Sleep apnoea is a risk factor for severe COVID-19

Satu Strausz,1,2,3 Tuomo Kiiskinen,1,4 Martin Broberg,1 Sanni Ruotsalainen,1 Jukka Koskela,1,5 Adel Bachour,6 FinnGen, Aarno Palotie,1,5,7 Tuula Palotie,2,3 Samuli Ripatti,1,5,8 Hanna M. Ollila1,5,9

ABSTRACT

Background Obstructive sleep apnoea (OSA) is associated with higher body mass index (BMI), diabetes, older age and male gender, which are all risk factors for severe COVID-19. We aimed to study if OSA is an independent risk factor for COVID-19 infection or for severe COVID-19.

Methods OSA diagnosis and COVID-19 infection were extracted from the hospital discharge, causes of death and infectious diseases registries in individuals who participated in the FinnGen study (n=260 405). Severe COVID-19 was defined as COVID-19 requiring hospitalisation. Multivariate logistic regression model was used to examine association. Comorbidities for either COVID-19 or OSA were selected as covariates. We performed a meta-analysis with previous studies.

Results We identified 445 individuals with COVID-19, and 38 (8.5%) of them with OSA of whom 19 out of 91 (20.9%) were hospitalised. OSA associated with COVID-19 hospitalisation independent from age, sex, BMI and comorbidities (p-unadjusted=5.13×10−5, OR-adjusted=2.93 (95% CI 1.02 to 8.39), p-adjusted=0.045). OSA was not associated with the risk of contracting COVID-19 (p=0.25). A meta-analysis of OSA and severe COVID-19 showed association across 15 835 COVID-19 positive controls, and n=1294 patients with OSA with severe COVID-19 (OR=2.37 (95% CI 1.14 to 4.95), p=0.021).

Conclusion Risk for contracting COVID-19 was the same for patients with OSA and those without OSA. In contrast, among COVID-19 positive patients, OSA was associated with higher risk for hospitalisation. Our findings are in line with earlier works and suggest OSA as an independent risk factor for severe COVID-19.

INTRODUCTION

COVID-19 is a severe respiratory disease caused by SARS-CoV-2 virus infection. A subset of patients face hospitalisation, respiratory failure or even death. The severity of COVID-19 is highly age dependent but also evidenced by the number of individuals that receive hospital and intensive care treatment.1,2 Finland has had a relatively small number of COVID-19 cases in the spring of 2020. However, approximately 1%–6% of those tested positive for the virus in Finland received hospital or intensive care treatment.3 These percentages are similar to those reported globally.1,2 Severe COVID-19 outcome is mediated primarily through respiratory distress.4,5 Risk factors for severe COVID-19 have been identified as older age, male sex, obesity, diabetes, cardiovascular disease and poor lung function.6 In addition, other respiratory diseases have been listed as potential contributors for COVID-19 severity. Indeed, there are studies suggesting that obstructive sleep apnoea (OSA) may be a risk factor for severe COVID-19.7–12 Such risk would have substantial effect as OSA is a common disease affecting at least 8% of the population with higher prevalence in older age groups reaching to over 20% in individuals over 60 years of age.13 The disease aetiology of OSA is characterised by repetitive apnoea-hypopnea cycles during sleep causing shortness of breath which can be associated with somnolence, severe oxygen desaturation, sleep disruption and increase in systolic and diastolic blood pressure.14 The known risk factors for OSA include obesity, high age, male sex and craniofacial and upper airway structure variations and anomalies.15 Similarly, OSA is associated with increased risk for cardiovascular mortality, especially if not treated. Finally, it is essential to note that treatment exists for the majority of patients with OSA so that night-time breathing can be
supported by continuous positive airway pressure (CPAP) or mandibular advancement device (MAD). This treatment substantially decreases the risk for cardiovascular events and death. Recently, questions have been raised about whether OSA constitutes a high risk for COVID-19 infection or COVID-19 hospitalisation.

We specifically aimed at evaluating if OSA associates with the risk for severe COVID-19 infection independently of other potential risk factors including age, sex, body mass index (BMI), hypertension, diabetes (including type 1 and type 2 diabetes), coronary heart disease (CHD), asthma and chronic obstructive pulmonary disease (COPD), and also whether the risk for contracting COVID-19 is elevated among patients with OSA.

**METHODS**

**Study sample set**

FinnGen (https://www.finngen.fi/en) is a large biobank study that aims to genotype 500 000 Finns including two types of biobank collections: (1) population-based epidemiological cohorts and (2) mostly disease-based collections in all University Hospitals in Finland (online supplemental table 1). FinnGen combines these data with longitudinal registry data that record healthcare events over the entire lifespan including the National Hospital Discharge Registry (available from 1968), the Causes of Death Registry (available from 1969), the National Infectious Diseases Registry (available from 1995) and the Medication Reimbursement Registry (available from 1995), all these using unique national personal identification codes, for the whole population of Finland for lifetime information since the start of each registry. FinnGen has harmonised data from these registries of 260 405 Finnish individuals. Registry data were available from the beginning of the registry until 31 December 2018 and Infectious Registry data until 30 October 2020. In addition, demographic and anthropometric data of BMI and smoking status are included.

The information of COVID-19 positive individuals was collected from The National Infectious Diseases Registry and the infection was verified by laboratory test using PCR testing. Data for risk factors, comorbidities and OSA diagnosis were obtained from the National Hospital Discharge Registry, the Causes of Death Registry and the Medication Reimbursement Registry, where the clinical endpoints had been generated using International Classification of Diseases codes for OSA, hypertension, diabetes (including type 1 and type 2 diabetes), CHD, asthma and COPD (online supplemental table 2).

Treatment information concerning OSA was collected from the patient records of Heart and Lung Center or Department of Oral and Maxillofacial Diseases, Helsinki University Hospital (HUH), Finland.

The diagnosis in this special healthcare derived data for OSA is typically based on the following criteria: subjective symptoms, clinical examination and sleep registration applying Apnoea-Hypopnea Index (AHI) ≥5 per hour for polysomnography or respiratory event index ≥5 per hour for out-of-centre sleep study.

For the meta-analysis, estimates were collected from the previous studies concerning the role of OSA on COVID-19 hospitalisation.

**Statistical methods**

Differences in baseline demographics and clinical characteristics were tested using on \( \chi^2 \) test. Fisher’s exact test was used if the expected cell size was ≤5. For continuous variables, Student’s t-test was used. We considered \( p<0.05 \) as statistically significant, and all tests were two sided (tables 1 and 2). All \( p \) values based on aforementioned tests are Bonferroni corrected. Logistic regression was used to calculate OR between hospitalised and non-hospitalised groups. Model 1 was adjusted for age and sex, BMI, and smoking status.

