

## Appendices

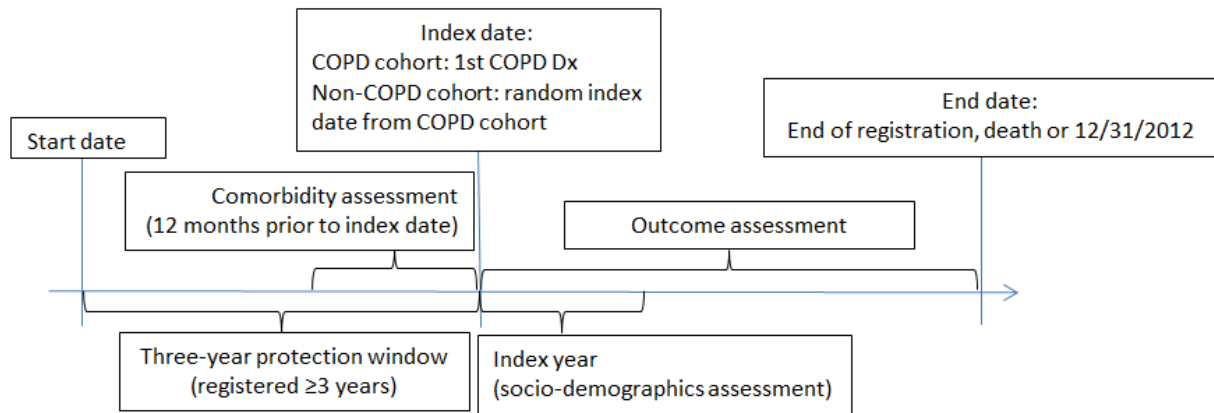
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## Appendix 1. Description of data source

A provincial health insurance program provides universal health care coverage to all legal residents of British Columbia (BC), Canada, one of the largest provinces, representing 13% of the Canadian population (4.4 million as of 2011)[12]. We retrieved data from the BC provincial health administrative databases for the period of January 1997 to December 2012 (16 years). These databases are linked at individual-level and provide information on health-care encounters of all legal residents of BC. We used registration files (capturing the status of insurance coverage of individuals)[2], vital statistics (capturing births and deaths)[3], the hospital discharge database (capturing inpatient encounters)[4], Medical Services Plan payment information (capturing outpatient encounters with physicians)[5], continuing care database (capturing home and community care services)[6], and PharmaNET (capturing all medication dispensations outside of hospital pharmacies, and regardless of any third-party insurance coverage)[7]. Previous analyses have showed a very low prevalence of missing data, under-reporting and misclassification in these databases [8, 9].

## Appendix 2. Schematic presentation of study design



**Appendix 3. Mapping the American Hospital Formulary Service (AHFS) medication categories to ICD-10 disease categories.**

| Disease category                               | ICD 10 code | AHFS Category Level 1              | AHFS level 1 code | AHFS Category Level 2                      | AHFS level 2 code |
|--|-------------|------------------------------------|-------------------|--|-------------------|
| Certain infectious and parasitic diseases      | A00-B99     | ANTI-INFECTIVE AGENTS              | 8                 | ANTHELMINTICS                              | 808               |
|  |             |                                    |                   | ANTIBACTERIALS                             | 812               |
|  |             |                                    |                   | ANTIFUNGAL (SYSTEMIC)                      | 814               |
|  |             |                                    |                   | ANTIMYCOBACTERIALS                         | 816               |
|  |             |                                    |                   | ANTIPROTOZOALS                             | 830               |
|  |             |                                    |                   | ANTIVIRALS (SYSTEMIC)                      | 818               |
|  |             |                                    |                   | URINARY ANTI-INFECTIVES                    | 836               |
| Neoplasms                                      | C00-D48     | ANTINEOPLASTIC AGENTS              | 10                | ANTINEOPLASTIC AGENTS                      | 1000              |
| Diseases of the blood and blood-forming origin | D50-D89     | NA                                 | NA                | NA   | NA                |
| Endocrine, nutritional and metabolic diseases  | E00-E90     | HORMONES AND SYNTHETIC SUBSTITUTES | 68                | ADRENALS                                   | 6804              |
|  |             |                                    |                   | ANDROGENS                                  | 6808              |
|  |             |                                    |                   | ANTIDIABETIC AGENTS                        | 6820              |
|  |             |                                    |                   | ANTIHYPOGLYCEMIC AGENTS                    | 6822              |
|  |             |                                    |                   | CONTRACEPTIVES                             | 6812              |
|  |             |                                    |                   | ESTROGENS AND ANTIESTROGENS                | 6816              |
|  |             |                                    |                   | GONADOTROPINS                              | 6818              |
|  |             |                                    |                   | PARATHYROID                                | 6824              |
|  |             |                                    |                   | PITUITARY                                  | 6828              |
|  |             |                                    |                   | PROGESTINS                                 | 6832              |
|  |             |                                    |                   | SOMATOSTATIN AGONISTS AND ANTAGONISTS      | 6829              |
|  |             |                                    |                   | SOMATOTROPIN AGONISTS AND ANTAGONISTS      | 6830              |
|  |             |                                    |                   | THYROID AND ANTITHYROID AGENTS             | 6836              |
| Mental and behavioural disorders               | F00-F99     | CENTRAL NERVOUS SYSTEM AGENTS      | 28                | ANTICONVULSANTS                            | 2812              |
|  |             |                                    |                   | PSYCHOTHERAPEUTIC AGENTS                   | 2816              |
| Diseases of the nervous system                 | G00-G99     | CENTRAL NERVOUS SYSTEM AGENTS      | 28                | ANALGESICS AND ANTIPIRETTICS               | 2808              |
|  |             |                                    |                   | ANOREXIGENICS; RESPIRATORY, CNS STIMULANTS | 2820              |
|  |             |                                    |                   | ANTIMANIC AGENTS                           | 2828              |
|  |             |                                    |                   | ANTIMIGRAINE AGENTS                        | 2832              |
|  |             |                                    |                   | ANTIPARKINSONIAN AGENTS (CNS)              | 2836              |
|  |             |                                    |                   | ANXIOLYTICS, SEDATIVES AND HYPNOTICS       | 2824              |

