**RESEARCH**

# Bronchitis, COPD, and pneumonia after viral endemic of patients with leprosy on Sorok Island in South Korea

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## Abstract

Viral respiratory diseases (VRDs) cause lung inflammation and inflammatory cytokine production. We study whether dapsone is responsible for its observed preventive treatment effects of the sustained viral RNA interferon response. Around 2008 and 2012, Korea's Dementia Management Act stipulated drastic changes in the administration of dementia medication by medical staff. Participants were randomized and we compared leprosy patients with VRDs after prescribing dapsone as a standard treatment from 2005 to 2019. Significance was evaluated based on the dapsone-prescribed (+) subgroup and the dapsone-unprescribed (−) subgroup of the VRD diagnosed (+) and VRD undiagnosed (−) subgroup. We analyzed VRD (+)/(− with dapsone (+)/(−) group and used a T-test, and designed the equation of acetylation with dapsone and acetylcholine (AA) equation. The 6394 VRD participants who received the dapsone intervention compared to the 3255 VRD participants in the control group demonstrated at T2 VRD (+) dapsone (−) (mean ($M$) = 224.80, SD = 97.50): T3 VRD (−) dapsone (+) ($M$ = 110.87, SD = 103.80), proving that VRD is low when dapsone is taken and high when it is not taken. The $t$ value is 3.10, and the $p$ value is 0.004395 (significant at $p < 0.05$). After an increase in VRDs peaked in 2009, bronchitis, COPD, and pneumonia surged in 2013. The AA equation was strongly negatively correlated with the prevalence of bronchitis and chronic obstructive pulmonary disease (COPD): with bronchitis, $r(15) = −0.823189$, $p = 0.005519$, and with COPD, $r(15) = −0.8161$, $p = 0.000207$ (significant at $p < 0.05$). Dapsone treated both bronchitis and COPD. This study provides theoretical clinical data to limit acetylcholine excess during the VRD pandemic for bronchitis, COPD, and pneumonia.

## Introduction

Complete blinded randomized controlled trial (RCT) study

Highlights

After an increase in viral respiratory diseases (VRDs) peaked in 2009, bronchitis, COPD, and pneumonia surged in 2013. Dapsone prescribed group has a lower prevalence of VRDs. The acetylation-acetylcholine (AA) equation, │Sum of dapsone prescribed group − the sum of increased acetylcholine group│, was strongly correlated with the prevalence of bronchitis and COPD, not bacteria origin pneumonia. We rediscovered in humans that type 1 interferon production reduced inhibitory M2 muscarinic receptor function and gene expression in cultured airway parasympathetic neurons by VRDs. Acetylcholine excess appears to inhibit acetylcholine receptors for interferon production against virus invasion.

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Sorok Island was established in May 1916 to quarantine leprosy patients. The public health report filed on June 4, 1946, increased the capacity of Sorokdo Leper Colony to between 8000 and 9000, making it the largest leprosarium in the world (Kim 2012; Jane 2010). Sister M. Stoeger and Sister M. Pissarek cared for the patients from 1962 to 2005 (Anthony 2019).

The antibiotic dapsone (4,4′-diaminodiphenyl sulfone, DDS) is predominantly associated with treating leprosy and is both an antibiotic and ANTI-inflammatory agent (Wolf et al. 2002). Dapsone has been used for leprosy, malaria, toxoplasmosis, and *Pneumocystis* pneumonia in persons with human immunodeficiency virus infection. Moreover, dapsone is prescribed for dermatitis herpetiformis, linear IgA dermatosis, bullous pemphigoid, subcorneal pustular dermatosis, erythema elevatum diutinum, bullous systemic lupus erythematosus, and other chronic inflammatory

diseases characterized by the infiltration of neutrophils or eosinophils (Wozel 2010).

Acetylation of dapsone showed genetic polymorphism and reproducible individual characteristics. Acetylation of dapsone and deacetylation of monoacetyl dapsone occurred concurrently, and plasma ratios of acetylated to parent drug were attained constantly but characteristic for the individual (Gelber et al. 1971). Acetylation of aspirin inhibits cyclic GMP–AMP synthase (cGAS)-mediated interferon production, and cGAS acetylation on Lys384, Lys394, or Lys414 contributes to keeping cGAS inactive (Dai et al. 2019). The gut microbiota drives systemic antiviral immunity of type I interferon (IFN-I) priming. DNA-containing membrane vesicles from the gut microbiota were found in circulation. They promoted the clearance of both herpes simplex virus type 1 of DNA virus and vesicular stomatitis virus of RNA virus in a GAS-STING-IFN-I axis (Erttmann et al. 2022).

