The impact of pneumococcal vaccination on pneumonia mortality among the elderly in Japan: A difference-in-difference study

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Background. It is plausible that the routine immunization among infants using pneumococcal conjugate vaccine 13 (PCV13) from 2013 and among the elderly using pneumococcal polysaccharide vaccine 23 (PPV23) from 2014 contributed to reducing the pneumonia mortality among the elderly in Japan. The present study aimed to estimate the causal effect of this vaccination on pneumonia mortality, using the available cause-of-death data and employing a difference-in-difference (DID) design.

Methods. Two types of mortality data, i.e., prefecture-dependent and age- and gender-specific mortality data, from 2003–2017 were retrieved. We used mortality due to malignant neoplasm and heart disease as control groups and employed a DID design with an assumed parallel mortality trend between pneumonia and control group mortality since 2013 to estimate the causal effect of pneumococcal vaccination from 2014.

Results. Our estimation based on malignant neoplasm and heart disease as controls indicated that the reduced pneumonia mortality in 2017 owing to pneumococcal vaccination was as large as 41.9 (33.2, 50.6) and 31.2 (23.8, 38.6) per 100,000 individuals, respectively. The largest mortality reduction was observed for the oldest group (aged ≥90 years), especially among men.

Discussion. The pneumococcal vaccination program, perhaps mainly represented by high vaccination coverage of PCV13 among children and partly by PPV23 administration with low coverage among the elderly in Japan, was shown to have reduced the pneumonia mortality in the elderly at the population level.

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3 **difference study**

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16   **Abstract**

17   **Background.** It is plausible that the routine immunization among infants using pneumococcal

18   conjugate vaccine 13 (PCV13) from 2013 and among the elderly using pneumococcal

19   polysaccharide vaccine 23 (PPV23) from 2014 contributed to reducing the pneumonia mortality

20   among the elderly in Japan. The present study aimed to estimate the causal effect of this

21   vaccination on pneumonia mortality, using the available cause-of-death data and employing a

22   difference-in-difference (DID) design.

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25   and heart disease as control groups and employed a DID design with an assumed parallel

26   mortality trend between pneumonia and control group mortality since 2013 to estimate the

27   causal effect of pneumococcal vaccination from 2014.

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29   that the reduced pneumonia mortality in 2017 owing to pneumococcal vaccination was as large

30   as 41.9 (33.2, 50.6) and 31.2 (23.8, 38.6) per 100,000 individuals, respectively. The largest

31   mortality reduction was observed for the oldest group (aged ≥90 years), especially among men.

32   **Discussion.** The pneumococcal vaccination program, perhaps mainly represented by high

33   vaccination coverage of PCV13 among children and partly by PPV23 administration with low

34   coverage among the elderly in Japan, was shown to have reduced the pneumonia mortality in

35   the elderly at the population level.

Introduction

Japan, as a superaged nation, has a unique structure of causes of death (Arai et al., 2015). After successfully controlling infectious diseases following World War II, the country experienced a so-called "epidemiologic transition" with a dramatic change in the disease and cause-of-death structures (Omran, 2005). In the recent decade, the four major causes of death have been malignant neoplasm, heart disease, cerebrovascular disease (CVD), and pneumonia, all of which are most frequently seen in the elderly (Ministry of Health, Labour and Welfare, 2018a) (Fig. 1A). While the CVD mortality has followed a declining trend, perhaps reflecting gradual improvements in the diagnosis, treatment, and management of patients, the mortality from the other three major causes has steadily increased over time (Fig. 1B). These increases are considered to reflect the aging process as a whole in addition to aging within the elderly group. Unfortunately, from a clinical point of view, there has been no breakthrough in the prevention or treatment for these three diseases (Ebihara, 2017).

Nevertheless, it is noteworthy that an important change has occurred in reducing the risk of community-acquired pneumonia, especially pneumococcal pneumonia caused by *Streptococcus pneumoniae*, which accounts for 18.8% of the total cases (The Japanese Respiratory Society, 2017; Miyashita & Yamauchi, 2018). Following the subsidy-based exploratory immunization that began in 2009 at a municipality level with small coverages, in 2014 Japan began a routine immunization program with the pneumococcal polysaccharide vaccine 23 (PPV23) among the elderly (Naito, Yokokawa & Watanabe, 2018). In that program, elderly individuals aged 65 years or older were eligible for vaccination; owing to the policy intent to cover the entire elderly population within 5 years, those who newly reached the age of 65, 70, 75, 80, 85, 90, 95, or 100 years from 2014–2018 were invited to receive the

60   immunization (Naito, Yokokawa & Watanabe, 2018). At yearly basis, crude vaccination

61   coverage of PPV23 among elderly from 2014-16 was estimated at 38.3%, 33.5% and 37.8%,

62   respectively (Ministry of Health, Labour and Welfare, 2018b). As of 2018, a vaccination

63   coverage slightly above 40% has been achieved among the elderly (Naito, Yokokawa &

64   Watanabe, 2018; Ministry of Health, Labour and Welfare, 2018b). In addition to vaccinating the

65   elderly with PPV23, which is considered to protect vaccinated individuals from 23 types of

66   pneumococci bacteria, the immunization of infants with the pneumococcal conjugate vaccine

67   (PCV)7 was introduced as voluntary vaccination from late 2010 with the initially estimated

68   coverage below 40%. Subsequently, public subsidy of PCV7 vaccination started in 2011 or 2012

69   depending on policy decision by local governments, and where subsidized, the vaccination

70   coverage was elevated to be greater than 80% in the corresponding cities. In 2013, PCV13

71   replaced PCV7, and the vaccination with PCV13 became a part of routine immunization

72   program. Regardless of PCV7 or PCV13, the first, second and third doses were given at 2

73   months old, 4 months old and 6 month old, respectively, with an optional supplementary dose at

74   12-15 months old. Yearly vaccination coverage among children for three doses of PCV13, as

75   calculated by the ratio of the total number of third doses to the demographic size of the subject

76   age group, from 2013-16 all exceeded 99.9% (i.e. 103.4%, 102.5%, 106.5% and 99.9%,

77   respectively), because people receiving this vaccination may have slightly extended to other

78   (perhaps older) age groups (Ministry of Health, Labour and Welfare, 2018b). Considering the

79   high vaccination coverage, this change has been expected to not only reduce the invasive

80   pneumococcal disease among infants but also reduce the transmission of these diseases from

81   children to the elderly (Bogaert, De Groot & Hermans, 2004).