|   |                    |   |    |  |      |
|---|--------------------|---|----|--|------|
|   |                    |   |    | CENTRAL NERVOUS SYSTEM AGENTS, MISC.     | 2892 |
|   |                    |   |    | GENERAL ANESTHETICS                      | 2804 |
|   |                    |   |    | OPIATE ANTAGONISTS                       | 2810 |
| Diseases of the eye and adnexa;<br>Diseases of the ear and mastoid process<br><br>(Combined into one category: diseases of the eye, ear and nose) | H00-H59<br>H60-H95 | EYE, EAR, NOSE AND THROAT (EENT) PREPS.   | 52 | ANTI-INFECTIVES (EENT)                   | 5204 |
|   |                    |   |    | ANTI-INFLAMMATORY AGENTS (EENT)          | 5208 |
|   |                    |   |    | ANTIALLERGIC AGENTS                      | 5202 |
|   |                    |   |    | ANTIGLAUCOMA AGENTS                      | 5240 |
|   |                    |   |    | CONTACT LENS SOLUTIONS                   | 5212 |
|   |                    |   |    | EENT DRUGS, MISCELLANEOUS                | 5292 |
|   |                    |   |    | LOCAL ANESTHETICS (EENT)                 | 5216 |
|   |                    |   |    | MOUTHWASHES AND GARGLES                  | 5228 |
|   |                    |   |    | MYDRIATICS                               | 5224 |
|   |                    |   |    | VASOCONSTRICTORS                         | 5232 |
| Diseases of the circulatory system  | I00-I99            | BLOOD FORMATION, COAGULATION + THROMBOSIS | 20 | ANTI-ANEMIA DRUGS                        | 2004 |
|   |                    |   |    | ANTI-HEMORRHAGIC AGENTS                  | 2028 |
|   |                    |   |    | ANTI-THROMBOTIC AGENTS                   | 2012 |
|   |                    |   |    | HEMATOPOIETIC AGENTS                     | 2016 |
|   |                    |   |    | HEMORRHOLOGIC AGENTS                     | 2024 |
| Diseases of the circulatory system  | I00-I99            | CARDIOVASCULAR DRUGS                      | 24 | ALPHA-ADRENERGIC BLOCKING AGENTS         | 2420 |
|   |                    |   |    | ANTI-LIPEMIC AGENTS                      | 2406 |
|   |                    |   |    | BETA-ADRENERGIC BLOCKING AGENTS          | 2424 |
|   |                    |   |    | CALCIUM-CHANNEL BLOCKING AGENTS          | 2428 |
|   |                    |   |    | CARDIAC DRUGS                            | 2404 |
|   |                    |   |    | HYPOTENSIVE AGENTS                       | 2408 |
|   |                    |   |    | RENIN-ANGIOTENSIN-ALDOSTERONE SYS. INHIB | 2432 |
|   |                    |   |    | SCLEROSING AGENTS                        | 2416 |
|   |                    |   |    | VASODILATING AGENTS                      | 2412 |
| Diseases of the respiratory system  | J00-J99            | RESPIRATORY TRACT AGENTS                  | 48 | ANTI-INFLAMMATORY AGENTS (RESPIRATORY)   | 4810 |
|   |                    |   |    | ANTI-TUSSIVES                            | 4808 |
|   |                    |   |    | CYSTIC FIBROSIS (CFTR) MODULATORS        | 4814 |
|   |                    |   |    | EXPECTORANTS                             | 4816 |
|   |                    |   |    | MUCOLYTIC AGENTS                         | 4824 |
|   |                    |   |    | PHOSPHODIESTERASE TYPE 4 INHIBITORS      | 4832 |
|   |                    |   |    | PULMONARY SURFACTANTS                    | 4836 |
|   |                    |   |    | RESPIRATORY TRACT AGENTS, MISCELLANEOUS  | 4892 |
| Diseases of the digestive   | K00-               | GASTROINTESTINAL DRUGS                    | 56 | ANTACIDS AND ADSORBENTS                  | 5604 |