### Table 1  Comparison of the baseline characteristics among COVID-19 positive individuals

<table>
<thead>
<tr>
<th></th>
<th>All ( n=445 )</th>
<th>Non-hospitalised ( n=354 )</th>
<th>Hospitalised ( n=91 )</th>
<th>( P_{\text{unadjusted}} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean in years, SD)</td>
<td>52.7 (17.4)</td>
<td>49.3 (16.3)</td>
<td>65.9 (14.8)</td>
<td>1.06×10^{-15}</td>
</tr>
<tr>
<td>Sex (male) (N, %)</td>
<td>166 (37.3)</td>
<td>133 (37.6)</td>
<td>33 (36.3)</td>
<td>1</td>
</tr>
<tr>
<td>OSA (N, %)</td>
<td>38 (8.5)</td>
<td>19 (5.4)</td>
<td>19 (20.9)</td>
<td>5.13×10^{-5}</td>
</tr>
<tr>
<td>BMI (mean kg/m², SD)</td>
<td>27.13 (5.44)</td>
<td>26.54 (5.20)</td>
<td>29.25 (5.78)</td>
<td>0.014*</td>
</tr>
<tr>
<td>Hypertension (N, %)</td>
<td>79 (17.8)</td>
<td>40 (11.3)</td>
<td>39 (42.9)</td>
<td>5.03×10^{-11}</td>
</tr>
<tr>
<td>Diabetes (N, %)</td>
<td>46 (10.3)</td>
<td>23 (6.5)</td>
<td>23 (25.3)</td>
<td>3.45×10^{-6}</td>
</tr>
<tr>
<td>CHD (N, %)</td>
<td>21 (4.7)</td>
<td>9 (2.5)</td>
<td>12 (13.2)</td>
<td>5.20×10^{-4}</td>
</tr>
<tr>
<td>Asthma/COPD</td>
<td>54 (12.1)</td>
<td>40 (11.3)</td>
<td>14 (15.4)</td>
<td>1</td>
</tr>
</tbody>
</table>

Differences and associations between non-hospitalised and hospitalised COVID-19 positive individuals. Baseline demographics and clinical characteristics \( P_{\text{unadjusted}} \) values were based on \( \chi^2 \) test. For continuous variables, we used Student’s t-test. BMI was measured of 264 participants including 206 non-hospitalised and 58 hospitalised individuals.

*Statistically significant.

BMI, body mass index; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; OSA, obstructive sleep apnoea.
sex. Model 2 was adjusted for BMI in addition to covariates of Model 1. Model 3 was adjusted for BMI, hypertension, diabetes, CHD, asthma and COPD, in addition to covariates of Model 1. This reflects a similar prevalence of OSA diagnoses in COVID-19 infected as in the normal population in FinnGen, where prevalence is 8%.18 Ninety-one (20.4%) patients required hospitalisation (36.3% male, mean age 65.9 years) including 19 patients with OSA (table 1).

Prevalence of OSA (p=5.13×10 −5), hypertension (p=5.03×10 −1), diabetes (p=3.45×10 −6) and CHD (p=5.20×10 −4) were statistically significantly higher in the hospitalised group. Similarly, age and BMI were higher among hospitalised individuals (p=1.06×10−15, p=0.014, respectively; table 1).

Table 3 ORs associating obstructive sleep apnoea with severe COVID-19

<table>
<thead>
<tr>
<th>OR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td>3.85</td>
<td>1.82 to 8.13</td>
</tr>
<tr>
<td>Model 2</td>
<td>3.45</td>
<td>1.27 to 9.35</td>
</tr>
<tr>
<td>Model 3</td>
<td>2.93</td>
<td>1.02 to 8.39</td>
</tr>
</tbody>
</table>

Model 1 is adjusted for age and sex. Model 2 is adjusted for body mass index (BMI) in addition to covariates of Model 1. Model 3 is adjusted for BMI, hypertension, diabetes, coronary heart disease, asthma and chronic obstructive pulmonary disease in addition to covariates of model 1.

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Prevalence of OSA (p=5.13×10 −5), hypertension (p=5.03×10 −1), diabetes (p=3.45×10 −6) and CHD (p=5.20×10 −4) were statistically significantly higher in the hospitalised group. Similarly, age and BMI were higher among hospitalised individuals (p=1.06×10−15, p=0.014, respectively; table 1).

To evaluate the performance of the diagnostic events, we compared the main risk factors among patients with COVID-19 between individuals with OSA (n=38) and those who did not have OSA diagnosis (n=407). Patients with OSA were statistically significantly older and their BMI was higher (mean age 61.3 years, BMI 31.15 kg/m², p=5.60×10−4, p=3.38×10−3, respectively) than non-OSA individuals (mean age 51.9 years, BMI 26.71 kg/m²). Also, comorbidities were more prevalent among OSA individuals (p=1.74×10−4) and they faced hospitalisation more often (p=3.21×10−5). We did not observe differences in risk factors when comparing non-hospitalised (n=19, male 63.2%, mean age 56.3 years) and hospitalised patients with OSA (n=19, male 36.8%, mean age 66.3 years; table 2). Furthermore, 7/19 patients with OSA were hospitalised due to COVID-19 did not have any other disease comorbidities. We did not observe significant differences concerning age or BMI between individuals who had only OSA as a comorbidity or also
other comorbidities in addition to OSA (62.8 years, 68.9 years, p=0.72, 30.26 kg/m², 32.67 kg/m², p=1.00, respectively). Time since the first diagnosis of OSA to COVID-19 infection was not significantly different between non-hospitalised and hospitalised groups (6.6 years, 8.6 years, p=0.37, respectively).

We tested if OSA is associated with the risk of severe COVID-19 infection, determined as being hospitalised (n=91), or COVID-19 infection in general (n=145). While OSA did not affect the risk of contracting COVID-19 (p=0.25), patients with OSA had a considerably elevated risk for being hospitalised due to severe COVID-19 (OR=2.93 (95% CI 1.02 to 8.39), p=0.045, adjusted for age, sex, BMI, hypertension, diabetes, CHD, asthma and COPD; table 3).

We performed a meta-analysis by pooling the comparable endpoints between the published studies 7-9 and examined the association with severe COVID-19 with and without adjusting for BMI. The studies, including our study, consisted of 15 835 COVID-19 positive individuals including 1294 patients with OSA. Overall, we observed over twofold increase in the pooled estimate prior to adjusting for BMI (OR=2.37 (1.14 to 4.95), p=0.092). Adjusted estimates were available in the study of Cade et al.6 (BMI) and Maas et al.8 (BMI, hypertension and diabetes) but not in the study of Cariou et al.7 The pooled estimate somewhat attenuated after adjustment for BMI (OR=1.55 (0.88 to 2.72), p=0.13; figure 1).