82   The routine administration of both these pneumococcal vaccines seemed likely to reduce

83   the pneumonia mortality among the elderly in Japan. A published study in Canada indicated that

84   the risk of death, frequency of complications, and length of hospital stay among pneumonia

85   patients were all reduced by prior pneumococcal vaccination (Fisman et al., 2006). Moreover,

86   PPV23 has been shown to prevent pneumonia in elderly people (Ortqvist et al., 1998).

87   Nevertheless, a population-based cohort study involving hospital-admitted pneumonia patients in

88   Canada demonstrated that, if admitted patients were vaccinated and followed up, PPV23

89   immunization was not associated with a reduced risk of death or further hospitalization

90   (Johnstone et al., 2010). Another cohort study in Italy has shown that while PPV23

91   administration certainly improved the survival rate of elderly individuals, those who received

92   PCV13 enjoyed a better survival rate (Baldo et al., 2016). Scientific evidence supporting the

93   effectiveness of pneumococcal vaccines for preventing pneumonia death is still scarce, and it has

94   not been directly assessed among the elderly in Japan.

95   A close look at the pneumonia mortality in Japan in recent years (Fig. 1B) reveals an

96   overall stagnation with a potential signature of decline. Notably, aging progressed during this

97   period both for the entire population and within the elderly population, and, in line with this, the

98   mortality due to two other major causes, i.e., malignant neoplasm and heart disease, steadily

99   increased from 2003–2017. This observation may offer an important avenue by which to study

100   the effectiveness of pneumococcal vaccination in Japan. The present study aimed to estimate the

101   impact of pneumococcal vaccination on pneumonia mortality among the elderly, using the cause-

102   of-death data in Japan and employing a quasi-experimental study design.

Materials & Methods

Mortality data

The present study was conducted using publicly available datasets on the cause-of-death in Japan

from 2003–2017 (Ministry of Health, Labour and Welfare, Japan, 2018a). The time frame of

2003–2017 was specifically selected because the elderly aged 80 years or older were grouped

together in the data from earlier years and also because the age-specific mortality trend appeared

to be approximately linear during this period based on a visual assessment. Otherwise, the data

were available in five-year age bands. We restricted ourselves to analyzing the mortality trends

of only three major causes of death, namely, malignant neoplasm, heart disease, and pneumonia,

because these were expected to increase with the aging population and there have not been any

breakthroughs other than pneumococcal vaccination that might abruptly reduce these mortalities.

We collected two types of mortality data. One was the prefecture-dependent mortality

rate per 100,000 individuals from 2003–2017. For this, the cause-specific mortality rates for 47

prefectures were amassed. The other dataset was the age- and gender-dependent mortality rate

per 100,000 individuals from 2003–2017. Ages were grouped in 5-year increments. Among the

elderly, pneumonia was ranked within the top five causes of death from around the ages of 65–

69 years old. Thus, our subject ages were split into six age-groups, i.e., those aged 65–69, 70–74,

75–79, 80–84, 85–89, and ≥90 years, stratified by gender. Moreover, to validate our underlying

assumption of parallel trend between pneumonia mortality and control disease selected either

from malignant neoplasm or heart disease, we also collected the mortality data due to chronic

obstructive pulmonary disease (COPD) and used it as the control during sensitivity analysis (see

statistical analysis). To do so, the COPD-induced mortality data for the entire Japan from 2003-

17 was collected, and compared against pneumonia mortality.

126   **Epidemiological analysis**

127   The present study employed a difference-in-difference (DID) design, which is a quasi-

128   experimental epidemiological study design that can be applied to observational data (Wing,

129   Simon & Bello-Gomez, 2018). To purify the causal impact of pneumococcal vaccination on

130   pneumonia mortality among the elderly, we compared the mortality trend of pneumonia death

131   against the mortality of two control cause-of-death groups, i.e., malignant neoplasm and heart

132   disease. From a visual assessment of the data shown in Figure 1B, the mortality of these three

133   major diseases have increased roughly in parallel over the last decades. Exploiting this

134   observation, we independently applied the DID design to both the prefecture and age/gender

135   data.

136   We used $g = 1,\ldots, G$ to index cross-sectional units, such as geographic areas, $a = 1,\ldots, A$

137   to index age groups, and $t = 2003,\ldots, 2017$ to indicate year. The term Y_{gt}^k represents the outcome

138   (i.e., mortality) against the mortality of control group k for unit g in year t. For the analysis of

139   prefectural data, we used the expected mortality value calculated as

140    $$E(Y_{gt}^k) = \alpha_0 + \alpha_1(t - t_0) + \beta(t - t_v)\left(T_g^k P_t\right) + \gamma T_g^k + \delta P_t, \quad (1)$$

141   to predict the pneumonia mortality and also the mortality of control disease k, where α_0 and α_1

142   describe the mortality of a control group that is assumed to share the same mortality trend in

143   parallel with the pneumonia group over a set time period, t_0 is the first year of our analysis (i.e.,

144    $t_0 = 2003$), β is the causal effect of vaccination on pneumonia mortality, t_v is the first year when

145   vaccination starts to influence the dynamics (i.e., $t_v = 2013$), γ is the group effect on pneumonia

146   mortality, and δ is the time effect on both pneumonia and control group k that was introduced at

147   the same time as the pneumococcal vaccination. Because routine pneumococcal immunization

148   with PCV for infants began in 2013, t_v was assumed to be 2013. Because Japan implemented

149   vaccination spending 5 years to cover all corresponding birth cohorts of elderly, and due to

150   gradual roll-out effect of indirect benefit, the causal effect in the present study is modeled as the

151   rate of change per year (i.e. expressed as yearly reduction rate in pneumonia mortality). T_g^k and P_t

152   are dichotomous dummy variables, defined as

$$T_g^k = \begin{cases} 1 \text{ for pneumonia group} \\ 0 \text{ for control group} \end{cases}, \quad (2)$$

154   and

$$P_t = \begin{cases} 1 \text{ for } t \geq 2014 \\ 0 \text{ otherwise} \end{cases}, \quad (3)$$

156   respectively.

157   Similarly, but separately, we analyzed the dataset of age- and gender-dependent mortality

158   data. The term Y_{sat}^k represents the outcome (i.e., the nationwide mortality) of age a and gender s

159   in year t against the mortality of control group k. We used the expected mortality value

160   calculated as

$$E(Y_{sat}^k) = \alpha_{0,sa} + \alpha_{1,sa}(t - t_0) + \beta_{sa}(t - t_v)\left(T_g^k P_t\right) + \gamma_{sa} T_g^k + \delta_{sa} P_t, \quad (4)$$

162   to predict the pneumonia mortality and also the mortality of a control disease, where t_0, t_v, and

163   dummy variables T_g^k and P_t are the same as in equation (1). The difference between model (4)

164   and model (1) is that the parameters, α_0, α_1, β, γ, and δ are all dealt with as a function of age a

165   and gender s for control disease group k in model (4).

