%)	229 (2.86%)
35–39	8968 (10.5%)	2701 (8.54%)	342 (4.27%)
40–44	13218 (15.5%)	4300 (13.6%)	738 (9.21%)
45–49	15275 (18.0%)	5447 (17.2%)	1280 (16.0%)
50–54	11910 (14.0%)	5012 (15.9%)	1475 (18.4%)
55–59	5457 (6.42%)	2715 (8.59%)	1022 (12.8%)
60–64	5100 (6.00%)	2628 (8.31%)	1081 (13.5%)
65–69	3931 (4.62%)	2118 (6.70%)	973 (12.1%)
70–74	1870 (2.20%)	926 (2.93%)	440 (5.49%)
75–79	783 (0.92%)	345 (1.09%)	180 (2.25%)
80>	327 (0.38%)	156 (0.49%)	57 (0.71%)

Values are represented in absolute number and percentages in brackets.

ticipants that reported perceiving tinnitus either sometimes or constantly were combined into an "any tinnitus" (AT) group, which totaled 39,625 (31.8%) participants. The prevalence of tinnitus increased with age, reaching the highest prevalence in the age group containing individuals between 60 and 80 years old and remaining stable in older age groups (Fig. 1A, B, Table 1). The increase in tinnitus prevalence with age appears to be mainly due to the increased prevalence of participants that reported constant tinnitus (CT; answered "yes, always" in the tinnitus questionnaire), whereas the prevalence of participants that answered having occasional tinnitus (answered "yes, sometimes" in the tinnitus questionnaire) remained stable (Table 1). When comparing across age groups, the highest proportion of individuals reporting AT was between 60 and 74 years old. The highest proportion reporting CT was between 65 and 69 years old. Both older age and male sex were found to be associated with an increased prevalence of tinnitus (Tables 2, 3).

3.2. Established associations between tinnitus, hearing impairment, cardiovascular diseases, diabetes mellitus, and psychiatric diseases in the Lifelines cohort

Binomial elastic-net regression, with $\boldsymbol{\alpha} = 0.9$, yielded a list of 50 and 38 parameters that contributed, at least partially, to predicting whether participants reported, any form of tinnitus. These parameters identified both well-established as well as novel tinnitus associations in the Lifelines cohort. Established tinnitus associations are presented in Table 2. Problems with hearing in daily life was the predictor showing the largest positive association with tinnitus (OR 3.265). The next largest positive associations with tinnitus were found for arrythmia, panic disorder without agoraphobia, male sex, transient ischemic attack and social phobia, with ORs ranging from 1.264 to 1.671. Additional positive associations with tinnitus were identified for major depressive disorder, agoraphobia without panic disorder, general anxiety disorder, underweight, other types of diabetes mellitus, dysthymia, edema, need for a hearing aid, smoking, self-reported hypertension, LDL cholesterol, self-reported hypercholesterolemia, HDL cholesterol, former smoking status, overweight, diabetes mellitus, age, elevated systolic blood pressure and elevated triglyceride levels, with ORs ranging from 1.010 to 1.229.

The greatest negative associations with tinnitus were found for type 1 diabetes mellitus, heart failure, heart attack and very high numbers of smoking pack years, with ORs ranging from 0.757 to 0.958. Furthermore, we identified negative associations with tinnitus for BMI and elevated mean arterial pressure.

3.3. Novel associations between tinnitus and thyroid disease, inflammatory diseases, and functional somatic syndromes in the Lifelines cohort

Based on the elastic-net regression we also identified novel associations between various diseases and disease parameters and tinnitus. Novel tinnitus associations are presented in Table 2. Rheumatoid arthritis (OR 1.359), Irritable bowel syndrome (OR 1.322), and chronic fatigue syndrome (OR 1.222) showed large positive associations with tinnitus (Table 2). Positive associations were also identified with other parameters within the thyroid and inflammatory disease groups and functional somatic syndromes, with ORs ranging from 1.001 to 1.172. Tinnitus was negatively associated with multiple sclerosis (OR 0.775) and some inflammatory biomarker levels, including elevated (OR 0.984) and lowered (OR 0.944) lymphocyte levels, lowered monocyte (0.824) and leukocytes levels (0.975), and elevated neutrophil:lymphocyte ratio levels (OR 0.944).

Table 2
Association analysis for associations with tinnitus in the Lifelines cohort study.