We investigated Hansen's disease (HD) patients with dapsone following the Dementia Management Act (DMA), enacted in 2011, in Sorokdo National Hospital. We analyzed the medical records of Sorokdo National Hospital from 2005 to 2020. We compared the incidence of viral respiratory diseases (VRDs) with dapsone prescriptions for persistent lung inflammation, inflammatory cytokine production, viral RNA, and sustained IFN response; indeed, these responses are recapitulated and contribute to the pathology of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.

## Methods

### Study design

Medical data on the correlation between DDS and respiratory diseases were then analyzed by the International Classification of Diseases (ICD) codes of VRDs. There was no significant change and no statistical correlation (Lee et al. 2020a). However, in the study of the dapsone effect in antihistamine refractory chronic idiopathic urticaria, VRDs occurred in only three patients in the placebo group (Morgan et al. 2014). A higher dose of dapsone was required when the patient developed a tracheal infection, but the patient had no similar VRDs (Zheng et al. 2021). We correlated dapsone to compete with the NLRP3 inflammasome (Lee et al. 2020a). As NLRP3 plays a critical role in viral immunopathology (Malinczak et al. 2021), we analyzed the relationship between bacterial respiratory diseases (RDs) and VRDs (Fig. S1).

HD patients took dapsone for their lives but did not take dementia symptom improvement drugs. We included a control cohort from February 1962 to November 21, 2005 (Lee 2022b). Around 2008 and 2012, Korea's Dementia Management Act (DMA) stipulated drastic changes in the administration of dementia medication by medical staff (Lee

et al. 2022). It facilitated the EDI code-based cohort studies, randomized the cohort at a complete-blinded state, and made the RCT study provide causality (Lee et al. 2022).

DMA separated the dapsone-prescribing (+) group from the dapsone non-prescribing (−) group. Psychiatrists prescribed AAD instead of dapsone to treat mild cognitive impairment (MCI) or Alzheimer's disease (AD). We connected the EMR database of the Sorokdo National Hospital, archived from January 2005 to June 2019, and searched the ICD-10 codes of RDs with dapsone. This cohort study is the second to be validated by RCT methodology because the intervention was performed for dementia treatment.

### Population demography

HD patients would spend their whole lives on Sorok Island. According to the request for disclosure of health checkup information from 2005 to 2020 on October 27, 2020, there were a total of 2186 people (1152 males, 1034 females), and the average age was 83.7 years (median ($M$) 84, interquartile range (IQR) 76.8–91.2, standard deviation (SD) 10.8, 95% confidence interval (CI): 0.45, 83.6–84.5) (Lee et al. 2022).

### Eligibility criteria

According to the Infectious Disease Control and Prevention Act, all Hansen subjects on Sorok Island have been registered and treated at Sorokdo National Hospital. This cohort consisted of HD patients, dapsone, and respiratory diseases in all Hansen subjects, according to the data received from Sorokdo National Hospital by South Korea's Official Information Disclosure Act. We searched all medical records of the Sorokdo National Hospital with ICD-10 codes in South Korea from 2005 when the government computerized the codes.

Study Setting for ICD Code of Korean Diseases and Medicines (ICD-10 Version: 2019).

For Respiratory Diseases (Table S2): J20.9, J15, J15.8, J15.9, J17.0, J18.8, J18.9, J20.9, J30.0, J30.4, J31.0, J31.1, J31.2, J32, J32.0, J32.4, J32.8, J32.9, J34.0, J34.2, J34.8, J35.0, J36, J37.0, J38.0, J38.3, J39.0, J40, J42, J44, J44.9, J45, J45.0, J45.1, J45.9, J46, J47, J69.0, J81, J85.1, J90, J93, J94.2, J95.3, J96.0, J98.1, J98.8, J98.9.

For VRD (Table S2-1): J00, J02, J02.9, J03, J03.9, J04.0, J06.0, J06.9, J09, J10.8, J12.9, J20.9.

### Complete blinded study and randomization

HD patients have taken dapsone for their life or four types of dementia symptom improvement drugs: acetylcholinesterase inhibitors (AChEIs) and the NMDA antagonist memantine

since 2008. The Korean government has established compulsory long-term care insurance (Chon 2014). The government successively established Community Dementia Reassurance Centers at all public Health Centers according to the National Duty for Dementia (Youn and Jeong 2018). In addition, medical teams reinforced the dementia management programs that administer AAD to MCI or AD patients as a preventive treatment (Lee et al. 2009; Ahn et al. 2015). The current mainstays of dementia treatment include AChEIs and memantine (Lee 2022b; Lee et al 2022). Ahn et al. (2015) insisted that the 1-year persistence rate of AChEIs should be precisely monitored to optimize treatment persistence for AD patients because patients are more likely to stop therapy than those in other countries. As a result, prescriptions for effective medications have increased. It overlaps with the enactment of the 2011 DMA. DMA significantly influenced the diagnosis and treatment of dementia. Medical staff treated HD patients with VRD or dementia, while no one knew about dapsone's relationship with viral inflammasomes. This is a complete blinded randomized study by DMA.