166   **Statistical analysis**

167   For each control disease, i.e., malignant neoplasm and heart disease, we separately

168   estimated the causal effect of pneumococcal vaccination β on pneumonia mortality for both

169   models (1) and (4). As part of sensitivity analysis, an additional analysis was conducted using the

170   COPD as a control disease, and we confirmed that the causal impact of pneumococcal

171 vaccination on pneumonia mortality among elderly would be maintained. The tenth revision of

172 the International Classification of Diseases (ICD-10) began to be strictly enforced in January

173 2017 with respect to the rule to specify the underlying cause of death (rather than identifying the

174 resulting pathophysiological process as the cause of death) (Ministry of Health, Labour and

175 Welfare, 2018a), and thus, the time-dependent decline in pneumonia mortality may potentially

176 be explained by this change. To avoid misattributing that overlapping effect, we estimated the

177 causal effect of vaccination by analyzing the mortality both with and without the 2017 data. The

178 non-linear least sum of squares method was employed to fit models (1) and (4) to the

179 corresponding data from 2003–2017. The 95% confidence intervals (CI) of parameters were

180 computed by the profile likelihood method. All statistical data were analyzed using JMP version

181 12.0.1 statistical software (SAS Institute Inc., Cary, NC, USA).

182 **Ethical considerations**

183 The present study analyzed data that is publicly available (Ministry of Health, Labour and

184 Welfare, 2018a). As such, the datasets used in our study were de-identified and fully anonymized

185 in advance, and the analysis of publicly available data without identity information does not

186 require ethical approval.

187 # Results

188 Table 1 shows the summary statistics of mortality for three causes of death, i.e., pneumonia,

189 malignant neoplasm and heart disease. All of them showed increasing trend with age. The gap of

190 mortality by age was greatest for pneumonia, e.g. while the pneumonia mortality among those

191 aged 65-69 years were 43 and 11 per 100,000 for male and female, respectively, these figures

192 among people aged 90 years and older were 2,883 and 1,438 per 100,000, respectively. We have

193   compared correlations of mortality between pneumonia and control disease (i.e. malignant

194   neoplasm or heart disease) by age group and gender (see Online Supplementary Table 1).

195   Comparing those correlations from 2003-13 and from 2014-17, we found that the parallel trend

196   between pneumonia and control disease was maintained better prior to 2013, and subsequently

197   the correlations were mostly diminished. During the latter part of the time period, the pneumonia

198   mortality data were probably affected by vaccination.

199   The estimated risk reductions of pneumonia mortality attributable to pneumococcal

200   vaccination, using the mortality of malignant neoplasm or heart disease as the control, are shown

201   in Figure 2. In all analyses, the upper 95% CI values were less than 0, and a time-dependent

202   increase in the causal reduction effect of pneumococcal vaccination on pneumonia mortality was

203   observed. Table 2 shows estimates of the causal parameter β which indicates the yearly reduction

204   rate of pneumonia mortality that can be attributed to pneumococcal vaccination (see Online

205   Supplementary Table 2 for other parameters). When the 2017 data were included, the analysis

206   with malignant neoplasm or heart disease as a control indicated that the reduced pneumonia

207   mortality in 2017 was as large as 41.9 (33.2, 50.6) or 31.2 (23.8, 38.6) per 100,000 individuals,

208   respectively. When the 2017 data were excluded from the analyses, these mortality reductions

209   did not deviate significantly and were estimated at 34.6 (22.0, 47.1) or 19.0 (8.3, 29.6) per

210   100,000 when malignant neoplasm or heart disease, respectively, was used as the control.

211   Comparisons of the expected and observed mortality values are shown in Figure 3, and

212   parameter estimates of the causal model are shown as Table 3. The observed values are

213   expressed as the distribution of mortality in the 47 prefectures (see Online Supplementary Table

214   3 for the observed values of the entire Japan). Both control diseases had a pattern of monotonic

215   increase in the mortality over time for both the expected and observed mortality; they shared this

216 increasing trend with pneumonia mortality through 2013. However, an abrupt decline in the

217 pneumonia mortality was observed beginning in 2013. This phenomenon was also captured by

218 the simple DID model described above; together, they support the causal effect of pneumococcal

219 vaccination on the decline in pneumonia mortality.

220   The estimated causal effects of pneumococcal vaccination in reducing age- and gender-

221 specific pneumonia mortality, using malignant neoplasm and heart disease as the control group

222 based on analyses with and without the 2017 data, are shown in Figure 4. We did not identify

223 statistically significant reductions in the pneumonia mortality among those aged from 65 to 79

224 years for either males or females in any of our analyses. In the older age groups, vaccine-induced

225 reductions in the pneumonia mortality were seen, and the estimated effect size grew with the

226 subject age, especially among men. In the analyses that included the 2017 data and used

227 malignant neoplasm or heart disease as the control, the pneumonia mortality in elderly males

228 aged ≥90 years was reduced every year from 2014 by 357.4 (95% CI: 314.0, 400.7) or 276.3

229 (95% CI: 237.3, 315.2) per 100,000 individuals, respectively, as a function of time since

230 vaccination effect. Similarly, the yearly reduction in pneumonia mortality among females was

231 estimated at 185.5 (95% CI: 156.2, 214.9) or 105.2 (95% CI: 70.2, 140.3) per 100,000

232 individuals when malignant neoplasm or heart disease, respectively, were used as the control.

233   There was a good overall level of agreement between the observed and expected

234 mortality data with respect to age and gender for pneumonia (Fig. 5A, B, E, and F) and the

235 control causes of death (Fig. 5C, D, G, and H). In different age and gender groups, a different

236 linear trend of mortality was shared between pneumonia and each control disease beginning in

237 2013, after which a clear decline in pneumonia mortality was identifiable, especially among

238 those aged ≥90 years.

239   As part of sensitivity analysis, Table 4 examines the causal effect when 2014 was used,

240   rather than 2013, as the year of change point, considering that the completion of vaccination

241   among elderly is 2014, while that of children was 2013. The yearly reduction rate in pneumonia

242   mortality was estimated to be greater for this model, compared with 2013 model. Causal

243   parameter estimates in the 2014 model were greater than those of 2013 model, because

244   substantial number of elderly started to be vaccinated within 2013 and corresponding herd

245   immunity effect was perhaps captured by the 2014 model.

246   The mortality of COPD was used as the control as part of sensitivity analysis. As was

247   also the case for malignant neoplasm and heart disease, the overall parallel trend between COPD

248   and pneumonia mortality prior to vaccination, and an assumed causal impact of vaccination on

249   mortality were reflected in the prediction using model (1) and qualitatively captured the observed

250   patterns for the entire Japan (see Online Supplementary Figure 1). The maximum likelihood

251   estimate of causal parameter remained to be negative (Online Supplementary Table 4), i.e. -2

252   (95% CI: -5, 1), not much deviated from the results using other control diseases (Table 3).