	No, tinnitus $N = 85026$	AT $N = 39625$	OR
Sex (male)	33140 (39.0%)	4587 (57.2%)	1.310*
Age	45.0 [36.0;52.0]	49.0 [41.0;58.0]	1.013*
Disease group 1 Hearing			
Are you limited by problems with your hearing in daily life?			3.265*
No, not limited at all	78590 (92.4%)	29654 (74.8%)	
Yes, severely limited	6263 (7.37%)	9475 (23.9%)	
Yes, somewhat limited	173 (0.20%)	496 (1.25%)	
Do you need a hearing aid?	1525 (1.79%)	2607 (6.58%)	1.115*
Disease group 2 Cardiovascular			
Heart attack	710 (0.84%)	573 (1.45%)	0.958*
Heart failure	502 (0.59%)	385 (0.97%)	0.858*
Irregular heartbeat or fast heartbeat	16673 (19.6%)	12485 (31.5%)	1.671*
Transient ischemic attack	5151 (6.06%)	3726 (9.40%)	1.284*
Edema	11341 (13.3%)	6981 (17.6%)	1.156*
Hypertension - self-report	16860 (19.8%)	10447 (26.4%)	1.102*
Systolic blood pressure - measured (≥140 mmHg)	13031 (15.3%)	7619 (19.2%)	1.012*
Diastolic blood pressure - measured (≥90 mmHg)	4618 (5.43%)	2590 (6.54%)	1.000
Mean arterial pressure			
Elevated (>110 mmHg)	4737 (5.57%)	2820 (7.12%)	0.991*
Lowered (<65 mmHg)	40 (0.05%)	16 (0.04%)	1.000
Smoking status - Current	13383 (15.7%)	6577 (16.6%)	1.000
Smoking status - Former	24674 (29.0%)	13815 (34.9%)	1.028*
Smoking - pack years			
0 pack years	71067 (84.0%)	32697 (82.9%)	Ref.
0–10 pack years	5932 (7.01%)	2534 (6.43%)	1.062*
10–20 pack years	3686 (4.36%)	1860 (4.72%)	1.076*
20–30 pack years	2223 (2.63%)	1310 (3.32%)	1.097*
30–40 pack years	1034 (1.22%)	611 (1.55%)	1.000
40 pack years	682 (0.81%)	420 (1.07%)	0.859*
Disease group 3 Metabolic			
Diabetes mellitus	1795 (2.11%)	1243 (3.14%)	1.014*
Diabetes type			
Type 1 (juvenile diabetes)	197 (0.23%)	73 (0.18%)	0.757*
Type 2 (adult-onset diabetes)	1379 (1.62%)	1028 (2.59%)	1.000
Other	224 (0.26%)	134 (0.34%)	1.210*
HbA1c (≥48 mmol/mol)	1600 (1.88%)	1061 (2.68%)	1.000
Glucose (≥7 mmol/L)	1592 (1.87%)	1027 (2.59%)	1.000
Hypercholesterolemia - self reported	10049 (11.8%)	6785 (17.1%)	1.049*
HDL cholesterol (<1 mmol/L)	4260 (5.01%)	2344 (5.92%)	1.041*
LDL cholesterol (>3 mmol/L)	44638 (52.5%)	23192 (58.5%)	1.078*
Tryglicerides (>2 mmol/L)	7401 (8.70%)	4255 (10.7%)	1.010*
Total cholesterol (>5 mmol/L)	39277 (46.2%)	20526 (51.8%)	1.000
Waist-hip ratio			
Overweight (≥0.9 for males/≥0.85 for females)	56667 (66.6%)	28520 (72.0%)	1.014*
BMI			
Overweight (≥25 kg/m2)	45146 (53.1%)	22775 (57.5%)	0.971*
Underweight (<18.5 kg/m2)	710 (0.84%)	292 (0.74%)	1.211*
Disease group 4 Psychiatric			
Major depressive disorder	1246 (1.47%)	1119 (2.82%)	1.229*
General anxiety disorder	2780 (3.27%)	2080 (5.25%)	1.218*
Social phobia	614 (0.72%)	512 (1.29%)	1.264*
Dysthymia	870 (1.02%)	703 (1.77%)	1.167*
Panic disorder without agoraphobia	1536 (1.81%)	1091 (2.75%)	1.401*
Agoraphobia without panic disorder	958 (1.13%)	496 (1.25%)	1.227*
Disease group 5 Thyroid			
Thyroid medication - current use	2451 (2.88%)	1486 (3.75%)	1.032*
Thyroid medication - past use	1746 (2.05%)	1038 (2.62%)	1.022*
Disease group 6 Inflammatory			
Rheumatoid arthritis	2059 (2.42%)	1835 (4.63%)	1.359*
Ulcerative colitis	465 (0.55%)	263 (0.66%)	1.172*
Crohn's disease	254 (0.30%)	150 (0.38%)	1.082*
Multiple sclerosis	229 (0.27%)	89 (0.22%)	0.775*
Psoriasis	2311 (2.72%)	1247 (3.15%)	1.001*
Trombocytes (10E9/L)			
> 400 × 10E9/L	966 (1.14%)	427 (1.08%)	1.000
< 150 × 10E9/L	1347 (1.58%)	707 (1.78%)	1.000
Lymphocytes (10E9/L)			
> 3.5 × 10E9/L	1599 (1.88%)	788 (1.99%)	0.984*
< 1 × 10E9/L	1240 (1.46%)	580 (1.46%)	0.944*
Leukocytes			
> 10 × 10E9/L	2043 (2.40%)	1084 (2.74%)	1.076*
< 4 × 10E9/L	4953 (5.83%)	2263 (5.71%)	0.975*