### Interventions

According to the DMA, the medical staff of Sorokdo National Hospital started a full investigation in 2011 for the treatment of dementia for all HD patients on Sorok Island. As a result, AAD was prescribed for Hansen subjects diagnosed with dementia, and doctors stopped prescribing dapsone for inactive HD patients. They have followed up on all HD patients since 2011.

As a result, DMA administered dapsone to the trial group, and we classified dapsone (−) subjects as the control group.

### Outcomes

Significance was evaluated based on a *p*-value of 0.05 in the DDS (+) subgroup and the DDS (−) subgroup of the VRD-diagnosed (+) subgroup and the VRD-undiagnosed (−) subgroup.

### Statistical analysis

We used the software programs Object-Relational DBMS and Google spreadsheet with SPSS. The Mann–Whitney U test, one-way repeated-measures ANOVA calculator, and post hoc Tukey honestly significant difference (HSD) test were applied. A significant T test was performed among the T1: DDS(+)/VRD(+), T2: DDS(−)/VRD(+), T3: DDS(+)/VRD(−), and T4: DDS(−)/VRD(−) groups.

### Results

Nine thousand six hundred forty-nine participants were randomized from 2005 to 2020 on Sorok Island. We performed primary (Tables S4–S4-11, Figs. S2–S6) and secondary (Tables S5-2–S5-13, Figs. S7–S11) analyses based on the *p* value. Because all the results were significant, we used primary data to report the results (Fig. 1).

**Fig. 1** Flow chart of participants in viral respiratory disease infection on Sorok Island
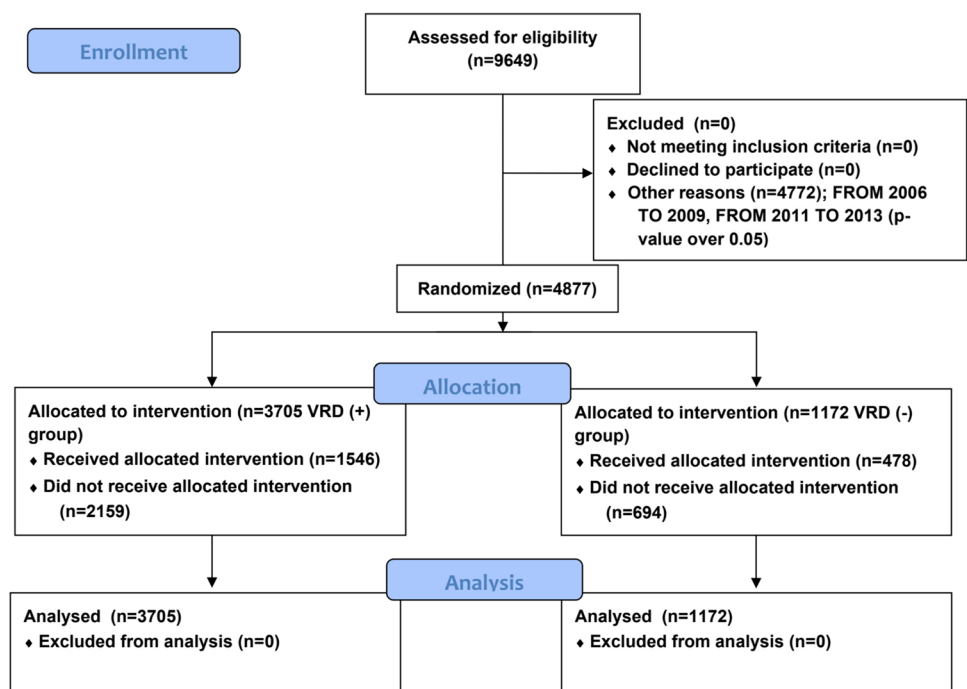
VRD (+) subjects (Ss) ($S = 6394$, mean ($M$) $= 426.27$) consisted of the DDS (+) ($S = 3022$, $M = 201.47$) and DDS −) groups ($S = 3372$, $M = 224.80$). VRD (−) subjects ($S = 3255$, $M = 217.00$) consisted of the DDS (+) ($S = 1663$, $M = 110.87$) and DDS (−) groups ($S = 1592$, $M = 106.13$).

The $f$-ratio value is 8.52. The $p$ value in the one-way ANOVA calculator for independent measures is 0.000094 (Table S4-1). However, there were caveats to post hoc Tukey's honestly significant difference. The pairwise comparisons (T1:T3, T1:T4, T2:T3, T2:T4, and T3:T4) were applicable except for T1:T2 and T2:T4 (Table S4-2) (Table 1).