253 Discussion

254   The present study estimated the causal effect of pneumococcal vaccination on pneumonia

255   mortality among the elderly in Japan. A DID study design, which is a quasi-experimental

256   epidemiological research design, was employed, using the time-dependent mortality of malignant

257   neoplasm and heart disease as the control groups because these causes of death demonstrated a

258   monotonic increase induced by population aging and shared this trend with pneumonia mortality

259   at least through 2013. The subsequent abrupt decline in pneumonia mortality was captured

260   through the analysis of prefectural data as well as of age- and gender-specific nationwide data.

261   Overall, the pneumonia mortality in 2017 was considered to have been reduced by 20–40 per

262   100,000 individuals owing to pneumococcal vaccination, with the largest causal effect occurring

263   among the oldest group, aged ≥90 years. To our knowledge, the present study is the first to have

264   assessed the combined causal impact of two pneumococcal vaccination programs, i.e., PCV13

265   among children and PPV23 among the elderly, in reducing pneumonia mortality in the elderly as

266   evaluated at the population level. The vaccination coverage of PCV13 among children has

267   achieved over 95%, while that among elderly with PPV23 has remained less than 50%, implying

268   that the large population impact may be represented by herd immunity due to PCV13.

269   It is remarkable that an explicit mortality reduction was identified by this quasi-

270   experimental study design. Our analyses revealed that larger causal impacts of pneumococcal

271   vaccination on pneumonia mortality were observed in the more recent years. Although this

272   causal impact was not clearly identified among elderly individuals aged from 65–79 years, a

273   clear impact was seen for people in their 80s and 90s. The question of whether PPV23

274   administration results in a visible causal impact among elderly people has been controversial:

275   while protection against invasive pneumococcal disease was identified (Cadeddu et al., 2012)

276   and a certain protection against pneumococcal pneumonia was reported (Chidiac and Ader,

277   2009; Falkenhorst et al., 2017), the effectiveness of PPV23 was smaller than that of PCV13

278   (Baldo et al., 2016) and sometimes was only minimal (Johnstone et al., 2010). However, the

279   indirect effect of PCV13 vaccination in infants and children on outcomes in adults and the

280   elderly has been reported (Simonsen et al., 2014; Regev-Yochay et al., 2017; Tsaban and Ben-

281   Shimol, 2017); this practice of pediatric vaccination clearly provides a herd immunity effect

282   among the elderly (Haber et al., 2007; Simonsen et al., 2011). Although our study endorses those

283   findings in other countries including North America, because of the population-based design of

284   this work, we were not able to disentangle the causal effects attributed to the two vaccines.

285   Considering limited coverage of PPV23 and high coverage of PCV13, it is likely that the

286   observed reduction in pneumonia mortality among elderly can be attributed to herd immunity

287   impact by PCV13. In fact, looking at the most vulnerable group aged 90 years and older (Figure

288   5A), the decline in pneumonia mortality has started to take place since subsidy among infants

289   from 2011, and the gradual decline afterwards is consistent with the gradual increase in

290   vaccinated children with PCV7 or PCV13. On the other hand, we do not identify visible impact

291   of PPV23 introduction from 2013. However, due to similar timing of introduction for both

292   vaccines, the observed effect can be still be partially attributed to not only PCV13 but also

293   PPV23, and the present study was not able to purify the unique effect of PCV13 alone from the

294   mixed population impact of PCV13 and PPV23.

295   On the basis of the nature of this study's DID design, other plausible explanations for the

296   time-dependent decline in pneumonia mortality were mostly excluded. Although the DID design

297   required the assumption of proportional trends among the pneumonia, malignant neoplasm, and

298   heart disease mortalities, the reasonable fits produced by these data justified the use of these

299   control diseases. Furthermore, the monotonic time-dependent increase was mechanistically

300   explainable based on progressive population aging. Because the 2017 data could have been

301   impacted by ICD-10's rule to identify the underlying cause of death, we conducted analyses both

302   with and without the 2017 data, but the overall qualitative patterns of our findings were not

303   altered by the exclusion. This finding supports our conclusion that the abrupt decline in

304   pneumonia mortality in 2017 is not fully explained by the ICD-10 change.

305   In Japan, the number of individuals who "died of old age" (i.e., natural death from an

306   ailment associated with aging) has steadily increased. It is possible that the category "died of old

307   age" absorbed the apparent reduction in pneumonia deaths in recent years. However, that

308   possibility leaves the question of why only pneumonia deaths, not those due to neoplasm or heart

309   disease, were selectively miscategorized. Our use of malignant neoplasm and heart disease as

310   controls in the DID design helped to eliminate several concerns that the recent reductions in

311   pneumonia mortality could be attributed to causes other than the two pneumococcal vaccination

312   programs.

313   The present study using mortality as the outcome succeeded in demonstrating that even

314   this type of quasi-experimental study can offer a vivid effect size estimate of pneumococcal

315   vaccination programs at the population level. To truly estimate the individual-based causal effect

316   of vaccination, it is critical to conduct a prospective study. Such a study should ideally control

317   the exposure (i.e., frequency of contact) to children, so that the indirect effect of PCV13

318   vaccination may be separated from the direct benefit of PPV23 vaccination.

319   Five limitations of this study should be noted. First, control groups other than malignant

320   neoplasm and heart disease deaths were not explored. It is possible that a more monotonically

321   increasing control (e.g., mortality following bone fracture) could be conceived and compared

322   against pneumonia mortality; however, we had access to only major causes of death by

323   prefecture and by age and gender. Second, the cause of death category of pneumonia includes

324   not only community-acquired pneumonia but also hospital-acquired infections and aspiration

325   pneumonia. The observed reduction in pneumonia mortality was not verified to have been caused

326   by a specific reduction in mortality from pneumococcal pneumonia, and moreover, possible

327   improvement in prognosis could have been absorbed as our causal effect of vaccination.

328   Nevertheless, even provided that we explored more detailed etiology of pneumonia, the time

329   trend might not be easily explainable. Third, the effectiveness estimate may be quantitatively

330   associated with the vaccination coverage both in children and the elderly; thus, variations in the

331   causal impact by prefecture could possibly be explained by differences in vaccination coverage.

332   Unfortunately, we were not able to conduct an analysis of this possibility owing to limitations

333   with our data. Fourth, PCV7 vaccination was introduced as voluntary vaccination in 2010, and

334   the subsidy-based program started in 2011 at the municipal level; either or both could have

335   affected the pneumonia mortality. However, coverage with the PCV7 vaccination remained very

336   low in 2014. Similarly, the overall vaccination coverage from the subsidy-based program

337   remained very low, not even reaching a few percent. Only in and after 2014 was the

338   pneumococcal vaccination coverage of both children and the elderly elevated to substantial

339   levels. Fifth, we did not have an access to the temporal datasets of invasive pneumococcal

340   disease (IPD) among children over time. It is fruitful to estimate the causal impact of

341   pneumococcal vaccination among children, looking into the corresponding data of IPD.