To investigate patients with OSA contracted with COVID-19 in more detail, we accessed the healthcare data of 305 COVID-19 positive individuals including 11 patients with OSA treated in Heart and Lung Center or Department of Oral and Maxillofacial Diseases, HUH, Finland by the end of October 2020. The mean age of the COVID-19 positive patients with OSA was 55.1 years, mean BMI was 35.08 kg/m² and 9 (81.8%) patients were male. Mean AHI was 43.3 events per hour (table 4) and all 11 patients had either moderate (AHI ≥15 but<30 events per hour) or severe (AHI ≥30 events per hour) OSA; 9 out of 11 had severe OSA and 2 out of 11 had moderate OSA. 8/11 had treated OSA; 7 patients had CPAP therapy and 1 patient had MAD. CPAP-treated patients used their appliances 98% of the nights with 6.3 hours mean time used. Mean AHI during treatment was 1.86 events/hour prior to the COVID-19 infection. Despite of the OSA treatment, all 11 patients required hospital treatment caused by pneumonia or other COVID-19 caused symptoms, such as high fever. All patients needed non-invasive ventilation and two required intubation. Treatment time in hospital was 15 days (mean, table 4).

### DISCUSSION

Here, we examined the role of OSA as a risk factor for COVID-19 leading to hospitalisation. Our analyses revealed 2.93-times higher risk for COVID-19 hospitalisation in patients with OSA, independently of BMI and other known risk factors for OSA, or those for severe COVID-19 infection. Despite the OSA treatment, all 11 patients required hospital treatment caused by pneumonia or other COVID-19 caused symptoms, such as high fever. All patients needed non-invasive ventilation and two required intubation. The overall treatment time in hospital was 15 days (mean, table 4).

#### Table 4 Healthcare data characteristics of individuals with obstructive sleep apnoea contracted with COVID-19

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n=11</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean in years)</td>
<td>55.1 (8.0)</td>
</tr>
<tr>
<td>Sex (male) (N, %)</td>
<td>9 (81.8)</td>
</tr>
<tr>
<td>BMI (mean kg/m², SD)</td>
<td>35.08 (5.96)</td>
</tr>
<tr>
<td>Diabetes (N, %)</td>
<td>3 (27.3)</td>
</tr>
<tr>
<td>Hypertension (N, %)</td>
<td>7 (63.6)</td>
</tr>
<tr>
<td>CHD (N, %)</td>
<td>3 (27.3)</td>
</tr>
<tr>
<td>CPAP (N, %)</td>
<td>7 (63.6)</td>
</tr>
<tr>
<td>MAD (N, %)</td>
<td>1 (9.1)</td>
</tr>
<tr>
<td>AHI (mean, events per hour)</td>
<td>43.3 (20.6)</td>
</tr>
<tr>
<td>ODI (mean, events per hour)</td>
<td>39.6 (15.7)</td>
</tr>
<tr>
<td>SpO₂ mean (mean%, SD)</td>
<td>91.0 (3.3)</td>
</tr>
<tr>
<td>SpO₂ min (mean%, SD)</td>
<td>79.4 (8.3)</td>
</tr>
<tr>
<td>AHI with CPAP (mean, events per hour)</td>
<td>1.86 (2.07)</td>
</tr>
<tr>
<td>ICU (N, %)</td>
<td>3 (27.3)</td>
</tr>
<tr>
<td>NIV (N, %)</td>
<td>11 (100)</td>
</tr>
<tr>
<td>Intubation (N, %)</td>
<td>2 (18.2)</td>
</tr>
</tbody>
</table>

AHI, Apnoea-Hypopnea Index; BMI, body mass index; CHD, coronary heart disease; CPAP, continuous positive airway pressure; ICU, intensive care unit; MAD, mandibular advancement devise; NIV, non-invasive ventilation; ODI, oxygen desaturation index; SpO₂, oxygen saturation.
COVID-19 suggesting that OSA is an independent risk factor for COVID-19.

Indeed, our findings are well in line with earlier works on COVID-19 comorbidities and OSA. Three studies have examined the association between COVID-19 and OSA before. Despite different endpoint definitions (contracting COVID-19, severity of the disease, mechanical ventilation, and death), these studies share similar findings with ours. All studies showed a significant association with COVID-19 severity and OSA.\(^7\)\(^-\)\(^9\) However, only one study showed a statistically significant association between OSA and severe COVID-19 after adjusting for BMI.\(^9\) These findings suggest that while OSA is likely a risk factor for COVID-19, evaluating the magnitude of this association would benefit from harmonised analyses across different cohorts where comorbidities are similarly assessed.

Building on these studies, we set to test the role of OSA on COVID-19 hospitalisation. In our study, patients with OSA had 2.95 times higher risk of being hospitalised and the estimate was comparable and independent of the risk in diabetes patients, where elevated risk has been reported earlier for severe COVID-19.\(^9\)\(^,\)\(^19\) There are at least two potential pathological mechanisms how OSA may relate to severe COVID-19. First, individuals with OSA often have one or more comorbidities that are known risk factors for severe COVID-19. For example, high BMI increases the risk for severe COVID-19. Furthermore, OSA exacerbates the effects of many underlying risk factors increasing blood pressure. Second, OSA may worsen the core symptoms of severe COVID-19, especially during the night, when decreased oxygen saturation levels occur in OSA.\(^14\) Our findings together with earlier reports suggest that OSA should be taken into account when assessing who will develop life-threatening complications of COVID-19 infection.

In addition, we collected treatment information concerning OSA of 11 patients who had contracted COVID-19. Despite of the OSA treatment, patients developed a severe form of COVID-19 and all patients required hospital care suggesting OSA as a risk factor even if treated.

Finally, based on our results and previous studies,\(^7\)\(^-\)\(^9\) we set a meta-analysis to strengthen the role of OSA on COVID-19 hospitalisation. We were able to establish OSA as a risk factor and show that the effect is related to COVID-19 severity indicating over 2-fold risk.

Our findings should be interpreted in the context that registry-based ascertainment through hospitalisation may miss non-hospitalised OSA cases (false negatives). In addition, the population prevalence of OSA is larger than the observed prevalence as OSA is still underdiagnosed in Finland. This may affect to our findings. The high percentage of individuals in hospitals likely reflect the age distribution of the first wave patients in Finland, where infections took place in individuals approximately 50 years of age, and selective testing in those that had clear or severe symptoms. Similarly, early on the testing was targeted towards older individuals and to those with comorbidities, as not enough testing capacity was available early in the spring 2020. Although sufficient capacity and different strategies are in place now, the number of patients with mild COVID-19 infection may have not been recorded in the registries from the early spring 2020. Finally, compared with other countries there have been relatively small numbers of COVID-19 infections in Finland till the end of October 2020 when these data were curated. Therefore, while the effect estimates are comparable to other studies on OSA and COVID-19, the confidence intervals are relatively large due to the smaller total number of COVID-19 positive individuals in Finland and in the study sample: less than 500 patients compared with several hundred in other studies. Also, FinnGen represents older population (mean 58.6 years) than the average age (mean 42.9 years) in Finland.\(^20\)

In conclusion, patients with OSA have the same risk of contracting COVID-19 than non-OSA individuals. Meanwhile, in this study, patients with OSA had 2.93 times higher risk to be hospitalised when affected by COVID-19 than non-OSA individuals. Our findings may suggest that, in assessment of patients with suspected or confirmed COVID-19 infection, OSA should be recognised as one of the comorbidity risk factors for developing a severe form of the disease. We believe that our finding may help in identifying high-risk individuals for severe forms of COVID-19 infection and therefore screening for previous indications of OSA could be beneficial among individuals testing positive for the virus.