|   |         |                                 |    |  |      |
|---|---------|---------------------------------|----|--|------|
| system                                    | K93     |                                 |    | ANTI-INFLAMMATORY AGENTS (GI DRUGS)      | 5636 |
|   |         |                                 |    | ANTIDIARRHEA AGENTS                      | 5608 |
|   |         |                                 |    | ANTIEMETICS                              | 5622 |
|   |         |                                 |    | ANTIFLATULENTS                           | 5610 |
|   |         |                                 |    | ANTIULCER AGENTS AND ACID SUPPRESSANTS   | 5628 |
|   |         |                                 |    | CATHARTICS AND LAXATIVES                 | 5612 |
|   |         |                                 |    | CHOLELITHOLYTIC AGENTS                   | 5614 |
|   |         |                                 |    | DIGESTANTS                               | 5616 |
|   |         |                                 |    | EMETICS                                  | 5620 |
|   |         |                                 |    | GI DRUGS, MISCELLANEOUS                  | 5692 |
|   |         |                                 |    | LIPOTROPIC AGENTS                        | 5624 |
|   |         |                                 |    | PROKINETIC AGENTS                        | 5632 |
| Diseases of the skin and subcutaneous tis | L00-L99 | SKIN AND MUCOUS MEMBRANE AGENTS | 84 | ANTI-INFECTIVES (SKIN + MUCOUS MEMBRANE) | 8404 |
|   |         |                                 |    | ANTI-INFLAMMATORY AGENTS (SKIN + MUCOUS) | 8406 |
|   |         |                                 |    | ANTIPRURITICS AND LOCAL ANESTHETICS      | 8408 |
|   |         |                                 |    | ASTRINGENTS                              | 8412 |
|   |         |                                 |    | CELL STIMULANTS AND PROLIFERANTS         | 8416 |
|   |         |                                 |    | DEPIGMENTING AND PIGMENTING AGENTS       | 8450 |
|   |         |                                 |    | DETERGENTS                               | 8420 |
|   |         |                                 |    | EMOLLIENTS, DEMULCENTS, AND PROTECTANTS  | 8424 |
|   |         |                                 |    | KERATOLYTIC AGENTS                       | 8428 |
|   |         |                                 |    | KERATOPLASTIC AGENTS                     | 8432 |
|   |         |                                 |    | SKIN AND MUCOUS MEMBRANE AGENTS, MISC.   | 8492 |
|   |         |                                 |    | SUNSCREEN AGENTS                         | 8480 |
| Diseases of the musculoskeletal system an | M00-M99 | NA                              | NA | NA                                       | NA   |
| Diseases of the genitourinary system      | N00-N99 | NA                              | NA | NA                                       | NA   |
| Pregnancy, childbirth and the puerperium  | O00-O99 | NA                              | NA | NA                                       | NA   |
| Certain conditions originating in the per | P00-P96 | NA                              | NA | NA                                       | NA   |
| Congenital malformations, deformations, a | Q00-Q99 | NA                              | NA | NA                                       | NA   |
| Symptoms, signs and abnormal clinical and | R00-R99 | Not included                    | NA | NA                                       | NA   |
| Injury, poisoning and certain other conse | S00-T98 | Not included                    | NA | NA                                       | NA   |
| Provisional codes for research and tempor | U00-U99 | Not included                    | NA | NA                                       | NA   |
| External causes of                        | V01-    | Not included                    | NA | NA                                       | NA   |