(*continued on next page*)

Table 2 (*continued*)

	No, tinnitus $N = 85026$	AT $N = 39625$	OR
Neutrophil granulocytes			
> 7.5 × 10E9/L	1058 (1.24%)	557 (1.41%)	1.013*
< 1.5 × 10E9/L	1427 (1.68%)	671 (1.69%)	1.000
Eosinophil granulocytes (10E9/L)			
> 0.5 × 10E9/L	2098 (2.47%)	997 (2.52%)	1.011*
< 0.1 × 10E9/L	19123 (22.5%)	8569 (21.6%)	1.028*
Monocytes (10E9/L)			
> 1 × 10E9/L	516 (0.61%)	273 (0.69%)	1.000
< 0.1 × 10E9/L	<10 (<0.02%)	<10 (<0.03%)	0.824*
Neutrophil:Lymphocyte ratio			
- 1SD	6361 (7.48%)	2980 (7.52%)	1.060*
- 2SD	<10 (<0.02%)	0 (0.00%)	0.371*
+ 1SD	6213 (7.31%)	2940 (7.42%)	1.000*
+ 2SD	3033 (3.57%)	1460 (3.68%)	0.944*
Lymphocyte:monocyte ratio			
- 1SD	10274 (12.1%)	5152 (13.0%)	0.999*
- 2SD	241 (0.28%)	131 (0.33%)	1.000
+ 1SD	8673 (10.2%)	3847 (9.71%)	1.027*
+ 2SD	3052 (3.59%)	1334 (3.37%)	1.031*
Disease group 7 Functional			
Chronic fatigue syndrome	801 (0.94%)	747 (1.89%)	1.222*
Fibromyalgia	2059 (2.42%)	1836 (4.63%)	1.072*
Irritable bowel syndrome	7030 (8.27%)	4680 (11.8%)	1.322*

Data presented as absolute number with percentage in brackets. Continuous data presented as median with IQRs. Total included participants in this analysis $N = 124{,}648$. OR: odds ratio; HDL: high-density lipoprotein. ORs >1.000 or <1.000 are considered significant. In penalized regression models, like elastic net regression used here, error estimations are uninformative and, therefore, confidence intervals are not reported.

* indicates significant associations.

3.4. Analyses of the constant tinnitus (CT) population show both similarities and differences with the any tinnitus (AT) population

Because of the large heterogeneity in tinnitus presentation, we then focused on the most robust tinnitus phenotype (CT/'Yes, always') and performed an elastic-net regression including the same parameters and tuned with an $\alpha = 0.3$. Male sex (OR 2.053) and age (1.035) showed stronger positive associations with this group (Table 3). Hearing problems showed a large increase of the positive association (OR 8.570), while need for a hearing aid stayed the same. The majority of the strongest positive associations overlap with the previous analysis, including major depressive disorder (OR 1.506), panic disorder without agoraphobia (OR 1.468), chronic fatigue syndrome (1.568), irritable bowel syndrome (1.353) and arrythmia (1.742). This includes both known and novel associations with tinnitus. For the negative associations, there is also a large overlap with the previous analysis, including type 1 diabetes (0.678), heart attack (0.750), lowered monocyte levels (0.717) and heart failure (0.821).

There were also differences in associations between the two analyses. Edema was positively associated with any tinnitus, but negatively associated with CT. Similar findings were identified for lower numbers of smoking pack years, elevated HbA1c, underweight, past thyroid medication use, Crohn's disease, elevated leukocyte levels and high lymphocyte:monocyte ratios. Negative associations for any tinnitus and positive associations with CT were identified for overweight, multiple sclerosis and lowered leukocyte levels.

4. Discussion

In this study, we investigated the prevalence and disease and lifestyle factors associated with tinnitus in the Dutch population-based Lifelines cohort. The analyzed Lifelines cohort includes 124,648 adult participants, of which 39,622 reported tinnitus perception. In comparison, the sample size of previous cohort studies ranged from 498 to 172,621, with a median sample size of 3753 (McCormack et al., 2016). By utilizing this large non-clinical population, we were able to estimate the prevalence of tinnitus and examine disease and lifestyle factors associated with tinnitus. Importantly, our approach, which utilized elastic-net regression, enabled us to include multiple predictors while taking into account their interrelations. In contrast, other studies have been much smaller, were often performed in selected clinical samples, and focused on specific predictors while ignoring other relevant determinants. Within this non-clinical population, we identified associations observed in previous studies, including hearing impairment, cardiovascular diseases, diabetes mellitus. Moreover, we were able to identify novel associations, including thyroid disease, inflammatory disease, and functional somatic syndromes.