Author affiliations
1Institute for Molecular Medicine Finland (FIMM), University of Helsinki, Helsinki, Finland
2Orthodontics, Department of Oral and Maxillofacial Diseases, Clinicum, Faculty of Medicine, University of Helsinki, Helsinki, Finland
3Department of Oral and Maxillofacial Diseases, Helsinki University Hospital (HUH), Helsinki, Finland
4Finnish Institute for Health and Welfare, Helsinki, Finland
5Broad Institute of MIT and Harvard, Cambridge, MA, USA
6Sleep Unit, Heart and Lung Center, Helsinki University Hospital (HUH), Helsinki, Finland
7Analytic and Translational Genetics Unit (ATGU), Department of Medicine, Department of Neurology and Department of Psychiatry, Massachusetts General Hospital, Boston, Massachusetts, USA
8Department of Public Health, University of Helsinki, Helsinki, Finland
9Stanford University School of Medicine, Palo Alto, CA, USA

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Contributors HO is the guarantor of the manuscript, TK, HO, SR and SS conceived the study and designed the study protocol. TK, HO and SS conducted the literature review, statistical analysis and drafted the manuscript. MB and SHu contributed statistical analysis and TK phenotyped study samples. AB, MB, JK, SR, SHu, AP, TP...
and SR reviewed the manuscript for intellectual content, made revisions as needed and approved the final version for publication. HQ, TP and SR supervised the study.

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**REFERENCES**


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**Data availability statement** Data are available upon reasonable request. The FinnGen individual level data may be accessed through applications to the Finnish Biobanks’ FinnBB portal, Fingerprint (www.finnbb.fi). Summary data can be accessed through the FinnGen site https://www.finngen.fi/en/access_results.

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Contributors of FinnGen

Steering Committee
Aarno Palotie   Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland
Mark Daly   Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland

Pharmaceutical companies
Howard Jacob  Abbvie, Chicago, IL, United States
Athena Matakidou  Astra Zeneca, Cambridge, United Kingdom
Heiko Runz  Biogen, Cambridge, MA, United States
Sally John  Biogen, Cambridge, MA, United States
Robert Plenge  Celgene, Summit, NJ, United States
Mark McCarthy   Genentech, San Francisco, CA, United States
Julie Hunkapiller Genentech, San Francisco, CA, United States
Meg Ehm  GlaxoSmithKline, Brentford, United Kingdom
Dawn Waterworth  GlaxoSmithKline, Brentford, United Kingdom
Caroline Fox  Merck, Kenilworth, NJ, United States
Anders Malarstig  Pfizer, New York, NY, United States
Kathy Klinger Sanofi, Paris, France
Kathy Call Sanofi, Paris, France

University of Helsinki & Biobanks
Tomi Mäkelä   HiLIFE, University of Helsinki, Finland, Finland
Jaakko Kaprio  Institute for Molecular Medicine Finland, HiLIFE, Helsinki, Finland, Finland
Petri Virolainen   Auria Biobank / Univ. of Turku / Hospital District of Southwest Finland, Turku, Finland
Kari Pulkki  Auria Biobank / Univ. of Turku / Hospital District of Southwest Finland, Turku, Finland
Terhi Kilpi  THL Biobank / Finnish Institute for Health and Welfare Helsinki, Finland
Markus Perola  THL Biobank / Finnish Institute for Health and Welfare Helsinki, Finland
Jukka Partanen  Finnish Red Cross Blood Service / Finnish Hematology Registry and Clinical Biobank, Helsinki, Finland
Anne Pitkäranta Hospital District of Helsinki and Uusimaa, Helsinki, Finland
Riitta Kaarteenaho  Northern Finland Biobank Borealis / University of Oulu / Northern Ostrobothnia Biobank, Hospit, Oulu, Finland
Seppo Vainio  Northern Finland Biobank Borealis / University of Oulu / Northern Ostrobothnia Hospital District, Oulu, Finland
Kimmo Savinainen  Finnish Clinical Biobank Tampere / University of Tampere / Pirkanmaa Hospital District, Tampere, Finland
Veli-Matti Kosma Biobank of Eastern Finland / University of Eastern Finland / Northern Savo Hospital District, Kuopio, Finland
Urho Kujala  Central Finland Biobank / University of Jyväskylä / Central Finland Health Care
District, Jyväskylä, Finland

Other Experts/ Non-Voting Members
Outi Tuovila Business Finland, Helsinki, Finland
Minna Hendolin Business Finland, Helsinki, Finland
Raimo Pakkanen Business Finland, Helsinki, Finland

Scientific Committee

Pharmaceutical companies
Jeff Waring Abbvie, Chicago, IL, United States
Bridget Riley-Gillis Abbvie, Chicago, IL, United States
Athena Matakidou Astra Zeneca, Cambridge, United Kingdom
Heiko Runz Biogen, Cambridge, MA, United States
Jimmy Liu Biogen, Cambridge, MA, United States
Shameek Biswas Celgene, Summit, NJ, United States
Julie Hunkapiller Genentech, San Francisco, CA, United States
Dawn Waterworth GlaxoSmithKline, Brentford, United Kingdom
Meg Ehm GlaxoSmithKline, Brentford, United Kingdom
Dorothee Diogo Merck, Kenilworth, NJ, United States
Caroline Fox Merck, Kenilworth, NJ, United States
Anders Malarstig Pfizer, New York, NY, United States
Catherine Marshall Pfizer, New York, NY, United States
Xinli Hu Pfizer, New York, NY, United States
Kathy Call Sanofi, Paris, France
Kathy Klinger Sanofi, Paris, France
Matthias Gossel Sanofi, Paris, France

University of Helsinki & Biobanks
Samuli Ripatti Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Helsinki, Finland
Johanna Schleutker Auria Biobank / Univ. of Turku / Hospital District of Southwest Finland, Turku, Finland
Markus Perola THL Biobank / Finnish Institute for Health and Welfare Helsinki, Finland
Mikko Arvas Finnish Red Cross Blood Service / Finnish Hematology Registry and Clinical Biobank, Helsinki, Finland
Olli Carpen Hospital District of Helsinki and Uusimaa, Helsinki, Finland
Reetta Hinttala Northern Finland Biobank Borealis / University of Oulu / Northern Ostrobothnia Hospital District, Oulu, Finland
Johannes Kettunen Northern Finland Biobank Borealis / University of Oulu / Northern Ostrobothnia Hospital District, Oulu, Finland
Reijo Laaksonen Finnish Clinical Biobank Tampere / University of Tampere / Pirkanmaa Hospital District, Tampere, Finland