|   |  |                          |  |  |      |
|---|--|--------------------------|--|--|------|
| morbidity and mortalit                    | Y98  |                          |  |  |      |
| Factors influencing health status and con | Z01-Z99  | Not included             | NA                                       | NA                                       | NA   |
| NA  | MIS  | ANTIHISTAMINE DRUGS      | 4  | FIRST GENERATION ANTIHISTAMINES          | 404  |
|   |  |                          |  | OTHER ANTIHISTAMINES                     | 492  |
|   |  |                          |  | SECOND GENERATION ANTIHISTAMINES         | 408  |
|   |  | AUTONOMIC DRUGS          | 12                                       | ANTICHOLINERGIC AGENTS                   | 1208 |
|   |  |                          |  | AUTONOMIC DRUGS, MISCELLANEOUS           | 1292 |
|   |  |                          |  | PARASYMPATHOMIMETIC (CHOLINERGIC AGENTS) | 1204 |
|   |  |                          |  | SKELETAL MUSCLE RELAXANTS                | 1220 |
|   |  |                          |  | SYMPATHOLYTIC ADRENERGIC BLOCKING AGENTS | 1216 |
|   |  |                          |  | SYMPATHOMIMETIC (ADRENERGIC) AGENTS      | 1212 |
|   |  |                          |  | BLOOD DERIVATIVES                        | 16   |
|   |  | DENTAL AGENTS            | 34                                       | DENTAL AGENTS                            | 3400 |
|   |  | DEVICES                  | 94                                       | DEVICES                                  | 9400 |
|   |  | DIAGNOSTIC AGENTS        | 36                                       | ADRENOCORTICAL INSUFFICIENCY             | 3604 |
|   |  |                          |  | DIAGNOSTIC AGENTS                        | 3600 |
|   |  |                          |  | DIPHTHERIA                               | 3628 |
|   |  |                          |  | DRUG HYPERSENSITIVITY                    | 3630 |
|   |  |                          |  | FUNGI                                    | 3632 |
|   |  |                          |  | GALLBLADDER FUNCTION                     | 3634 |
|   |  |                          |  | GASTRIC FUNCTION                         | 3636 |
|   |  |                          |  | INTESTINAL ABSORPTION                    | 3638 |
|   |  |                          |  | KIDNEY FUNCTION                          | 3640 |
|   |  |                          |  | LIVER FUNCTION                           | 3644 |
|   |  |                          |  | MUMPS                                    | 3652 |
|   |  |                          |  | MYASTHENIA GRAVIS                        | 3656 |
|   |  |                          |  | OCULAR DISORDERS                         | 3658 |
|   |  |                          |  | PANCREATIC FUNCTION                      | 3661 |
|   |  |                          |  | PITUITARY FUNCTION                       | 3666 |
|   |  | ROENTGENOGRAPHY          | 3668                                     |  |      |
|   |  | THYROID FUNCTION         | 3660                                     |  |      |
|   |  | TUBERCULOSIS             | 3684                                     |  |      |
|   |  | URINE AND FECES CONTENTS | 3688                                     |  |      |
|   | DISINFECTANTS (FOR NON-DERMATOLOGIC USE)<br>ELECTROLYTIC, CALORIC, AND WATER BALANCE | 38                       | DISINFECTANTS (FOR NON-DERMATOLOGIC USE) | 3800                                     |      |
| 40  |  | ACIDIFYING AGENTS        | 4004                                     |  |      |
|   |  | ALKALINIZING AGENTS      | 4008                                     |  |      |