The prevalence of tinnitus in the Lifelines population cohort ranged from 6.4% reporting constant perception of tinnitus (CT) to 25.4% reporting occasional or intermittent perception of tinnitus. We also observed an increase in the prevalence with age and a higher prevalence in males. Previous results on the effects of age are conflicting, with some studies reporting decreasing tinnitus prevalence after the age of 70 years (Shargorodsky et al., 2010; Sindhusake et al., 2003) and others reporting increasing tinnitus prevalence beyond the age of 70 years (McCormack et al., 2016), including a study with a similar European population (Martinez et al., 2015). We found that the prevalence of participants reporting occasional tinnitus remained relatively stable over the different age groups, whereas the prevalence of participants reporting constant tinnitus increased in higher age groups (Table 1). Our study reported decreasing prevalence of tinnitus in the highest age groups, similar to some of the studies included in a previous meta-analysis (McCormack et al., 2016). The reason for this decline is unclear. In general, there are large variations across studies in estimations of prevalence owing to the lack of objective measures for diagnosing tinnitus and the inconsistency among studies in defin-

Table 3
Association analysis for associations with constant tinnitus in the Lifelines cohort study.

	No, never *N* = 85026	CT *N* = 8014	OR
Sex (male)	33140 (39.0%)	4587 (57.2%)	2.053*
Age	45.0 [36.0;52.0]	53.0 [47.0;63.0]	1.035*
Disease group 1 Hearing			
Are you limited by problems with your hearing in daily life?			8.570*
No, not limited at all	78590 (92.4%)	4164 (52.0%)	
Yes, severely limited	173 (0.20%)	301 (3.76%)	
Yes, somewhat limited	6263 (7.37%)	3549 (44.3%)	
Do you need a hearing aid?	1525 (1.79%)	1193 (14.9%)	1.114*
Disease group 2 Cardiovascular			
Heart attack	710 (0.84%)	170 (2.12%)	0.750*
Heart failure	502 (0.59%)	104 (1.30%)	0.821*
Irregular heartbeat or fast heartbeat	16673 (19.6%)	2603 (32.5%)	1.742*
Transient ischemic attack	5151 (6.06%)	790 (9.86%)	1.201*
Edema	11341 (13.3%)	1304 (16.3%)	0.972*
Hypertension - self-report	16860 (19.8%)	2398 (29.9%)	1.066*
Systolic blood pressure - measured (≥140 mmHg)	13031 (15.3%)	1881 (23.5%)	0.973*
Diastolic blood pressure - measured (≥90 mmHg)	4618 (5.43%)	627 (7.82%)	1.147*
Mean arterial pressure			
Elevated (>110 mmHg)	4737 (5.57%)	710 (8.86%)	0.916*
Lowered (<65 mmHg)	40 (0.05%)	<10 (<0.12%)	1.187*
Smoking status - Current	13383 (15.7%)	1123 (14.0%)	1.000
Smoking status - Former	24674 (29.0%)	3363 (42.0%)	1.112*
Smoking - pack years			
0 pack years	71067 (83.6%)	6859 (85.7%)	Ref.
0–10 pack years	5932 (6.98%)	360 (4.50%)	0.938*
10–20 pack years	3814 (4.49%)	301 (3.76%)	0.944*
20–30 pack years	2328 (2.74%)	259 (3.24%)	1.008*
30–40 pack years	1165 (1.37%)	126 (1.57%)	0.786*
40 pack years	682 (0.80%)	101 (1.26%)	0.758*
Disease group 3 Metabolic			
Diabetes mellitus	1795 (2.11%)	333 (4.16%)	1.000
Diabetes type			
Type 1 (juvenile diabetes)	197 (0.23%)	<10 (<0.12%)	0.678*
Type 2 (adult-onset diabetes)	1379 (1.62%)	298 (3.72%)	1.060*
Other	224 (0.26%)	22 (0.27%)	1.290*
HbA1c (≥48 mmol/mol)	1600 (1.88%)	255 (3.18%)	0.723*
Glucose (≥7 mmol/L)	1592 (1.87%)	236 (2.94%)	0.998*
Hypercholesterolemia - self reported	10049 (11.8%)	1821 (22.7%)	1.086*
HDL cholesterol (<1 mmol/L)	4260 (5.01%)	535 (6.68%)	1.111*
LDL cholesterol (>3 mmol/L)	44638 (52.5%)	5196 (64.8%)	1.089*
Tryglicerides (>2 mmol/L)	7401 (8.70%)	1001 (12.5%)	1.000
Total cholesterol (>5 mmol/L)	39277 (46.2%)	4675 (58.3%)	1.108*
Waist-hip ratio			
Overweight (≥0.9 for males/≥0.85 for females)	56667 (66.6%)	6291 (78.5%)	1.061*
BMI			
Overweight (≥25 kg/m2)	45146 (53.1%)	5049 (63.0%)	1.001*
Underweight (<18.5 kg/m2)	710 (0.84%)	34 (0.42%)	0.910*
Disease group 4 Psychiatric			
Major depressive disorder	1246 (1.47%)	251 (3.13%)	1.506*
General anxiety disorder	2780 (3.27%)	398 (4.97%)	1.136*
Social phobia	614 (0.72%)	91 (1.14%)	1.275*
Dysthymia	870 (1.02%)	143 (1.78%)	1.342*
Panic disorder without agoraphobia	1536 (1.81%)	198 (2.47%)	1.468*
Agoraphobia without panic disorder	2235 (2.63%)	325 (4.06%)	1.135*
Disease group 5 Thyroid			
Thyroid medication - current use	2451 (2.88%)	339 (4.23%)	1.298*
Thyroid medication - past use	1746 (2.05%)	226 (2.82%)	0.933*
Disease group 6 Inflammatory			
Rheumatoid arthritis	2059 (2.42%)	405 (5.06%)	1.297*
Ulcerative colitis	465 (0.55%)	67 (0.84%)	1.588*
Crohn's disease	254 (0.30%)	29 (0.36%)	0.994*
Multiple sclerosis	229 (0.27%)	26 (0.32%)	1.292*
Psoriasis	2311 (2.72%)	271 (3.38%)	1.043*
Trombocytes (10E9/L)			
> 400 × 10E9/L	966 (1.14%)	75 (0.94%)	0.951*
< 150 × 10E9/L	1347 (1.58%)	162 (2.02%)	0.922*
Lymphocytes (10E9/L)			
> 3.5 × 10E9/L	1599 (1.88%)	144 (1.80%)	0.936*
< 1 × 10E9/L	1240 (1.46%)	123 (1.53%)	0.736*
Leukocytes			
> 10 × 10E9/L	2043 (2.40%)	188 (2.35%)	0.992*
< 4 × 10E9/L	4953 (5.83%)	495 (6.18%)	1.076*