342   To confirm our findings, a precise estimation of the causal effect of pneumococcal

343   vaccination among the elderly must be determined by conducting a study with a prospective

344   design. Nevertheless, by using only the available census-based observational data, we showed

345   that a DID design can be exploited to examine the population impact of pneumococcal

346   vaccination on pneumonia mortality among the elderly. We believe that our approach will shed

347   light on the assessment of the combined effectiveness of pneumococcal vaccinations in Japan.

348   Conclusions

349   The present study employed a DID design using the time-dependent mortality of malignant

350   neoplasm and heart disease as control groups to estimate the causal effect of pneumococcal

351   vaccination on pneumonia mortality among the elderly in Japan. From 2014, an abrupt decline in

352   pneumonia mortality was seen; specifically, the mortality was reduced by 20–40 per 100,000

353 individuals because of pneumococcal vaccination, with the largest causal effect among the oldest

354 group aged 90 years and older.

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427 Figure legends

428 **Figure 1. Mortality trends of major causes of death in Japan, 1947–2017.**

429 A) Long-term mortality trends for the four leading causes of death in Japan, i.e., malignant

430 neoplasm, heart disease, cerebrovascular disease, and pneumonia, are shown along with the long-

431 term trend for tuberculosis mortality, which has substantially decreased since 1947. B) Enlarged

432 view of recent mortality trends for three major causes of death, i.e., malignant neoplasm, heart

433 disease, and pneumonia, that mostly maintain a parallel monotonic increasing trend. In 2009, the

434 subsidized immunization with pneumococcal conjugate vaccine (PCV) was initiated in a limited

435 number of municipalities. In 2014, routine immunization with PCV began, targeting those who

436 newly reached 65, 70, 75, 80, 85, 90, 95, or 100 years of age in the corresponding year from

437 2014–2018. The routine pneumococcal immunization of children started in 2013.

438 **Figure 2. Causal effect of the pneumococcal vaccine as estimated from prefectural**

439 **mortality data.**

440 A–D) The causal effect of the pneumococcal vaccine based on an analysis including (A–B) or

441 excluding (C–D) the 2017 data and using malignant neoplasm (A, C) or heart disease (B, D) as

442 the control. The vertical axis measures the causal effect that is calculated by β (Year−2013)

443 described from equation (1), where β is the yearly reduction in the pneumonia mortality per

444 100,000 individuals. The solid line shows the estimated causal effect, while the dashed and dash-

445 dotted lines show the 95% upper and lower confidence intervals, respectively.

446 **Figure 3. Comparison of observed and predicted mortality from the analysis of**

447 **prefectural data.**

448 A–B) Mortality calculated using malignant neoplasm (A) or heart disease (B) as the control

449 group. Grey circles represent the predicted mortality of malignant neoplasm (A) or heart disease

450 (B), squares show the median of malignant neoplasm (A) or heart disease (B) mortality among

451 the 47 prefectures, and error bars indicate the minimum and maximum values. The vertical axis

452 represents the mortality per 100,000 individuals. Black circles represent the predicted pneumonia

453 mortality, triangles show the median of pneumonia mortality among the 47 prefectures, and error

454 bars indicate the minimum and maximum values. The arrow indicates the year 2013 in which

455 routine immunization started among elderly.

456 **Figure 4. Age- and gender-specific causal effect of pneumococcal vaccination.**

457 A–D) The age- and gender-specific causal effect of the pneumococcal vaccine based on an

458 analysis including (A–B) or excluding (C–D) the 2017 data and using malignant neoplasm (A,

459 C) or heart disease (B, D) as the control. The causal effect in decreasing pneumonia mortality is

460 marked as a dashed line, and the 95% confidence intervals of the causal effect are presented

461 using error bars.

462 **Figure 5. Comparison of observed and predicted age- and gender-specific mortality.**

463 A–B) Age-stratified pneumonia mortality in males (A) or females (B), using malignant neoplasm

464 as the control for calculating predicted mortality. Each line represents the modelled (predicted)

465   mortality. Each sign represents the observed mortality data. Since 2014, the year routine

466   immunization was introduced, the observed pneumonia mortality shows a decreasing trend. C–

467   D) Malignant neoplasm mortality by age in males (C) and females (D). E–F) Age-stratified

468   pneumonia mortality in males (E) or females (F), using heart disease as the control for

469   calculating predicted mortality. G–H) Heart disease mortality by age in males (G) or females

470   (H).

471

472   **Supplementary Figure S1. Comparison of observed and predicted mortality of**

473   **pneumonia and chronic obstructive pulmonary disease (COPD) from 2003-2017, Japan.**

474   Predicted mortality for the entire Japan was calculated, using the COPD mortality as the control

475   group. The vertical axis represents the mortality per 100,000 individuals. Each line represents the

476   predicted mortality, while each mark represents the observed data.

477

478 **Tables**

479 **Table 1. Summary statistics of mortality by cause of death, gender and age**

Disease	Gender	Age (years)	With 2017			Without 2017		
			Min	Average	Max	Min	Average	Max
malignant neoplasm	male	65-69	618	680	768	622	685	768
malignant neoplasm	male	70-74	926	1036	1217	946	1044	1217
malignant neoplasm	male	75-79	1292	1519	1695	1307	1535	1695
malignant neoplasm	male	80-84	1925	2141	2242	1953	2157	2242
malignant neoplasm	male	85-89	2723	2834	2933	2784	2842	2933
malignant neoplasm	male	90 & over	3309	3431	3603	3309	3430	3603
malignant neoplasm	female	65-69	286	297	315	286	297	315
malignant neoplasm	female	70-74	388	421	458	395	424	458
malignant neoplasm	female	75-79	546	613	659	567	618	659
malignant neoplasm	female	80-84	842	906	965	863	910	965
malignant neoplasm	female	85-89	1217	1297	1387	1237	1303	1387
malignant neoplasm	female	90 & over	1648	1691	1752	1648	1692	1752
heart disease	male	65-69	168	190	217	168	191	217
heart disease	male	70-74	253	297	357	259	300	357
heart disease	male	75-79	425	518	612	425	524	612
heart disease	male	80-84	814	964	1083	822	975	1083
heart disease	male	85-89	1623	1823	2082	1623	1837	2082
heart disease	male	90 & over	3407	3664	3935	3407	3677	3935
heart disease	female	65-69	53	69	83	53	677	83
heart disease	female	70-74	100	1374	172	108	136	172
heart disease	female	75-79	2185	287	356	225	292	356
heart disease	female	80-84	508	640	759	514	649	759
heart disease	female	85-89	1167	1396	1624	1167	1411	1624
heart disease	female	90 & over	3071	3317	3533	3071	3333	3533
pneumonia	male	65-69	43	63	72	57	65	72
pneumonia	male	70-74	93	147	175	130	151	175
pneumonia	male	75-79	211	357	431	285	367	431
pneumonia	male	80-84	521	850	991	692	873	991
pneumonia	male	85-89	1231	1870	2199	1577	1916	2199
pneumonia	male	90 & over	2883	4147	4764	3421	4237	4764
pneumonia	female	65-69	11	19	23	16	19	23
pneumonia	female	70-74	24	46	58	39	47	58
pneumonia	female	75-79	67	120	149	94	123	149
pneumonia	female	80-84	187	320	389	252	330	389
pneumonia	female	85-89	490	805	978	630	828	978
pneumonia	female	90 & over	1438	2176	2531	1744	2229	2531