|  |  |                                  |    |   |      |
|--|--|----------------------------------|----|---|------|
|  |  |                                  |    | AMMONIA DETOXICANTS                     | 4010 |
|  |  |                                  |    | CALORIC AGENTS                          | 4020 |
|  |  |                                  |    | DIURETICS                               | 4028 |
|  |  |                                  |    | ION-REMOVING AGENTS                     | 4018 |
|  |  |                                  |    | IRRIGATING SOLUTIONS                    | 4036 |
|  |  |                                  |    | REPLACEMENT PREPARATIONS                | 4012 |
|  |  |                                  |    | SALT AND SUGAR SUBSTITUTES              | 4024 |
|  |  |                                  |    | URICOSURIC AGENTS                       | 4040 |
|  |  | ENZYMES                          | 44 | ENZYMES                                 | 4400 |
|  |  | GOLD COMPOUNDS                   | 60 | GOLD COMPOUNDS                          | 6000 |
|  |  | HEAVY METAL ANTAGONISTS          | 64 | HEAVY METAL ANTAGONISTS                 | 6400 |
|  |  | LOCAL ANESTHETICS (PARENTERAL)   | 72 | LOCAL ANESTHETICS (PARENTERAL)          | 7200 |
|  |  | MISCELLANEOUS THERAPEUTIC AGENTS | 92 | 5-ALPHA-REDUCTASE INHIBITORS            | 9208 |
|  |  |                                  |    | ALCOHOL DETERRENTS                      | 9204 |
|  |  |                                  |    | ANTIDOTES                               | 9212 |
|  |  |                                  |    | ANTIGOUT AGENTS                         | 9216 |
|  |  |                                  |    | BONE RESORPTION INHIBITORS              | 9224 |
|  |  |                                  |    | CARIOSTATIC AGENTS                      | 9228 |
|  |  |                                  |    | COMPLEMENT INHIBITORS                   | 9232 |
|  |  |                                  |    | DISEASE-MODIFYING ANTIRHEUMATIC AGENTS  | 9236 |
|  |  |                                  |    | GONADOTROPIN-RELEASING HORMONE ANTAGNTS | 9240 |
|  |  |                                  |    | IMMUNOMODULATORY AGENTS                 | 9220 |
|  |  |                                  |    | IMMUNOSUPPRESSIVE AGENTS                | 9244 |
|  |  |                                  |    | OTHER MISCELLANEOUS THERAPEUTIC AGENTS  | 9292 |
|  |  |                                  |    | PROTECTIVE AGENTS                       | 9256 |
|  |  | OXYTOCICS                        | 76 | OXYTOCICS                               | 7600 |
|  |  | PHARMACEUTICAL AIDS              | 96 | PHARMACEUTICAL AIDS                     | 9600 |
|  |  | SMOOTH MUSCLE RELAXANTS          | 86 | GENITOURINARY SMOOTH MUSCLE RELAXANTS   | 8612 |
|  |  |                                  |    | RESPIRATORY SMOOTH MUSCLE RELAXANTS     | 8616 |
|  |  | VITAMINS                         | 88 | MULTIVITAMIN PREPARATIONS               | 8828 |
|  |  |                                  |    | VITAMIN A                               | 8804 |
|  |  |                                  |    | VITAMIN B COMPLEX                       | 8808 |
|  |  |                                  |    | VITAMIN C                               | 8812 |
|  |  |                                  |    | VITAMIN D                               | 8816 |
|  |  |                                  |    | VITAMIN E                               | 8820 |



|  |  |                                      |    |                                      |      |
|--|--|--------------------------------------|----|--------------------------------------|------|
|  |  |                                      |    | VITAMIN K ACTIVITY                   | 8824 |
|  |  | CONTRACEPTIVES (E.G. FOAMS, DEVICES) | 32 | CONTRACEPTIVES (E.G. FOAMS, DEVICES) | 3200 |
|  |  | SERUMS, TOXOIDS, AND VACCINES        | 80 | SERUMS                               | 8004 |
|  |  |                                      |    | TOXOIDS                              | 8008 |
|  |  |                                      |    | VACCINES                             | 8012 |

### Appendix 3. Detailed description of regression analysis and inference estimation.

A two-part generalized model was developed to estimate the excess costs of COPD and the impact of baseline risk factors over time. The unit of observation was person-year from the index date to the end of follow-up. To avoid under-reporting bias when individuals were temporarily absent from BC, we excluded person-years with less than 300 days of registration unless death occurred.

Excess cost was estimated as the adjusted difference in predicted costs of a COPD patient and the non-COPD match. We respectively estimated the excess costs of overall direct medical costs, COPD-attributable costs, comorbidity-attributable costs (overall and for 16 disease areas), non-attributable costs, as well as the component costs of these categories related to hospitalisation, outpatient services, medications and community care.

Covariates of interest included COPD status (COPD=1, no COPD=0), baseline risk factors: age groups (45-54 years, 55-64 years,  $\geq 65$  years), sex (male, female) and baseline comorbidity burden (none: CCI score=0; mild, CCI score=1, moderate, CCI score=2; high, CCI score $\geq 3$ ), an indicator of numbers of observation period since the index date. We examined the three-way interactions between COPD status, baseline risk factors and the duration of follow up (number of years) to estimate the effects of baseline risk factors on excess costs over time. In addition, we included an indicator for the index year and an interaction term between index year and COPD status, which was to capture the excess costs of acute care in the first year of COPD diagnosis.