(*continued on next page*)

Table 3 (*continued*)

	No, never $N = 85026$	CT $N = 8014$	OR
Neutrophil granulocytes			
> 7.5 × 10E9/L	1058 (1.24%)	101 (1.26%)	1.201*
< 1.5 × 10E9/L	1427 (1.68%)	133 (1.66%)	0.894*
Eosinophil granulocytes (10E9/L)			
> 0.5 × 10E9/L	2098 (2.47%)	204 (2.55%)	1.053*
< 0.1 × 10E9/L	19123 (22.5%)	1625 (20.3%)	1.019*
Monocytes (10E9/L)			
> 1 × 10E9/L	516 (0.61%)	60 (0.75%)	0.893*
< 0.1 × 10E9/L	<10 (<0.02%)	<10 (<0.12%)	0.717*
Neutrophil:Lymphocyte ratio			
- 1SD	6361 (7.48%)	601 (7.50%)	1.191*
- 2SD	<10 (<0.02%)	0 (0.00%)	1.000
+ 1SD	6213 (7.31%)	593 (7.40%)	0.976*
+ 2SD	3033 (3.57%)	287 (3.58%)	0.943*
Lymphocyte:monocyte ratio			
- 1SD	10274 (12.1%)	1177 (14.7%)	0.908*
- 2SD	241 (0.28%)	30 (0.37%)	1.102*
+ 1SD	8673 (10.2%)	677 (8.45%)	1.039*
+ 2SD	3052 (3.59%)	196 (2.45%)	0.927*
Disease group 7 Functional			
Chronic fatigue syndrome	801 (0.94%)	192 (2.40%)	1.568*
Fibromyalgia	2059 (2.42%)	406 (5.07%)	1.255*
Irritable bowel syndrome	7030 (8.27%)	892 (11.1%)	1.353*

Data presented as absolute number with percentage in brackets. Continuous data presented as median with IQRs. Total included participants in this analysis $N = 93{,}040$. OR: odds ratio;. ORs >1.000 or <1.000 are considered significant. In penalized regression models, like elastic net regression used here, error estimations are uninformative and, therefore, confidence intervals are not reported.

* indicates significant associations.

ing and reporting tinnitus (McCormack et al., 2016; van den Berge et al., 2017). Nevertheless, our numbers are in line with a recent systematic review that used consistent assessment criteria to evaluate tinnitus prevalence (and severity) over 39 independent studies (Dawes et al., 2020; McCormack et al., 2016). In this systematic review, tinnitus prevalence was estimated to be between 11.9 and 30.3%, increased with age, and was higher in males. We therefore conclude that the Lifelines cohort study shows similar prevalence numbers compared to previously reported estimates of tinnitus prevalence.