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Arto Mannermaa  Biobank of Eastern Finland / University of Eastern Finland / Northern Savo Hospital District, Kuopio, Finland
Juha Paloneva  Central Finland Biobank / University of Jyväskylä / Central Finland Health Care District, Jyväskylä, Finland
Urho Kujala  Central Finland Biobank / University of Jyväskylä / Central Finland Health Care District, Jyväskylä, Finland

Other Experts/ Non-Voting Members
Outi Tuovila  Business Finland, Helsinki, Finland
Minna Hendolin  Business Finland, Helsinki, Finland
Raimo Pakkanen  Business Finland, Helsinki, Finland

Clinical Groups
Neurology Group
Hilkka Soininen  Northern Savo Hospital District, Kuopio, Finland
Valtteri Julkunen  Northern Savo Hospital District, Kuopio, Finland
Anne Remes  Northern Ostrobothnia Hospital District, Oulu, Finland
Reetta Kälviäinen  Northern Savo Hospital District, Kuopio, Finland
Mikko Hiltunen  Northern Savo Hospital District, Kuopio, Finland
Jukka Peltola  Pirkanmaa Hospital District, Tampere, Finland
Pentti Tienari  Hospital District of Helsinki and Uusimaa, Helsinki, Finland
Juha Rinne  Hospital District of Southwest Finland, Turku, Finland
Adam Ziemann  Abbvie, Chicago, IL, United States
Jeffrey Waring  Abbvie, Chicago, IL, United States
Sahar Esmaeeli  Abbvie, Chicago, IL, United States
Nizar Smaoui  Abbvie, Chicago, IL, United States
Anne Lehtonen  Abbvie, Chicago, IL, United States
Susan Eaton  Biogen, Cambridge, MA, United States
Heiko Runz  Biogen, Cambridge, MA, United States
Sanni Lahdenperä  Biogen, Cambridge, MA, United States
Shameek Biswas  Celgene, Summit, NJ, United States
John Michon  Genentech, San Francisco, CA, United States
Geoff Kerchner  Genentech, San Francisco, CA, United States
Julie Hunkapiller  Genentech, San Francisco, CA, United States
Natalie Bowers  Genentech, San Francisco, CA, United States
Edmond Teng  Genentech, San Francisco, CA, United States
John Eicher  Merck, Kenilworth, NJ, United States
Vinay Mehta  Merck, Kenilworth, NJ, United States
Padhraig Gormley  Merck, Kenilworth, NJ, United States
Kari Linden  Pfizer, New York, NY, United States
Christopher Whelan  Pfizer, New York, NY, United States
Fanli Xu  GlaxoSmithKline, Brentford, United Kingdom
David Pulford  GlaxoSmithKline, Brentford, United Kingdom

**Gastroenterology Group**

Martti Färkkilä  Hospital District of Helsinki and Uusimaa, Helsinki, Finland
Sampsu Pikkarainen  Hospital District of Helsinki and Uusimaa, Helsinki, Finland
Airi Jussila  Pirkanmaa Hospital District, Tampere, Finland
Timo Blomster  Northern Ostrobothnia Hospital District, Oulu, Finland
Mikko Kiviniemi  Northern Savo Hospital District, Kuopio, Finland
Markku Voutilainen  Hospital District of Southwest Finland, Turku, Finland
Bob Georgantas  Abbvie, Chicago, IL, United States
Graham Heap  Abbvie, Chicago, IL, United States
Jeffrey Waring  Abbvie, Chicago, IL, United States
Nizar Smaoui  Abbvie, Chicago, IL, United States
Fedik Rahimov  Abbvie, Chicago, IL, United States
Anne Lehtonen  Abbvie, Chicago, IL, United States
Keith Usiskin  Celgene, Summit, NJ, United States
Joseph Maranville  Celgene, Summit, NJ, United States
Tim Lu  Genentech, San Francisco, CA, United States
Natalie Bowers  Genentech, San Francisco, CA, United States
Danny Oh  Genentech, San Francisco, CA, United States
John Michon  Genentech, San Francisco, CA, United States
Vinay Mehta  Merck, Kenilworth, NJ, United States
Kirsti Kalpala  Pfizer, New York, NY, United States
Melissa Miller  Pfizer, New York, NY, United States
Xinli Hu  Pfizer, New York, NY, United States
Linda McCarthy  GlaxoSmithKline, Brentford, United Kingdom

**Rheumatology Group**

Kari Eklund  Hospital District of Helsinki and Uusimaa, Helsinki, Finland
Antti Palomäki  Hospital District of Southwest Finland, Turku, Finland
Pia Isomäki  Pirkanmaa Hospital District, Tampere, Finland
Laura Pirilä  Hospital District of Southwest Finland, Turku, Finland
Oili Kaipiainen-Seppänen  Northern Savo Hospital District, Kuopio, Finland
Johanna Huhtakangas  Northern Ostrobothnia Hospital District, Oulu, Finland
Bob Georgantas  Abbvie, Chicago, IL, United States
Jeffrey Waring  Abbvie, Chicago, IL, United States
Fedik Rahimov  Abbvie, Chicago, IL, United States
Apinya Lertratanakul  Abbvie, Chicago, IL, United States
Nizar Smaoui  Abbvie, Chicago, IL, United States
Anne Lehtonen  Abbvie, Chicago, IL, United States
David Close  Astra Zeneca, Cambridge, United Kingdom
Marla Hochfeld  Celgene, Summit, NJ, United States
<table>
<thead>
<tr>
<th>Name</th>
<th>Affiliation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natalie Bowers</td>
<td>Genentech, San Francisco, CA, United States</td>
</tr>
<tr>
<td>John Michon</td>
<td>Genentech, San Francisco, CA, United States</td>
</tr>
<tr>
<td>Dorothee Diogo</td>
<td>Merck, Kenilworth, NJ, United States</td>
</tr>
<tr>
<td>Vinay Mehta</td>
<td>Merck, Kenilworth, NJ, United States</td>
</tr>
<tr>
<td>Kirsu Kalpala</td>
<td>Pfizer, New York, NY, United States</td>
</tr>
<tr>
<td>Nan Bing</td>
<td>Pfizer, New York, NY, United States</td>
</tr>
<tr>
<td>Xinli Hu</td>
<td>Pfizer, New York, NY, United States</td>
</tr>
<tr>
<td>Jorge Esparza Gordillo</td>
<td>GlaxoSmithKline, Brentford, United Kingdom</td>
</tr>
<tr>
<td>Nina Mars</td>
<td>Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Helsinki, Finland</td>
</tr>
</tbody>
</table>