### T test

T1 ($M = 201.47$, SD $= 33.86$):T3 ($M = 110.87$, SD $= 103.80$) demonstrated that the VRD (+/−) groups in DDS (+) were clearly distinguished as of 2010. This describes that as of 2010, more people stopped taking dapsone. If HD subjects

stopped taking dapsone, their condition would deteriorate because of exacerbated VRDs, and be hospitalized. We can find that the number of VRD patients was comparable (148 in 2005 and 155 in 2019). Very few people have been hospitalized for VRD in the group taking dapsone since 2013. The $t$ value is 3.21, and the $p$ value is 0.003287 (significant at $p < 0.05$) (Table S4-4, S4-5, and Fig. S3).

T1 ($M = 201.47$, SD $= 33.86$):T4 ($M = 106.13$, SD $= 70.30$) demonstrated that the number of people who took dapsone more increased since 2008 than those who did not take dapsone. This means that those who continued to take dapsone during the care of the two sisters from 1962 to 2005 began to understand the difference between taking dapsone and not taking it. After DMA in 2012 was enforced, there was the largest difference of 22 and 269 patients in 2013. The $t$ value is 4.73, and the $p$ value is 0.000058 (significant at $p < 0.05$) (Table S4-6, S4-7, and Fig. S4).

T2 ($M = 224.80$, SD $= 97.50$):T3 ($M = 110.87$, SD $= 103.80$) definitely proves that VRD is very low when

**Table 1** Viral respiratory disease (VRD) prevalence in the dapsone groups from 2005 to 2019

| Year | T1[*] | T2[*] | T3[*] | T4[*] | Sum | Mean | SD[f] | 95% CI[g] | [CI[g] | CI[g]] | χ2[*] | p value |
|------|------|------|------|------|-----|------|-----|--------|------|------|------|--------|
| 2005 | 148 | 95 | 233 | 268 | 744 | 186 | 78.86 | 11.41 | 174.59 | 264.86 | **13.5772** | **0.000229** |
| 2006 | 166 | 111 | 237 | 208 | 722 | 180.5 | 54.74 | 8.05 | 172.45 | 235.24 | *3.0793* | *0.079295* |
| 2007 | 170 | 115 | 252 | 185 | 722 | 180.5 | 56.37 | 8.29 | 172.21 | 236.87 | *0.2794* | *0.597118* |
| 2008 | 207 | 128 | 219 | 148 | 702 | 175.5 | 44.34 | 6.61 | 168.89 | 219.84 | *0.3293* | *0.566073* |
| 2009 | 222 | 135 | 196 | 115 | 668 | 167 | 50.31 | 7.69 | 159.31 | 217.31 | *0.0498* | *0.823418* |
| 2010 | 202 | 170 | 186 | 105 | 663 | 165.75 | 42.55 | 6.54 | 159.21 | 208.30 | **6.2203** | **0.012629** |
| 2011 | 205 | 164 | 170 | 117 | 656 | 164 | 36.18 | 5.58 | 158.42 | 200.18 | *0.8918* | *0.344987* |
| 2012 | 237 | 211 | 103 | 102 | 653 | 163.25 | 70.95 | 10.97 | 152.28 | 234.20 | *0.3981* | *0.528071* |
| 2013 | 269 | 349 | 8 | 23 | 649 | 162.25 | 172.68 | 26.79 | 135.46 | 334.93 | *3.7892* | *0.051583* |
| 2014 | 236 | 349 | 6 | 32 | 623 | 155.75 | 164.85 | 26.16 | 129.59 | 320.60 | **9.0547** | **0.00262** |
| 2015 | 227 | 325 | 7 | 44 | 603 | 150.75 | 150.82 | 24.33 | 126.42 | 301.57 | **14.7575** | **0.000122** |
| 2016 | 207 | 319 | 4 | 61 | 591 | 147.75 | 142.63 | 23.25 | 124.50 | 290.38 | **27.7773** | **< 0.00001[e]** |
| 2017 | 193 | 301 | 14 | 55 | 563 | 140.75 | 131.44 | 21.96 | 118.79 | 272.19 | **9.1835** | **0.002442** |
| 2018 | 178 | 303 | 15 | 60 | 556 | 139 | 129.14 | 21.66 | 117.34 | 268.14 | **8.2801** | **0.004008** |
| 2019 | 155 | 297 | 13 | 69 | 534 | 133.5 | 123.66 | 21.21 | 112.29 | 257.16 | **10.9433** | **0.000939** |
| Sum | 3022 | 3372 | 1663 | 1592 | | | | | | | | |
| Mean | 201.47 | 224.80 | 110.87 | 106.13 | | | | | | | | |
| SD | 33.86 | 97.50 | 103.80 | 70.30 | | | | | | | | |
| 95% CI | 1.21 | 3.29 | 4.99 | 3.46 | | | | | | | | |
| [ | 200.26 | 221.51 | 105.87 | 102.68 | | | | | | | | |
| ] | 202.67 | 228.09 | 115.86 | 109.59 | | | | | | | | |