We also identified diseases associated with tinnitus in the Lifelines cohort. We specifically examined associations between tinnitus and the following broad disease categories: hearing loss, cardiovascular diseases, metabolic diseases, functional somatic syndromes, and psychiatric diseases. Within these broad categories, we identified disease associations that were both established and novel.

First and as expected, we identified associations between tinnitus perception and hearing problems. This association was higher in the CT compared to the AT group. Our observations support previous findings from other cohort studies, one which assessed hearing impairment using audiometric examination (Dawes et al., 2020; Nondahl et al., 2011) and the other which examined associations with diseases of the ear, including vestibular neuronitis and Meniere's disease (which both had the highest odds ratios) (Dawes et al., 2020; Kostev et al., 2019).

Second, we identified associations between tinnitus and cardiovascular diseases, consistent with a previous report (Kostev et al., 2019) but different from another large study (Dawes et al., 2020; Nondahl et al., 2011). Within this disease category, our study found a positive association between the perception of tinnitus and systolic blood pressure in AT, but a negative association in CT. Diastolic blood pressure was positively associated only in the group that reported CT, but showed not to be associated with AT. Self-reported hypertension was associated with tinnitus in both groups. Previous studies have also identified an association between blood pressure and tinnitus. Our study shows a discrepancy between blood pressure measurements and self-reported hypertension association, where the effect sizes of the measurements are smaller compared to self-reported hypertension. A systematic review of 19 studies showed that hypertension is a risk factor for tinnitus (Yang et al., 2015), whereas a cohort study by Kostev et al. found that hypotension was significantly associated with tinnitus (Kostev et al., 2019). This previous study also found an association between the previous occurrence of a transient ischemic attack (TIA) and tinnitus. A previous case-control study reported the increased risk of ischemic cerebrovascular disease in tinnitus suffers (Huang et al., 2017).

The relation between heart failure and tinnitus is still unclear. Our study identified a negative association with self-reported heart failure with both tinnitus groups. A cross-sectional study showed that after multivariable analysis, tinnitus was positively associated with <45% left ventricular ejection fraction and serum BNP levels >11.1 mmol/L (>200 mg/dL), indicating heart failure (Borghi et al., 2011). Furthermore, we found a negative association with self-reported heart attack with both tinnitus groups. Again, here another study reported a positive association with coronary heart disease (Kostev et al., 2019). A relation between heart failure, heart attack, and hypertension with tinnitus might be possible due to changes in blood circulation in the inner ear or relevant brain structures. Psychological stress has been shown to be associated with increased inflammation levels and increased incidence of cardiovascular disease, however, whether this relation is causal remains unknown (Wirtz and von Känel, 2017). More studies investigating this relation are warranted.

Third, we identified associations between tinnitus and metabolic disease characteristics. Our study found that hypercholesterolemia, higher levels of LDL cholesterol and lower levels of HDL cholesterol were associated with tinnitus perception in both groups. In contrast, other studies have not found significant associations between tinnitus and hypercholesterolemia or serum cholesterol levels (M-Shirazi et al., 2011; Nondahl et al., 2011).

However, some literature on hearing loss suggests that hypercholesterolemia triggers vascular stenosis in the spiral ganglion neurons in the cochlea, resulting in ischemia and hearing loss (Malgrange et al., 2015). It is possible that hearing loss as a result of hypercholesterolemia-induced vascular stenosis could result in the development of tinnitus and lead to the association identfied in our study. Our study as well as several previous studies have identified significant associations between diabetes mellitus and tinnitus perception (Li et al., 2018; Spankovich et al., 2017), although some other studies did not identify this association (Gibrin et al., 2013; Martines et al., 2015). Type 1 diabetes mellitus seems to be negatively associated with tinnitus, whereas type 2 diabetes showes a positive association with participants that report constant tinnitus. For the group reporting any tinnitus, type 2 diabetes is not associated. HbA1c, an important biomarker for glucose regulation, was negatively associated with CT. Lower levels of HbA1c indicate better glucose regulation and, in turn, better disease outcomes in diabetes mellitus patients (Krhač and Lovrenčić, 2019). Therefore, our findings suggest that individuals with higher HbA1c levels are less likely to have tinnitus. This is a discrepancy between self-reported diabetes history and blood biomarker levels, could be explained by the fact that HbA1c levels can be overestimated which is caused by comorbidities (Inoue et al., 2015). The relation between hearing disorders and diabetes mellitus has been understudied. A possible pathological mechanims could be explained via diabetic angiopathy resulting in damage, potentially in the cochlea or the auditory nerve (Jacobs et al., 2012; Li et al., 2018), which ultimately gives rise to hearing disorders and tinnitus. However, more clinical and cellular studies are needed.