**Pulmonology Group**

<table>
<thead>
<tr>
<th>Name</th>
<th>Affiliation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tarja Laitinen</td>
<td>Pirkanmaa Hospital District, Tampere, Finland</td>
</tr>
<tr>
<td>Margit Pelkonen</td>
<td>Northern Savo Hospital District, Kuopio, Finland</td>
</tr>
<tr>
<td>Paula Kauppi</td>
<td>Hospital District of Helsinki and Uusimaa, Helsinki, Finland</td>
</tr>
<tr>
<td>Hannu Kankaanranta</td>
<td>Pirkanmaa Hospital District, Tampere, Finland</td>
</tr>
<tr>
<td>Terttu Harju</td>
<td>Northern Ostrobothnia Hospital District, Oulu, Finland</td>
</tr>
<tr>
<td>Nizar Smaoui</td>
<td>Abbvie, Chicago, IL, United States</td>
</tr>
<tr>
<td>David Close</td>
<td>Astra Zeneca, Cambridge, United Kingdom</td>
</tr>
<tr>
<td>Steven Greenberg</td>
<td>GlaxoSmithKline, Brentford, United Kingdom</td>
</tr>
<tr>
<td>Hubert Chen</td>
<td>Genentech, San Francisco, CA, United States</td>
</tr>
<tr>
<td>Natalie Bowers</td>
<td>Genentech, San Francisco, CA, United States</td>
</tr>
<tr>
<td>John Michon</td>
<td>Genentech, San Francisco, CA, United States</td>
</tr>
<tr>
<td>Jo Betts</td>
<td>GlaxoSmithKline, Brentford, United Kingdom</td>
</tr>
<tr>
<td>Soumitra Ghosh</td>
<td>GlaxoSmithKline, Brentford, United Kingdom</td>
</tr>
</tbody>
</table>

**Cardiometabolic Diseases Group**

<table>
<thead>
<tr>
<th>Name</th>
<th>Affiliation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Veikko Salomaa</td>
<td>Finnish Institute for Health and Welfare Helsinki, Finland</td>
</tr>
<tr>
<td>Teemu Niiranen</td>
<td>Finnish Institute for Health and Welfare Helsinki, Finland</td>
</tr>
<tr>
<td>Markus Juonala</td>
<td>Hospital District of Southwest Finland, Turku, Finland</td>
</tr>
<tr>
<td>Kaj Metsärinne</td>
<td>Hospital District of Southwest Finland, Turku, Finland</td>
</tr>
<tr>
<td>Mika Kähönen</td>
<td>Pirkanmaa Hospital District, Tampere, Finland</td>
</tr>
<tr>
<td>Juhani Junnila</td>
<td>Northern Ostrobothnia Hospital District, Oulu, Finland</td>
</tr>
<tr>
<td>Markku Laakso</td>
<td>Northern Savo Hospital District, Kuopio, Finland</td>
</tr>
<tr>
<td>Jussi Pihlajamäki</td>
<td>Northern Savo Hospital District, Kuopio, Finland</td>
</tr>
<tr>
<td>Juha Sinisalo</td>
<td>Hospital District of Helsinki and Uusimaa, Helsinki, Finland</td>
</tr>
<tr>
<td>Marja-Riitta Taskinen</td>
<td>Hospital District of Helsinki and Uusimaa, Helsinki, Finland</td>
</tr>
<tr>
<td>Tiinamaaja Tuomi</td>
<td>Hospital District of Helsinki and Uusimaa, Helsinki, Finland</td>
</tr>
<tr>
<td>Jari Laukkanen</td>
<td>Central Finland Health Care District, Jyväskylä, Finland</td>
</tr>
<tr>
<td>Ben Challis</td>
<td>Astra Zeneca, Cambridge, United Kingdom</td>
</tr>
<tr>
<td>Andrew Peterson</td>
<td>Genentech, San Francisco, CA, United States</td>
</tr>
</tbody>
</table>
Julie Hunkapiller Genentech, San Francisco, CA, United States
Natalie Bowers Genentech, San Francisco, CA, United States
John Michon Genentech, San Francisco, CA, United States
Dorothee Diogo Merck, Kenilworth, NJ, United States
Audrey Chu Merck, Kenilworth, NJ, United States
Vinay Mehta Merck, Kenilworth, NJ, United States
Jaakko Parkkinen Pfizer, New York, NY, United States
Melissa Miller Pfizer, New York, NY, United States
Anthony Muslin Sanofi, Paris, France
Dawn Waterworth GlaxoSmithKline, Brentford, United Kingdom

Oncology Group
Heikki Joensuu Hospital District of Helsinki and Uusimaa, Helsinki, Finland
Tuomo Meretoja Hospital District of Helsinki and Uusimaa, Helsinki, Finland
Olli Carpen Hospital District of Helsinki and Uusimaa, Helsinki, Finland
Lauri Aaltonen Hospital District of Helsinki and Uusimaa, Helsinki, Finland
Annika Auranen Pirkanmaa Hospital District, Tampere, Finland
Peeter Karihtala Northern Ostrobothnia Hospital District, Oulu, Finland
Saila Kauppila Northern Ostrobothnia Hospital District, Oulu, Finland
Paivi Auvinen Northern Savo Hospital District, Kuopio, Finland
Klaus Elenius Hospital District of Southwest Finland, Turku, Finland
Relja Popovic Abbvie, Chicago, IL, United States
Jeffrey Waring Abbvie, Chicago, IL, United States
Bridget Riley-Gillis Abbvie, Chicago, IL, United States
Anne Lehtonen Abbvie, Chicago, IL, United States
Athena Matakidou Astra Zeneca, Cambridge, United Kingdom
Jennifer Schutzman Genentech, San Francisco, CA, United States
Julie Hunkapiller Genentech, San Francisco, CA, United States
Natalie Bowers Genentech, San Francisco, CA, United States
John Michon Genentech, San Francisco, CA, United States
Vinay Mehta Merck, Kenilworth, NJ, United States
Andrey Loboda Merck, Kenilworth, NJ, United States
Aparna Chhibber Merck, Kenilworth, NJ, United States
Heli Lehtonen Pfizer, New York, NY, United States
Stefan McDonough Pfizer, New York, NY, United States
Marika Crohns Sanofi, Paris, France
Diptee Kulkarni GlaxoSmithKline, Brentford, United Kingdom