The chi-square is 281.826

The $p$ value is $< 0.00001$. I t is significant at $p < 0.05$

Bold means significant; italic, non-significant

[*] Four groups were classified: T1 group is DDS-prescribed (+) with VRD-diagnosed (+) subjects, T2 group is DDS-unprescribed (−) with VRD-diagnosed (+) subjects, T3 group is DDS-prescribed (+) with VRD-undiagnosed (−) subjects, and T4 group is DDS-unprescribed (−) with VRD-undiagnosed (−) subjects

[**] Chi-square, e indicates a $p$ value $< 0.05$, f standard deviation (SD), g confidence interval (CI)

*VRD*, viral respiratory disease

dapsone is taken and very high when not taken. The *t* value is 3.10, and the *p* value is 0.004395 (significant at $p < 0.05$) (Table S4-8, S4-9, and Fig. S5).

The T2 ($M = 224.80$, SD $= 97.50$):T4 ($M = 106.13$, SD $= 70.30$) test confirms that the VRD increases when not taking dapsone. The *t* value is 3.82, and the *p* value is 0.000672 (significant at $p < 0.05$) (Table S4-10, S4-11, and Fig. S6).

T2:T3 and T2:T4 can explain no prevalence during the pandemic period of SARS-CoV (2002), influenza A virus subtypes H1N1 (2009), MERS (2015), and SARS-CoV-2 (2020) on Sorok Island. In addition, the T1:T3, T1:T4, T2:T3, and T2:T4 tests indicate that as of 2010, the group with dapsone (+) and the group without dapsone (−) were separated, and the group taking dapsone should have milder symptoms of VRD. SARS-CoV-2 as RNA-virus activates cGAS– stimulator of interferon genes (STING) signaling in endothelial cells through mitochondrial DNA release, which leads to type I IFN production, and pharmacological inhibition of STING reduces severe lung inflammation and disease severity (Domizio et al. 2022). This provides evidence that dapsone inhibits interferon, which is an exacerbation of the viral respiratory disease (Fig. 2).

## Immune and interferon-related respiratory diseases

We explored interferon-related diseases and classified those as (1) immune-related inflammatory diseases, (2) bronchitis, (3) bacteria-origin pneumonia, and (4) chronic obstructive pulmonary disease (COPD) from Tables S2, S2-1, and S2-2 (Table 2).

Immune-related inflammatory diseases showed a sharp increase in prevalence from 2008 to 2015, followed by a decrease. COPD increased slowly from 2008 to 2011, rapidly increased in 2012 and 2013, and decreased. Bronchitis levels rose rapidly from 2012 to 2014 and then decreased. Pneumonia increased sharply in 2013 compared to previous years.

Since 2008, immune-related inflammatory diseases have increased rapidly. It is a period of viral respiratory disease: 2008–2010 endemic on Sorok Island. Since 2012, COPD has increased, as have bronchitis and pneumonia frequencies. We observed a decrease in the average age of death in the group taking AAD and psychotropic drugs from 2008 to 2015 (Lee 2022b) (Fig. S12). We investigated asthma and lung function trajectories leading to COPD from the ICD-10 codes asthma (J45), predominantly allergic asthma (J45.0), non-allergic asthma (J45.1), asthma, unspecified (J45.9), and status asthmaticus (J46) and COPD patients: other chronic obstructive pulmonary disease (J44), chronic obstructive pulmonary disease, unspecified (J44.9), and bronchiectasis (J47) to identify the prevalence of asthma–COPD relationships. The prevalence of asthma–COPD was not associated at all. However, we only observed a much higher prevalence of COPD than asthma. Asthma and lung function trajectories did not lead to COPD (Fig. S13).

## Factors from the number of diagnosed Alzheimer's disease patients and dapsone use group

Because pharmaceutical companies that produce AChEI reported its frequent side effects like pharyngitis, pneumonia, increased cough, and bronchitis (Lee et al. 2020b), and AAD use in dementia-related disorders increased mortality (Stone 2005; Jong Hoon 2022), we used the pile-up data from Sorok Island_Cohort-Lee, Jong Hoon (2022), "Basic cohort study: dapsone is an anticatalysis for AD exacerbation," Mendeley Data, V2 (Data S1).

We formulated the factor to calculate the relationship between acetylation and acetylcholine.