Important lifestyle factors that are associated with both cardiovascular and metabolic diseases are smoking and obesity. Interestingly, in our study, only former smoking status was positively associated with both tinnitus groups, whereas current smoking status was not associated. A recent meta-analysis found positive associations between tinnitus and both former and current smoking status (Veile et al., 2018). Discrepancies between this meta-analysis and our results could be attributed to differences in timepoints of data collection in our study: tinnitus was assessed during the first follow-up, whereas smoking status was assessed during baseline. Alternatively, there may be underlying relationships between tinnitus and smoking that we accounted for by including multiple predictors. Our study identified a postive association between tinnitus and waist-hip ratio for both groups. Interestingly, overweight measured by BMI was also negatively associated with any tinnitus and positively, albeit with a very small effect size, with CT. Underweight, measured by BMI, was negatively associated with CT and positively with any tinnitus. Other studies identified positive associations between obesity and tinnitus (Martines et al., 2015; Nondahl et al., 2011).

Finally, we also identified associations between both tinnitus groups and major depressive disorder and various anxiety disorders. These findings support previous findings from other cohort studies that also identified significant associations between tinnitus and depression in older adults (Loprinzi et al., 2013) and tinnitus and depressive and anxiety disorders (Kostev et al., 2019; McKenna et al., 1991; Nondahl et al., 2011). A review reported that depression and anxiety were more prevalent and more severe among tinnitus sufferers (Durai and Searchfield, 2016). Depression and anxiety may contribute to the susceptibility of tinnitus, and may not be per se a consequence of tinnitus, however longitudinal studies are needed to disentangle the causality of neuropsychiatric disorders and tinnitus (Pattyn et al., 2016).

In addition to these broadly established disease categories, we found previously unidentified cardiovascular associations with tinnitus in this cohort. First, we found that an irregular or abnormally fast heart rhythm was positively associated with tinnitus perception. No other studies have identified this association, although previous work has shown that brain areas controlling heart rate variability influence tinnitus-related distress (Vanneste and De Ridder, 2013). Second, our study also identified an association between tinnitus perception and edema, which might be related to cardiovascular mechanisms. To our knowledge no other studies have investigated this association; therefore, this finding should be replicated in future studies.

In this study, we also identified novel and less established associations between tinnitus and thyroid disease, inflammatory diseases, and functional somatic syndromes. This study found a positive association with current thyroid medication use, which is in line with another large study, which found a positive association between tinnitus and self-reported current thyroid medication use (Kim et al., 2015), while no associations were found with thyroid disease in another study (Kostev et al., 2019). Past use of thyroid medication was postively associated with any tinnitus, but negatively associated with CT. The normalization of thyroid biomarkers in patients that are adequately treated by thyroid medication might explain this discrepancy. These associations between tinnitus and thyroid disease motivate future studies that specifically focus on the relation between tinnitus and thyroid disease.

Our study identified an association between tinnitus and inflammatory diseases and biomarkers of inflammatory diseases. Only a few other studies explored this potential mechanism (Ozbay et al., 2015; Szczepek et al., 2014). Neutrophil-lymphocyte ratio has a negative association with tinnitus in our study; this direction was also shown in another study investigating biomarkers for tinnitus (Ozbay et al., 2015). It is unclear whether these inflammatory processes occur in the peripheral auditory system or higher up in the central auditory system, causing damage and/or plasticity leading to tinnitus. Basic studies have identified inflammatory activation following noise exposure resulting in hearing loss and tinnitus (Wang et al., 2019), which motivates more clinical studies investigating this mechanism.

Lastly, this is the first study to identify associations between tinnitus and multiple functional somatic syndromes, including fibromyalgia, chronic fatigue syndrome, and irritable bowel syndrome. Given the presentation and unknown etiology of tinnitus, tinnitus arguably meets the criteria of a functional somatic syndrome (Wessely et al., 1999). Furthermore, these associations also open up a discussion on what underlying mechanisms these functional syndromes and tinnitus might have in common. Why are some people more vulnerable to develop tinnitus? Do environmental or genetic characteristics of these people lead to higher vulnerability? Future studies should further investigate associations between tinnitus and different functional somatic syndromes to determine if they share underlying neurobiological mechanisms.

Comparing the results of our study to a recent study that investigated the bothersomenness of tinnitus (Dawes et al., 2020) in a large cohort study, allows us to speculate about tinnitus bothersomeness within our cohort. A few parameters overlap between the studies, including age, sex, hearing difficulties, metabolic risk and smoking (Dawes et al., 2020). Interestingly, female sex was associated with bothersome tinnitus, whereas male sex was assocated with tinnitus in general. Tinnitus has been associated with age; however, in another study bothersome tinnitus was not found to be associated with age. Smoking and metabolic risk did not seem to be associated with tinnitus or bothersome tinnitus (Dawes et al., 2020). Based on these results, it seems that mostly psychological factors influence the bothersomeness of tinnitus.