Ophthalmology Group
Kai Kaarniranta Northern Savo Hospital District, Kuopio, Finland
Joni Turunen Hospital District of Helsinki and Uusimaa, Helsinki, Finland
Terhi Olliila Hospital District of Helsinki and Uusimaa, Helsinki, Finland
Sanna Seitsonen Hospital District of Helsinki and Uusimaa, Helsinki, Finland
<table>
<thead>
<tr>
<th>Name</th>
<th>Organization</th>
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</tr>
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<tbody>
<tr>
<td>Hannu Uusitalo</td>
<td>Pirkanmaa Hospital District, Tampere, Finland</td>
<td>Finland</td>
</tr>
<tr>
<td>Vesa Aaltonen</td>
<td>Hospital District of Southwest Finland, Turku, Finland</td>
<td>Finland</td>
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<tr>
<td>Hannele Uusitalo-Järvinen</td>
<td>Pirkanmaa Hospital District, Tampere, Finland</td>
<td>Finland</td>
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<tr>
<td>Marja Luodonpää</td>
<td>Northern Ostrobothnia Hospital District, Oulu, Finland</td>
<td>Finland</td>
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<tr>
<td>Nina Hautala</td>
<td>Northern Ostrobothnia Hospital District, Oulu, Finland</td>
<td>Finland</td>
</tr>
<tr>
<td>Heiko Runz</td>
<td>Biogen, Cambridge, MA, United States</td>
<td>United States</td>
</tr>
<tr>
<td>Erich Strauss</td>
<td>Genentech, San Francisco, CA, United States</td>
<td>United States</td>
</tr>
<tr>
<td>Natalie Bowers</td>
<td>Genentech, San Francisco, CA, United States</td>
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</tr>
<tr>
<td>Hao Chen</td>
<td>Genentech, San Francisco, CA, United States</td>
<td>United States</td>
</tr>
<tr>
<td>John Michon</td>
<td>Genentech, San Francisco, CA, United States</td>
<td>United States</td>
</tr>
<tr>
<td>Anna Podgornaia Merck</td>
<td>Merck, Kenilworth, NJ, United States</td>
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</tr>
<tr>
<td>Vinay Mehta</td>
<td>Merck, Kenilworth, NJ, United States</td>
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</tr>
<tr>
<td>Dorothee Diogo</td>
<td>Merck, Kenilworth, NJ, United States</td>
<td>United States</td>
</tr>
<tr>
<td>Joshua Hoffman</td>
<td>GlaxoSmithKline, Brentford, United Kingdom</td>
<td>United Kingdom</td>
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**Dermatology Group**

<table>
<thead>
<tr>
<th>Name</th>
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<th>Location</th>
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<tbody>
<tr>
<td>Kaisa Tasanen</td>
<td>Northern Ostrobothnia Hospital District, Oulu, Finland</td>
<td>Finland</td>
</tr>
<tr>
<td>Laura Huilaja</td>
<td>Northern Ostrobothnia Hospital District, Oulu, Finland</td>
<td>Finland</td>
</tr>
<tr>
<td>Katarina Hannula-Jouppi</td>
<td>Hospital District of Helsinki and Uusimaa, Helsinki, Finland</td>
<td>Finland</td>
</tr>
<tr>
<td>Teea Salmi</td>
<td>Pirkanmaa Hospital District, Tampere, Finland</td>
<td>Finland</td>
</tr>
<tr>
<td>Sirkku Peltonen</td>
<td>Hospital District of Southwest Finland, Turku, Finland</td>
<td>Finland</td>
</tr>
<tr>
<td>Leena Koulu</td>
<td>Hospital District of Southwest Finland, Turku, Finland</td>
<td>Finland</td>
</tr>
<tr>
<td>Ilkka Harvima</td>
<td>Northern Savo Hospital District, Kuopio, Finland</td>
<td>Finland</td>
</tr>
<tr>
<td>Kirsi Kalpala</td>
<td>Pfizer, New York, NY, United States</td>
<td>United States</td>
</tr>
<tr>
<td>Ying Wu</td>
<td>Pfizer, New York, NY, United States</td>
<td>United States</td>
</tr>
<tr>
<td>David Choy</td>
<td>Genentech, San Francisco, CA, United States</td>
<td>United States</td>
</tr>
<tr>
<td>John Michon</td>
<td>Genentech, San Francisco, CA, United States</td>
<td>United States</td>
</tr>
<tr>
<td>Nizar Smaoui</td>
<td>Abbvie, Chicago, IL, United States</td>
<td>United States</td>
</tr>
<tr>
<td>Fedik Rahimov</td>
<td>Abbvie, Chicago, IL, United States</td>
<td>United States</td>
</tr>
<tr>
<td>Anne Lehtonen</td>
<td>Abbvie, Chicago, IL, United States</td>
<td>United States</td>
</tr>
<tr>
<td>Dawn Waterworth</td>
<td>GlaxoSmithKline, Brentford, United Kingdom</td>
<td>United Kingdom</td>
</tr>
</tbody>
</table>

**FinnGen Teams**

**Administration Team**

<table>
<thead>
<tr>
<th>Name</th>
<th>Organization</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anu Jalanko</td>
<td>Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland</td>
<td>Finland</td>
</tr>
<tr>
<td>Risto Kajanne</td>
<td>Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland</td>
<td>Finland</td>
</tr>
<tr>
<td>Ulrike Lyhs</td>
<td>Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland</td>
<td>Finland</td>
</tr>
</tbody>
</table>
Communication