[Acetylation-acetylcholine (AA) equation]:

$$\text{The Dapsone IFN1 factor} = |\text{DDS}(+) - \text{sum AD}(+)| \tag{1}$$

A total was calculated for all the people taking dapsone and all the individuals diagnosed with AD taking AAD, subtracting 1 from the other, processing the data as an absolute value (Table S6). We used the Pearson correlation coefficient calculator and Spearman's rho calculator to correlate the factors and the prevalence of bronchitis, pneumonia, and COPD.

Our calculations can be summarized as follows:

Pearson correlation coefficient calculator

The AA equation and bronchitis were strongly negatively correlated, $r(15) = -0.823189$, $p = 0.005519$. The result is significant at $p < 0.05$.

The AA equation and pneumonia variables were weakly and negatively correlated, $r(15) = -0.4402$, $p = 0.100742$. Therefore, the result is not significant at $p < 0.05$.

The AA equation and COPD were found to be strongly negatively correlated, $r(15) = -0.8161$, $p = 0.000207$. The result is significant at $p < 0.05$.

Spearman's rho calculator gave the same result: the association between the two variables of bronchitis and COPD with the AA equation was considered statistically significant by normal standards. Pneumonia would not be considered statistically (Supplement S6.1, S6.2, and S6.3) (Fig. 3).

The AA equation was correlated with the prevalence of bronchitis and COPD. This means that dapsone treated and AAD exacerbated them, but dapsone not with pneumonia caused by bacteria. Ameliorating viral disease with dapsone (Lee et al. 2020a; Kanwar et al. 2021, 2022) or the downstream IFN-stimulated cascade with anti-IFNAR2 in the onset stages of disease (Lee 2022a) must attenuate overactive immune-mediated respiratory inflammatory diseases.
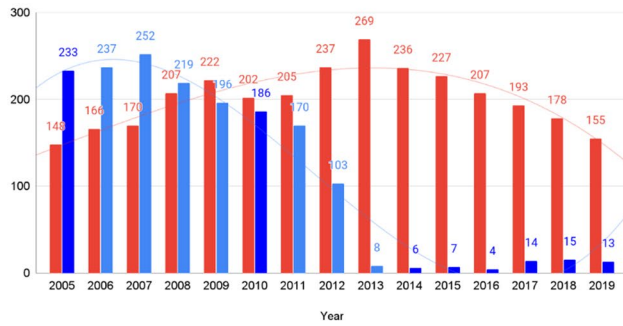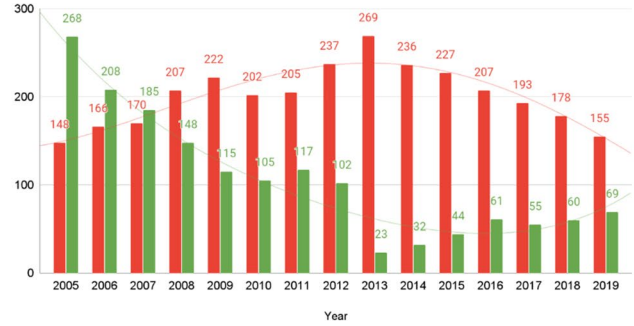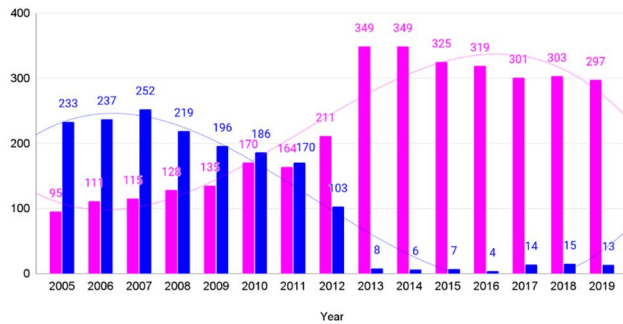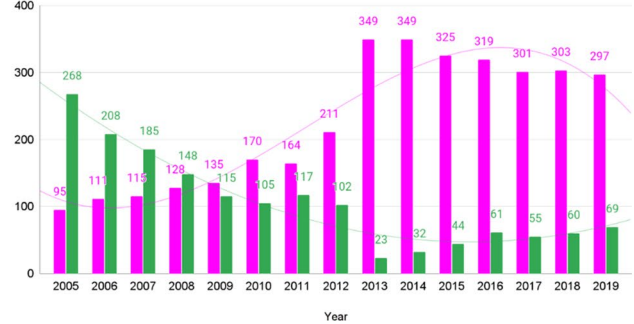
**Fig. 2** Study for T1, T2, T3, and T4. T1 group is dapsone prescribed with VRD-diagnosed subjects, T2 group is dapsone unprescribed with VRD-diagnosed subjects, T3 group is dapsone prescribed with VRD-undiagnosed subjects, and T4 group is dapsone unprescribed with VRD-undiagnosed subjects. After the Dementia Management Act was enacted in 2010, it became clear whether dapsone was prescribed because leprosy patients at Sorok Island should visit Sorokdo National Hospital to receive treatment. The column chart for the T test—changes started in 2010, and the VRD patterns are apparent in T1, T2, T3, and T4 from 2005 to 2019. The proportion of T2 patients without dapsone and with VRD increased significantly. T2:T3 graph shows that HD patients with prescribed dapsone have a very low prevalence of VRD. T1:T3 and T1:T4 demonstrate that VRD $(+/-)$ groups in the dapsone $(+)$ are distinguished as 2010. Furthermore, trend lines $(R^2 > 0.95)$ show significant relationships between the VRD $(+/-)$ and DDS $(+/-)$ groups. We plotted the trend line using a cubic polynomial equation, and the equation used was presented