480 Mortality per 100,000 individuals is shown. Minimum and maximum refer to the largest and smallest yearly
481 mortality values from the year 2003 up to 2016 or 2017.

482

483   **Table 2. Estimates of the age-dependent causal effect parameter of pneumococcal**

484   **vaccination by age group and gender in Japan**

Age (years)	With 2017 data				Without 2017 data			
	malignant neoplasm		heart disease		malignant neoplasm		heart disease	
	Male	Female	Male	Female	Male	Female	Male	Female
65-69	16 (-28, 59)	1 (-19, 21)	2 (-37, 41)	3 (-22, 27)	22 (-42, 86)	3 (-27, 32)	6 (-50, 63)	5 (-30, 40)
70-74	23 (-20, 67)	5 (-15, 24)	2 (-37, 41)	5 (-19, 30)	34 (-30, 98)	8 (-22, 37)	9 (-47, 66)	9 (-26, 44)
75-79	33 (-11, 75)	3 (-16, 23)	-9 (-48, 30)	8 (-16, 33)	53 (-11, 117)	8 (-21, 37)	4 (-53, 60)	16 (-19, 51)
80-84	-31 (-74, 12)	-18 (-38, 2)	-42 (-81, -3)	7 (-18, 31)	-8 (-72, 56)	-11 (-41, 18)	-20 (-76, 36)	21 (-14, 56)
85-89	-143 (-186, -99)	-60 (-80, -40)	-98 (-137, -59)	-12 (-37, 12)	-116 (-180, -52)	-49 (-79, -20)	-52 (-108, 4)	12 (-23, 47)
90 & over	-357 (-401, -314)	-199 (-218, -179)	-276 (-315, -237)	-137 (-162, -113)	-339 (-403, -275)	-186 (-215, -156)	-226 (-282, -170)	-105 (-140, -70)

485

486   Figures should be interpreted as the yearly rate of reduction in pneumonia mortality per 100,000

487   individuals. Malignant neoplasm and heart disease were used as control groups. Upper and lower

488   95% confidence intervals, derived from profile likelihood, are shown in parenthesis.

489

490 **Table 3. Estimates of the regression parameters for the causal effect model of**

491 **pneumococcal vaccination applied to prefectural data in Japan**

	With 2017 data		Without 2017 data	
	malignant neoplasm	heart disease	malignant neoplasm	heart disease
α_0	267 (264, 271)	141 (138, 144)	268 (264, 271)	142 (138, 145)
α_1	4 (3, 4)	3 (3, 4)	4 (3, 4)	3 (3, 4)
β	-10 (-13, -8)	-8 (-10, -6)	-9 (-12, -6)	-5 (-7, -2)
γ	-187 (-190, -183)	-58 (-61, -55)	-187 (-191, -184)	-59 (-62, -56)
δ	1 (-5, 6)	-5 (-9, 0)	-0 (-6, 6)	-7 (-12, -1)

492

493 Figures should be interpreted as the yearly rate of reduction in pneumonia mortality per 100,000

494 individuals. Malignant neoplasm and heart disease were used as control groups. Upper and lower

495 95% confidence intervals, derived from profile likelihood, are shown in parenthesis.

496

497 **Table 4. Estimates of the causal effect of pneumococcal vaccination on pneumonia death**

498 **by age group and gender.**

Age (years)	With 2017 data				Without 2017 data			
	malignant neoplasm		heart disease		malignant neoplasm		heart disease	
	Male	Female	Male	Female	Male	Female	Male	Female
65-69	20 (-52, 92)	1 (-32, 34)	2 (-64, 68)	3 (-38, 44)	34 (-90, 158)	4 (-53, 62)	9 (-104, 123)	7 (-63, 77)
70-74	24 (-48, 96)	4 (-29, 37)	0 (-66, 67)	6 (-35, 47)	41 (-83, 165)	8 (-49, 66)	13 (-101, 126)	12 (-58, 82)
75-79	42 (-30, 114)	5 (-29, 38)	-13 (-79, 53)	11 (-30, 52)	84 (-40, 208)	13 (-45, 70)	8 (-106, 121)	24 (-46, 94)
80-84	-38 (-110, 34)	-25 (-58, 8)	-57 (-124, 9)	8 (-33, 49)	0 (-124, 124)	-15 (-73, 42)	-23 (-137, 90)	33 (-37, 103)
85-89	-195 (-267, -123)	-84 (-118, -51)	-140 (-206, -73)	-18 (-59, 23)	-167 (-291 -43)	-74 (-133, -17)	-73 (-186, 41)	24 (-46, 94)
90 & over	-491 (-563, -419)	-275 (-308, -242)	-376 (-442, -310)	-183 (-224, -142)	-510 (-634, -386)	-283 (-340, -226)	-322 (-436, -209)	-146 (-216, -76)
Prefecture	2 (-4, 8)		-3 (-8, 2)		1 (-5, 8)		-6 (-11, 0)	

499

500 Figures should be interpreted as the yearly rate of reduction in pneumonia mortality per 100,000

501 individuals. Malignant neoplasm and heart disease were used as control groups. Except for the

502 last row, age-dependent model results are shown, while the last row give estimates from

503 prefecture-dependent model. Upper and lower 95% confidence intervals, derived from profile

504 likelihood, are shown in parenthesis.

Figure 1. Mortality trends of major causes of death in Japan, 1947–2017.