Mari Kaunisto  Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland

Analysis Team

Justin Wade Davis  Abbvie, Chicago, IL, United States
Bridget Riley-Gillis  Abbvie, Chicago, IL, United States
Danjuma Quarless  Abbvie, Chicago, IL, United States
Slavé Petrovski  Astra Zeneca, Cambridge, United Kingdom
Jimmy Liu  Biogen, Cambridge, MA, United States
Chia-Yen Chen  Biogen, Cambridge, MA, United States
Paola Bronson  Biogen, Cambridge, MA, United States
Robert Yang  Celgene, Summit, NJ, United States
Joseph Maranville  Celgene, Summit, NJ, United States
Shameek Biswas  Celgene, Summit, NJ, United States
Diana Chang  Genentech, San Francisco, CA, United States
Julie Hunkapiller  Genentech, San Francisco, CA, United States
Tushar Bhangale  Genentech, San Francisco, CA, United States
Natalie Bowers  Genentech, San Francisco, CA, United States
Dorothee Diogo  Merck, Kenilworth, NJ, United States
Emily Holzinger  Merck, Kenilworth, NJ, United States
Padhraig Gormley  Merck, Kenilworth, NJ, United States
Xulong Wang  Merck, Kenilworth, NJ, United States
Xing Chen  Pfizer, New York, NY, United States
Ása Hedman  Pfizer, New York, NY, United States
Kirsi Auro  GlaxoSmithKline, Brentford, United Kingdom
Clarence Wang  Sanofi, Paris, France
Ethan Xu  Sanofi, Paris, France
Franck Auge  Sanofi, Paris, France
Clement Chatelain  Sanofi, Paris, France
Mitja Kurki  Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland / Broad Institute, Cambridge, MA, United States
Samuli Ripatti  Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland
Mark Daly  Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland
Juha Karjalainen  Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland / Broad Institute, Cambridge, MA, United States
Aki Havulinna  Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland
Anu Jalanko  Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland
Kimmo Palin  University of Helsinki, Helsinki, Finland
Priit Palta  Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland
Pietro Della Briotta Parolo  Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland
Wei Zhou, Broad Institute, Cambridge, MA, United States
Susanna Lemmelä, Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland
Manuel Rivas, University of Stanford, Stanford, CA, United States
Jarmo Harju, Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland
Aarno Palotie, Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland
Arto Lehisto, Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland
Andrea Ganna, Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland
Vincent Llorens, Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland
Antti Karlsson, Auria Biobank / Univ. of Turku / Hospital District of Southwest Finland, Turku, Finland
Kati Kristiansson, THL Biobank / Finnish Institute for Health and Welfare Helsinki, Finland
Mikko Arvas, Finnish Red Cross Blood Service / Finnish Hematology Registry and Clinical Biobank, Helsinki, Finland
Kati Hyvärinen, Finnish Red Cross Blood Service / Finnish Hematology Registry and Clinical Biobank, Helsinki, Finland
Jarmo Ritari, Finnish Red Cross Blood Service / Finnish Hematology Registry and Clinical Biobank, Helsinki, Finland
Tiina Wahlfors, Finnish Red Cross Blood Service / Finnish Hematology Registry and Clinical Biobank, Helsinki, Finland
Miika Koskinen, Hospital District of Helsinki and Uusimaa, Helsinki, Finland BB/HUS/Univ Hosp Districts
Olli Carpen, Hospital District of Helsinki and Uusimaa, Helsinki, Finland BB/HUS/Univ Hosp Districts
Johannes Kettunen, Northern Finland Biobank Borealis / University of Oulu / Northern Ostrobothnia Hospital District, Oulu, Finland
Katri Pylkäs, Northern Finland Biobank Borealis / University of Oulu / Northern Ostrobothnia Hospital District, Oulu, Finland
Marita Kalaoja, Northern Finland Biobank Borealis / University of Oulu / Northern Ostrobothnia Hospital District, Oulu, Finland
Minna Karjalainen, Northern Finland Biobank Borealis / University of Oulu / Northern Ostrobothnia Hospital District, Oulu, Finland
Tuomo Mantere, Northern Finland Biobank Borealis / University of Oulu / Northern Ostrobothnia Hospital District, Oulu, Finland
Eeva Kangasniemi, Finnish Clinical Biobank Tampere / University of Tampere / Pirkanmaa Hospital District, Tampere, Finland
Sami Heikkinen, Biobank of Eastern Finland / University of Eastern Finland / Northern Savo Hospital District, Kuopio, Finland
Arto Mannermaa, Biobank of Eastern Finland / University of Eastern Finland / Northern Savo Hospital District, Kuopio, Finland
Eija Laakkonen, Central Finland Biobank / University of Jyväskylä / Central Finland Health Care District, Jyväskylä, Finland
Juha Kononen, Central Finland Biobank / University of Jyväskylä / Central Finland Health Care District, Jyväskylä, Finland
District, Jyväskylä, Finland

Sample Collection Coordination
Anu Loukola   Hospital District of Helsinki and Uusimaa, Helsinki, Finland

Sample Logistics
Päivi Laiho   THL Biobank / Finnish Institute for Health and Welfare Helsinki, Finland
Tuuli Sistonen   THL Biobank / Finnish Institute for Health and Welfare Helsinki, Finland
Essi Kaiharju   THL Biobank / Finnish Institute for Health and Welfare Helsinki, Finland
Markku Laukkanen   THL Biobank / Finnish Institute for Health and Welfare Helsinki, Finland
Elina Järvensivu   THL Biobank / Finnish Institute for Health and Welfare Helsinki, Finland
Sini Lähteemäki   THL Biobank / Finnish Institute for Health and Welfare Helsinki, Finland
Lotta Männikkö   THL Biobank / Finnish Institute for Health and Welfare Helsinki, Finland
Regis Wong   THL Biobank / Finnish Institute for Health and Welfare Helsinki, Finland

Registry Data Operations
Kati Kristiansson   THL Biobank / Finnish Institute for Health and Welfare Helsinki, Finland
Hannele Mattsson   THL Biobank / Finnish Institute for Health and Welfare Helsinki, Finland
Susanna Lemmelä   Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland
Tero Hiekkalinna   THL Biobank / Finnish Institute for Health and Welfare Helsinki, Finland
Manuel González Jiménez. THL Biobank / Finnish Institute for Health and Welfare Helsinki, Finland

Genotyping
Kati Donner   Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland

Sequencing Informatics
Priit Palta   Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland
Kalle Pärn   Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland
Javier Nunez-Fontarnau   Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland

Data Management and IT Infrastructure
Jarmo Harju   Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland
Elina Kilpeläinen   Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland
Timo P. Sipilä   Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland
Georg Brein   Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland
Alexander Dada   Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland
Ghazal Awaisa   Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland
Anastasia Sheherban   Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland
Tuomas Sipilä   Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland
Clinical Endpoint Development
Hannele Laivuori Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland
Aki Havulinna Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland
Susanna Lemmelä Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland
Tuomo Kiiskinen Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland

Trajectory Team
Tarja Laitinen Pirkanmaa Hospital District, Tampere, Finland
Harri Siirtola University of Tampere, Tampere, Finland
Javier Gracia Tabuenca University of Tampere, Tampere, Finland

Biobank Directors
Lila Kallio Auria Biobank, Turku, Finland
Sirpa Soini THL Biobank, Helsinki, Finland
Jukka Partanen Blood Service Biobank, Helsinki, Finland
Kimmo Pitkänen Helsinki Biobank, Helsinki, Finland
Seppo Vainio Northern Finland Biobank Borealis, Oulu, Finland
Kimmo Savinainen Tampere Biobank, Tampere, Finland
Veli-Matti Kosma Biobank of Eastern Finland, Kuopio, Finland
Teijo Kuopio Central Finland Biobank, Jyväskylä, Finland
Supplementary Table 1. The prospective epidemiological and disease-based cohorts, and hospital biobank samples in FinnGen Data Freeze 6

<table>
<thead>
<tr>
<th>Cohort</th>
<th>N</th>
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<tr>
<td>Auria Biobank</td>
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<td>Blood Service Biobank</td>
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<td>Helsinki Biobank</td>
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<td>11402</td>
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<tr>
<td><strong>Total:</strong></td>
<td><strong>260405</strong></td>
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THL= Finnish Institute for Health and Welfare Helsinki, Finland
**Supplementary Table 2. ICD-codes for OSA and comorbidities**

<table>
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<th>Condition</th>
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<th>ICD-8</th>
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<td>CHD</td>
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<td>COPD</td>
<td>J43, J44</td>
<td>492, 4912</td>
<td>492, 491.04</td>
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</tbody>
</table>

By combining codes from different registries, we generate phenotype endpoints. Finnish national version for each International Statistical Classification of Diseases (ICD)-codes were used. These ICD-code criteria are all regular expressions for a hierarchical search. OSA=obstructive sleep apnoea, CHD=coronary heart disease.