## Limitations

The limitation is that this study was conducted in an island area and on HD patients. Since dapsone's maximal allowance price in South Korea was very low in 2016, pharmaceutics, which produced it in Korea, stopped the production of dapsone except for the supply for HD patients (Lee 2021). More studies are required to compare COVID-19 survival rates later.

## Discussion

### We recommend taking dapsone continuously for Hansen's disease patients if there are no side effects

Dapsone activates specific T cells of hypersensitive patients expressing the risk allele HLA-B* 13: 01.

HLA-B*13:01-CD8^{+} T cells (cytotoxic T lymphocytes) induce a dapsone-responsive immune response (Zhao et al. 2019). The multidrug therapy containing rifampin and clofazimine with dapsone was decisive for treating leprosy (Ramos-e-Silva and Rebello 2001). According to our survey, some HD patients on Sorok Island have taken dapsone for over 20 years. Remarkably, we noted that some people took dapsone for more than 50 years (Lee 2022b; Lee et al. 2022; Kanwar et al. 2021). Therefore, if there are no dapsone side effects, we recommend taking dapsone continuously.

### COPD was associated with AChEIs and IFN1

COPD was associated with incident nonamnestic MCI in a dose-dependent manner in the Mayo Clinic Study on Aging (Singh et al. 2014). The risk of COPD exacerbation may increase in the first 90 days of AChEI therapy in patients