Detailed regression and estimation procedures were described below:

The first part of the two part model was a logistic regression model which estimated the probability of zero costs during any observation period as a function of covariates.

The second part was a gamma regression model with log link to estimate costs in the subset of individuals who incurred any costs during that period. This model has been shown to perform well in the estimation of population averaged health care costs[10].

Generalized Estimating Equations was applied to obtain valid inference for the clustered data around each matched pair.

Based on the regression coefficients obtained from the two-part model, we estimated overall per-person-year costs as the probability of incurring any costs (obtained from model part 1) multiplied by the predicted costs for non-zero costs (obtained from model part 2).

Following this step, we estimated the population-averaged, covariate-adjusted excess costs of COPD overall and in difference disease domains using the G-computation technique(2). The estimation was done in a counterfactual framework, where we first estimated the excess costs for each participant by contrasting the differences in the predicted per-person-year costs as if the participant had COPD, versus as if he/she did not have COPD. In other words, we set each study subject as a case and at the same time his/her own control in two contrary (and potentially

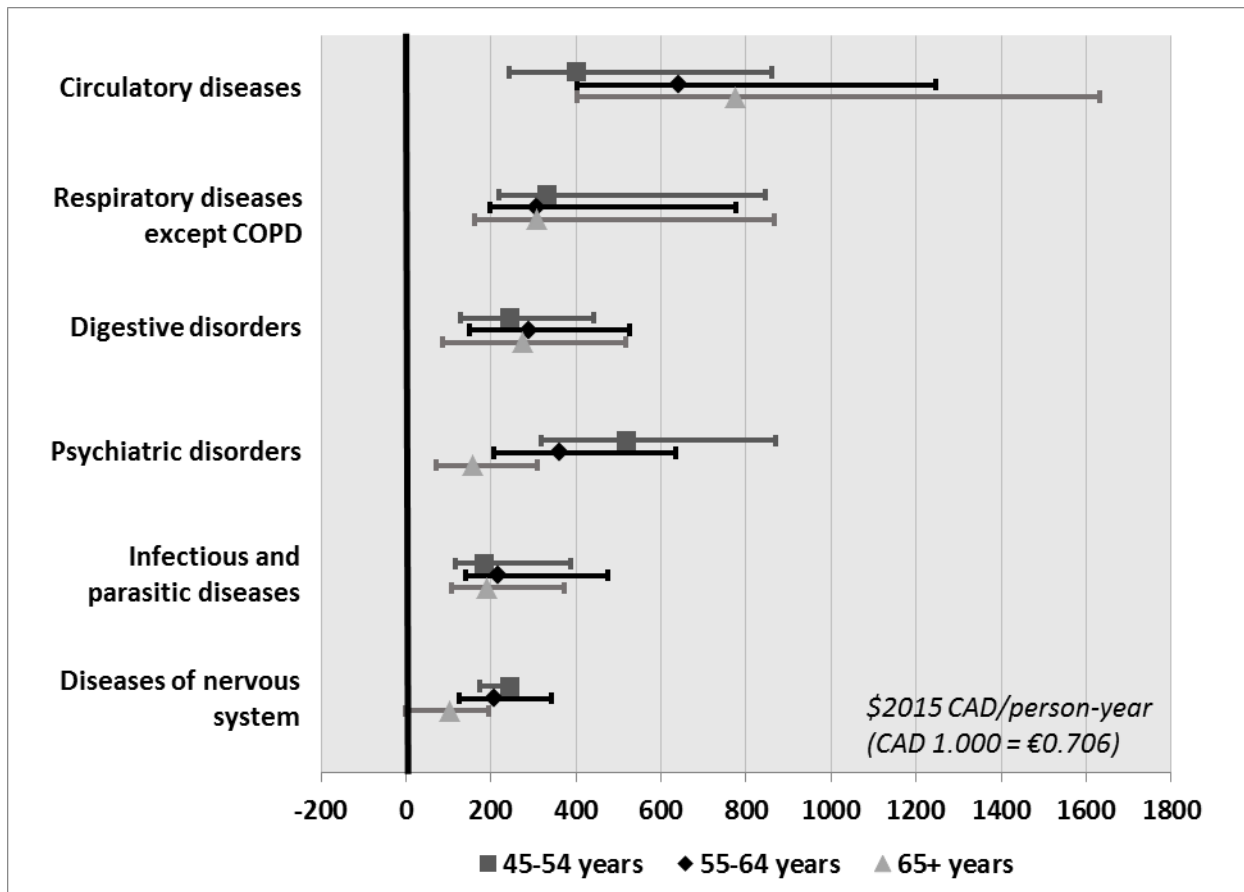
counterfactual) scenarios, and estimated excess costs as the difference in predicted costs for this subject under these two scenarios (contrasting case versus control). Meanwhile, other covariates were set at the observed value. Then, we averaged the estimated excess costs of each study participant across the entire sample.