A) Long-term mortality trends for the four leading causes of death in Japan, i.e., malignant neoplasm, heart disease, cerebrovascular disease, and pneumonia, are shown along with the long-term trend for tuberculosis mortality, which has substantially decreased since 1947. B) Enlarged view of recent mortality trends for three major causes of death, i.e., malignant neoplasm, heart disease, and pneumonia, that mostly maintain a parallel monotonic increasing trend. In 2009, the subsidized immunization with pneumococcal conjugate vaccine (PCV) was initiated in a limited number of municipalities. In 2014, routine immunization with PCV began, targeting those who newly reached 65, 70, 75, 80, 85, 90, 95, or 100 years of age in the corresponding year from 2014–2018. The routine pneumococcal immunization of children started in 2013.

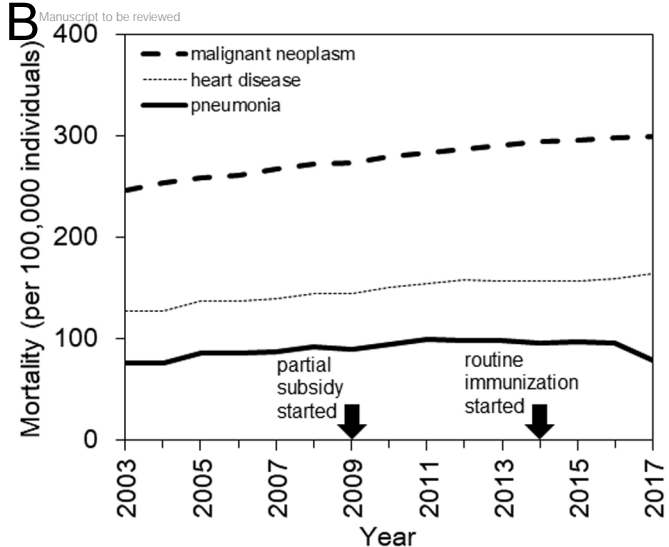
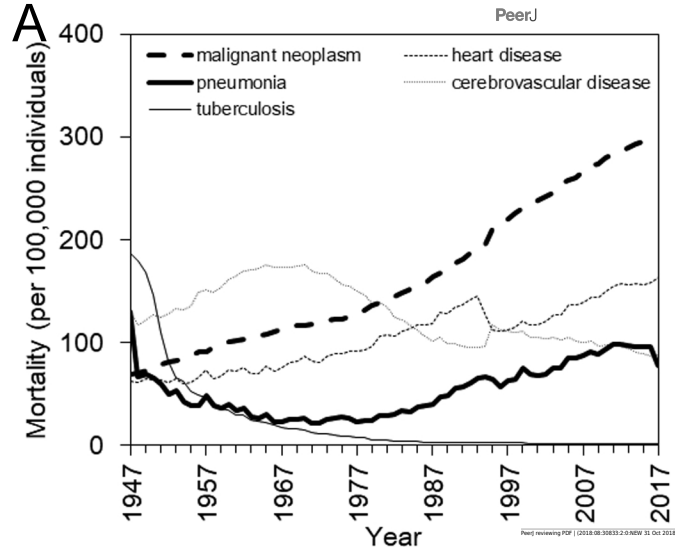
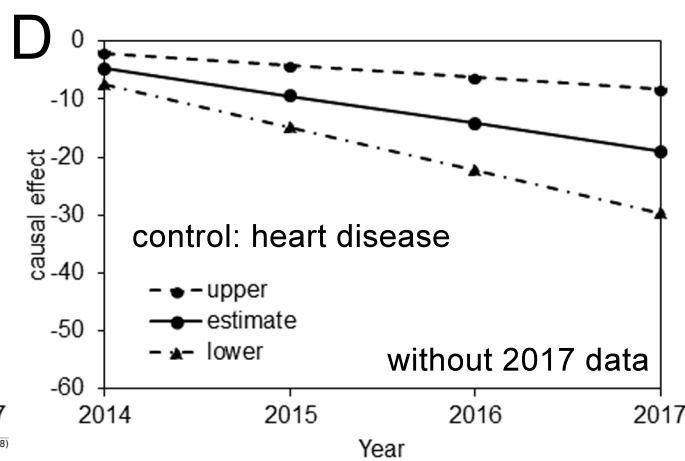
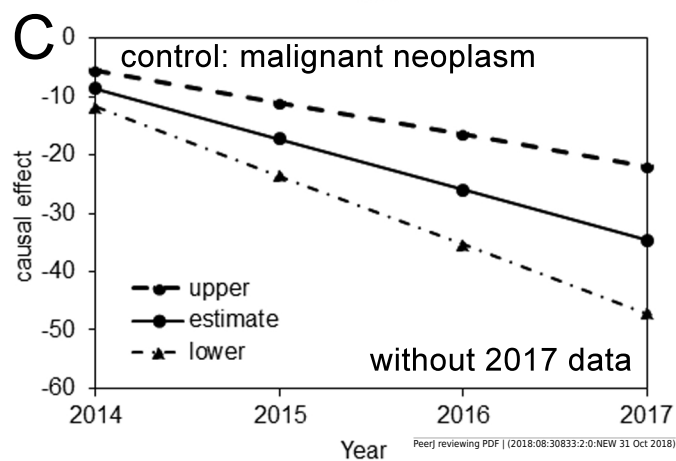
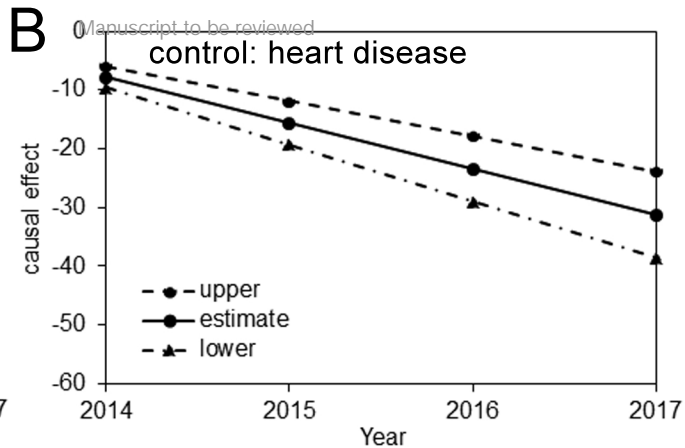
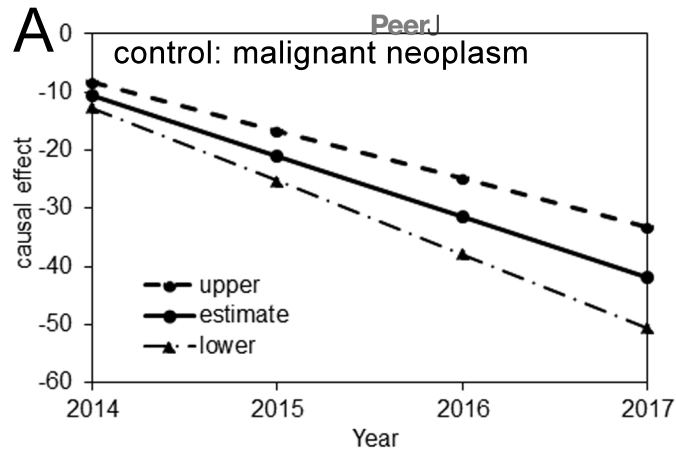



Figure 2. Causal effect of the pneumococcal vaccine as estimated from prefectural mortality data.