The large size and breadth of parameters available for investigation in the Lifelines population cohort make it a powerful tool to investigate tinnitus associations in a non-clinical population. Nevertheless, limitations of this study need to be recognized. A key

limitation of the present study is the limited phenotyping of tinnitus. The 'yes, sometimes' group in this study is likely a very heterogeneous group, including participants that perceive tinnitus daily, but also participants that perceive tinnitus less frequent. Data on how often tinnitus is perceived would aid in further profiling these participants, though Lifelines has not included these detailed questionnaires. However, this limitation is shared by all other tinnitus studies because of the lack of reliable objective measures of tinnitus, the questionable reliability of self-report measures of tinnitus (see Dawes et al., 2020), and the uncertainty of the criteria most relevant for the characterization of tinnitus and tinnitus subtypes. Moreover, differences in the assessment of tinnitus make a comparison between studies difficult. Our study did not incorporate one of the definitions of tinnitus, namely whether tinnitus lasted more than five minutes at a time (Davis, 1989), which was used in the UK biobank to assess tinnitus (Dawes et al., 2020). Relatedly, our study did not assess either the severity or bothersomeness of tinnitus. This information could be a valuable explanatory variable for some of the effects reported in this study. Importantly, the classification of chronic versus intermittent tinnitus used in this study cannot be unequivocally assigned to other characteristics of either the tinnitus percept, severity, or bothersomeness. In fact, a recent study highlighted the complex associations between intermittent tinnitus and constant tinnitus with age, THI subscale scores, and tinnitus duration (Koops et al., 2019). Thus, our study cannot distinguish whether novel associations identified in this study were identified because they are associated specifically with non-bothersome tinnitus or because of the larger size and greater power afforded by this dataset. Inclusion of additional assessments of tinnitus would permit better identification of disease and lifestyle factors associations with specific tinnitus characteristics. The tinnitus assessment in our study did not include a 'Do not know' option, which could make comparisons with other studies (e.g. the UK Biobank) difficult (Dawes et al., 2020).

A second limitation of this study is the limited phenotyping of hearing status. Other population cohort studies (e.g. the UK Biobank, HUNT, KNHANES) include audiometric assessment of participants (Dawes et al., 2020; Kim et al., 2015; Krog et al., 2010). Although our study identified a positive association between hearing impairment and tinnitus, inclusion of audiometric assessments of Lifelines participants would enhance the utility of the Lifelines cohort study for future hearing-related studies. A third limitation of this study arises from the fact that assessment of tinnitus perception was acquired later than the other measures used in this study. Thus, changes in the disease and lifestyle-related factors during the intervening time could influence the associations identified between these measures and tinnitus in this cohort.

Although not *per se* a limitation in the design of this study, because of its cross-sectional design, this study can only identify associations (and not causal relations) with tinnitus. The Lifelines cohort study is still ongoing and would thus allow for longitudinal assessments of tinnitus, if included, which would permit examination of the natural history of tinnitus within this non-clinical population as has been done in a handful of previous studies (Dawes et al., 2020). Since tinnitus was assessed between 2011 and 2015, and the other measures were collected between 2006 and 2014, we should recognize we have a mixed study design (cross-sectional and longitudinal). Fourth, self-reported health-related questionnaires used in this study sometimes lack additional data needed for better interpretation of the data. For example, the question on edema does not specify where edema is located and the question on arrythmia does not specify whether the heart rate is too high or too low.

Finally, in addition to the large size and broad examination of the Lifelines population cohort, this dataset now includes directly sampled or imputed genome-wide genotype data for a large fraction of the participates as part of the UMCG Genetics lifelines Initiative (UGLI). Thus, Lifelines offers a unique tool to investigate the genetics of tinnitus, about which only recently the first major GWAS study has been published (Clifford et al., 2020).

5. Conclusions

We found that the prevalence and demographics of tinnitus within the Lifelines population cohort match results reported in previous studies. Additionally, within this cohort, we replicated several established disease and lifestyle factors associated with tinnitus, including hearing loss, cardiovascular disease, metabolic, psychiatric disease and lifestyle-related factors (e.g., smoking, waist-hip ratio). Finally, we were able to identify novel associations with tinnitus, including for thyroid disease, inflammatory diseases, and functional somatic syndromes. These findings provide essential characterization necessary for future studies using the lifelines cohort study to investigate tinnitus within a non-clinical population, including tinnitus patients that do not seek medical help. Because of its large size and broad assessment of factors contributing to health and disease, including genetic data, the Lifelines cohort study has great potential for future research to identify the factors and underlying physiological and genetic mechanisms contributing to tinnitus.

CRediT authorship contribution statement

Nick M.A. Schubert: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Visualization, Writing – original draft. **Judith G.M. Rosmalen:** Conceptualization, Methodology, Supervision, Writing – review & editing. **Pim van Dijk:** Funding acquisition, Supervision, Writing – review & editing. **Sonja J. Pyott:** Conceptualization, Funding acquisition, Project administration, Supervision, Writing – review & editing.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.heares.2021.108355.

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