We used a similar methodology to estimate the adjusted effects of baseline risk factors on excess costs. This was done through building a higher level of counterfactual framework to estimate excess costs at different categories of selected baseline risk factor, and compare the cost differences across categories over the entire sample. Assuming we controlled all confounding covariates, we can interpret such covariate-adjusted effects as causal effects.

Inference for estimated excess costs was obtained using parametric bootstrapping with 50 replications.

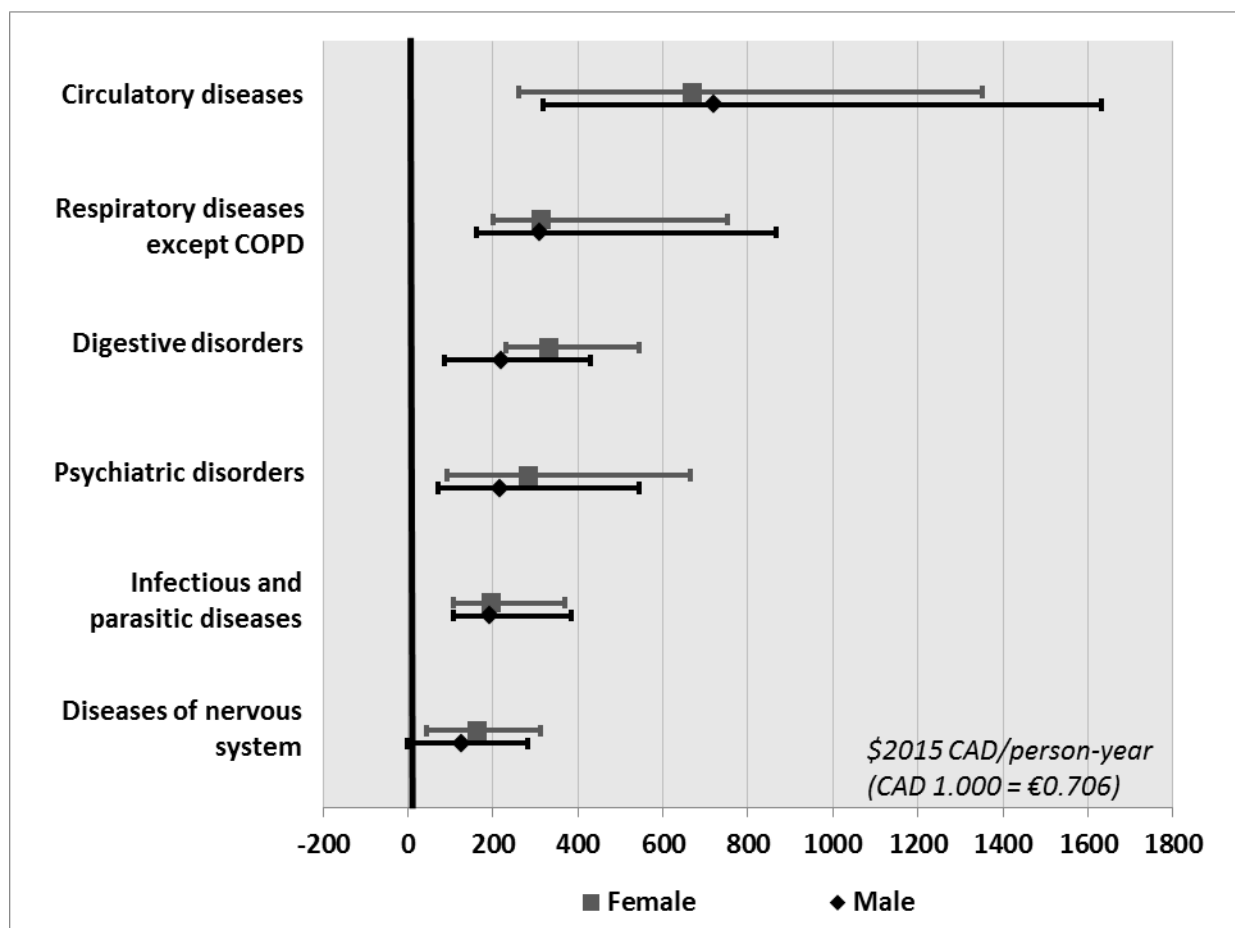
#### Appendix 4. Estimated excess costs due to COPD during the 10-year follow period, by baseline age and major comorbid conditions.