A–D) The causal effect of the pneumococcal vaccine based on an analysis including (A–B) or excluding (C–D) the 2017 data and using malignant neoplasm (A, C) or heart disease (B, D) as the control. The vertical axis measures the causal effect that is calculated by β (Year−2013) described from equation (1), where β is the yearly reduction in the pneumonia mortality per 100,000 individuals. The solid line shows the estimated causal effect, while the dashed and dash-dotted lines show the 95% upper and lower confidence intervals, respectively.

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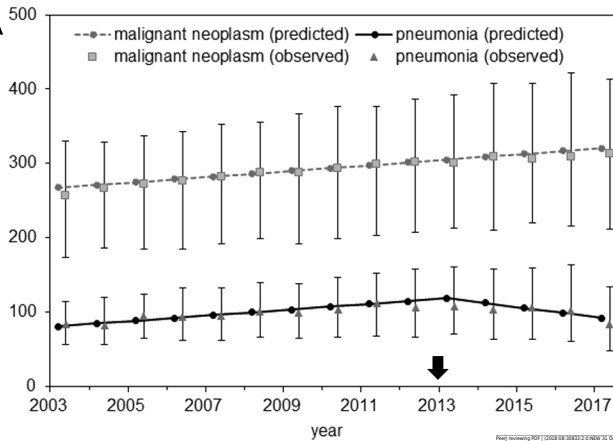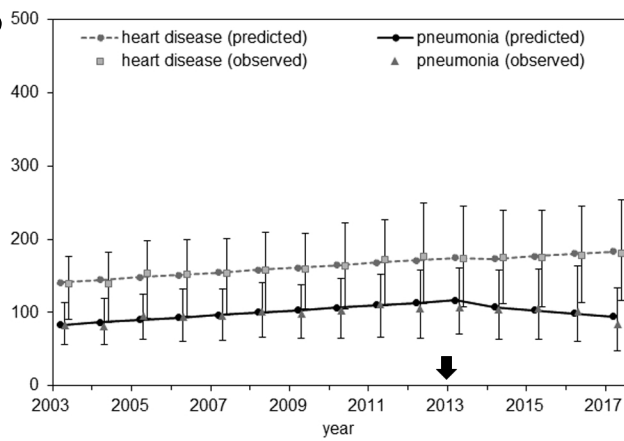
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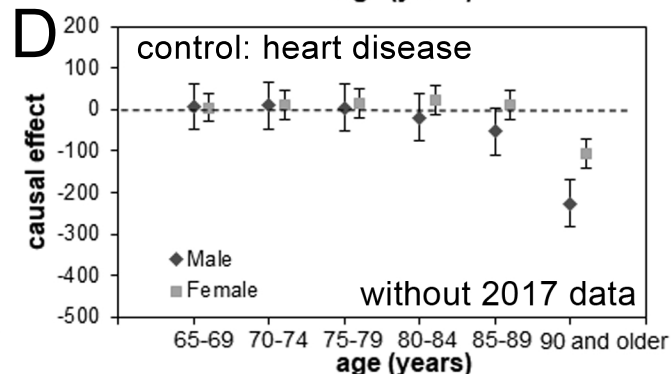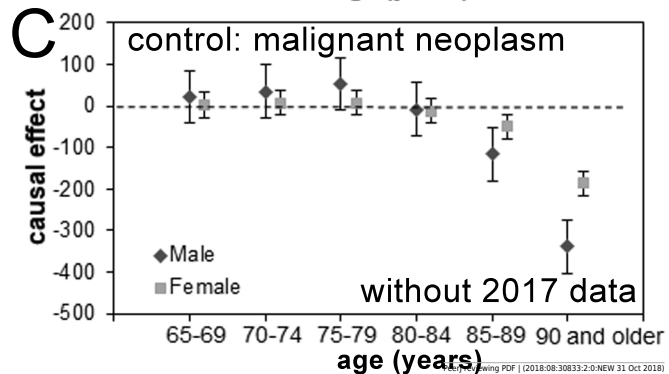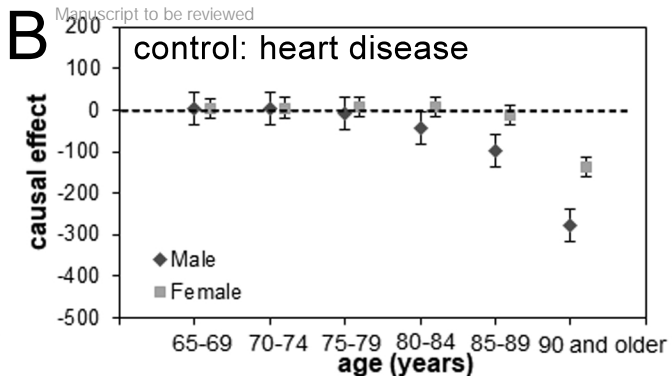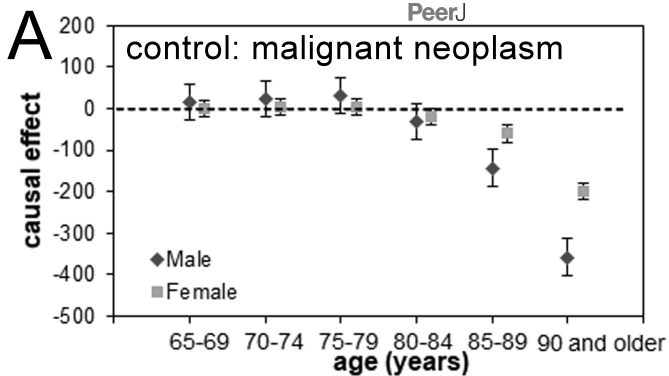
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A–B) Age-stratified pneumonia mortality in males (A) or females (B), using malignant neoplasm as the control for calculating predicted mortality. Each line represents the modelled (predicted) mortality. Each sign represents the observed mortality data. Since 2014, the year routine immunization was introduced, the observed pneumonia mortality shows a decreasing trend. C–D) Malignant neoplasm mortality by age in males (C) and females (D). E–F) Age-stratified pneumonia mortality in males (E) or females (F), using heart disease as the control for calculating predicted mortality. G–H) Heart disease mortality by age in males (G) or females (H).