Error bars denote 95% confidence interval of the estimated costs.



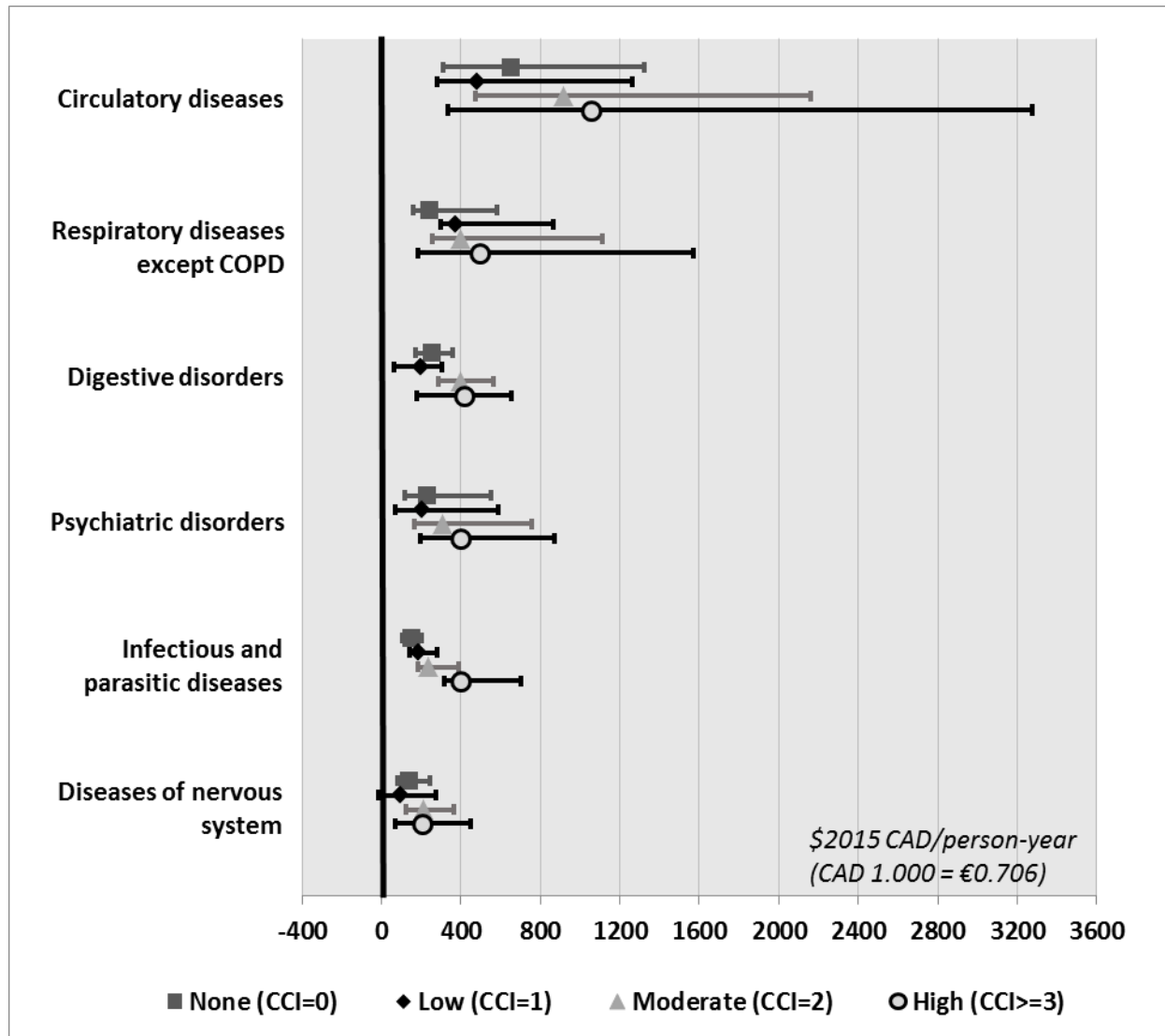
## Appendix 5. Estimated excess costs due to COPD during the 10-year follow period, by sex and major comorbid conditions.

Error bars denote 95% confidence interval of the estimated costs.



## Appendix 6. Estimated excess costs due to COPD during the 10-year follow period, by baseline comorbidity status.

Comorbidity status was measured with Charlson comorbidity index (CCI, excluding COPD) and major comorbid conditions. Error bars denote 95% confidence interval of the estimated costs.



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