**Table 2** Respiratory disease (RD) prevalence on Sorok Island

| Disease name | ICD | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 | 2019 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Asthma | J45 | 6 | 5 | 5 | 5 | 5 | 5 | 5 | 4 | 2 | 3 | 2 | 1 | 1 | 1 | |
| Predominantly allergic asthma | J45.0 | | | 40 | 40 | | | | | | | | | | | |
| Nonallergic asthma | J45.1 | | | 36 | | | | | | | | | | | | |
| Asthma, unspecified | J45.9 | | | | | | | | | 5 | 6 | 7 | 6 | 5 | 3 | 2 |
| Status asthmaticus | J46 | | | | 4 | 4 | 4 | | | | | | | | | |
| Vasomotor rhinitis | J30.0 | | | 3 | 45 | 54 | 96 | 99 | 182 | 180 | 110 | 96 | 28 | 30 | 29 | 9 |
| Allergic rhinitis, unspecified | J30.4 | 11 | 11 | 60 | 189 | 205 | 197 | 151 | 142 | 178 | 129 | 102 | 71 | 47 | 40 | 21 |
| Chronic rhinitis | J31.0 | 10 | 40 | 40 | 16 | 95 | 91 | 64 | 19 | 15 | 18 | 19 | 16 | 14 | 11 | 1 |
| Chronic sinusitis | J32 | | | | 571 | 636 | 567 | 455 | 345 | 291 | 155 | 128 | | 106 | | 5 |
| Chronic maxillary sinusitis | J32.0 | | | | | | | | | 1 | 9 | 20 | | 17 | | 5 |
| Chronic pansinusitis | J32.4 | | 4 | | | | | | | | | 2 | 2 | 4 | 4 | 4 |
| Other chronic sinusitis | J32.8 | | | | | | | | | | | | 1 | 1 | 1 | 1 |
| Chronic sinusitis, unspecified | J32.9 | 11 | 19 | 18 | 16 | 15 | 15 | 44 | 41 | 42 | 33 | 32 | 32 | 29 | | |
| Chronic laryngitis | J37.0 | 6 | 6 | 6 | | 7 | 6 | 6 | 6 | 5 | 7 | 12 | 15 | 11 | 8 | 3 |
| Chronic nasopharyngitis | J31.1 | | | | | | | | 2 | 2 | 17 | 33 | 49 | 38 | 30 | 8 |
| Chronic pharyngitis | J31.2 | | 27 | | | | | | | 79 | 168 | 226 | | 188 | 130 | |
| Abscess, furuncle, and carbuncle of nose | J34.0 | 47 | 1 | 1 | 122 | 127 | 59 | 59 | 43 | 24 | 51 | 47 | 47 | 41 | 25 | 16 |
| Deviated nasal septum | J34.2 | | | | 5 | 56 | 56 | 56 | 120 | 70 | 51 | 65 | 22 | 26 | 27 | 6 |
| Other specified disorders of nose and nasal sinuses | J34.8 | 2 | 4 | | 4 | 4 | 4 | 3 | 3 | 5 | 5 | 7 | 6 | 2 | 2 | 2 |
| Chronic tonsillitis | J35.0 | | | | | | | | | | 5 | 10 | 12 | 7 | | |
| Peritonsillar abscess | J36 | | | | | | | | 7 | 7 | 7 | 7 | 7 | 7 | | |
| Retropharyngeal and parapharyngeal abscess | J39.0 | | | | | | | | 16 | 16 | 16 | | | | | |
| Immune related inflammatory diseases | | 47 | 114 | 210 | 1017 | 1224 | 1116 | 956 | 951 | 945 | 804 | 829 | 329 | 584 | 325 | 85 |
| Acute bronchitis, unspecified | J20.9 | 11 | 11 | 1 | 1 | 1 | 1 | 1 | 515 | 675 | 655 | 354 | 225 | 222 | 219 | 4 |
| Acute bronchitis, unspecified | J20.9 | 11 | 11 | 1 | 1 | 1 | 1 | 1 | 515 | 675 | 655 | 354 | 225 | 222 | 219 | 4 |
| Bronchitis, not specified as acute or chronic | J40 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 1 | 1 | | | | | |
| Unspecified chronic bronchitis | J42 | 11 | 58 | 28 | 41 | 41 | 41 | 30 | 13 | 13 | | | | | | |
| Bronchitis | | 37 | 84 | 34 | 47 | 47 | 47 | 36 | 1047 | 1364 | 1311 | 708 | 450 | 444 | 438 | 8 |
| Bacterial pneumonia, NEC | J15 | | | 1 | | | | | 17 | 6 | 2 | | 1 | | | |
| Other bacterial pneumonia | J15.8 | | 16 | | 86 | 89 | 88 | 143 | 3 | 3 | | | | 16 | | |
| Bacterial pneumonia, unspecified | J15.9 | 5 | 5 | 5 | 95 | 5 | 6 | 136 | 258 | 638 | 218 | 68 | 32 | 5 | 4 | 4 |
| Pneumonia in bacterial diseases classified elsewhere | J17.0 | | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | | | | | |
| Other pneumonia, organism unspecified | J18.8 | | 17 | | 111 | 111 | 110 | 110 | 110 | 127 | 17 | 17 | 17 | | | |
| Pneumonia, unspecified | J18.9 | 36 | 36 | 36 | 36 | 15 | 7 | 7 | 7 | 7 | 9 | 16 | 23 | 18 | 13 | 8 |
| Pneumonia | | 41 | 94 | 62 | 366 | 264 | 249 | 419 | 415 | 801 | 266 | 101 | 73 | 39 | 24 | 13 |
| PNEUMONITIS DUE TO FOOD AND VOMIT | J69.0 | | 5 | 5 | 6 | 6 | 1 | 9 | 61 | 89 | 34 | 39 | 36 | 35 | 34 | 1 |
| Other chronic obstructive pulmonary disease | J44 | | | | 65 | 64 | 64 | 64 | | | | | | | | |

**Table 2** (continued)

| Disease name | ICD | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 | 2019 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Chronic obstructive pulmonary disease, unspecified | J44.9 | 35 | 29 | 144 | 242 | 356 | 404 | 382 | 1257 | 1447 | 948 | 631 | 473 | 375 | 212 | |
| Bronchiectasis | J47 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 3 | 3 | 2 | 2 | 2 | | |
| COPD | 37 | 31 | 146 | 309 | 422 | 470 | 448 | 1259 | 1450 | 951 | 633 | 475 | 377 | 212 | 0 | |
| Pulmonary Edema | J81 | | | | | | | | | | | 3 | 2 | 2 | 2 | 1 |
| Abscess of lung with pneumonia | J85.1 | | 5 | 5 | 5 | | | | | | | | | | | |
| Pleural effusion, NEC | J90 | | | | | | | | | | | 2 | 1 | 2 | | |
| Pneumothorax | J93 | 1 | 5 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 2 | | | | |
| Hemothorax | J94.2 | | | | | | | | | | 2 | 1 | 1 | | | |
| Chronic pulmonary insufficiency following surgery | J95.3 | | | | | | | | | | | 1 | | 1 | | |
| Acute respiratory failure | J96.0 | | | | 20 | | | | | | | | | | | |
| Pulmonary collapse | J98.1 | | | | | | | | | | | 1 | | | | |
| Other specified respiratory disorders | J98.8 | | | | | | | | | | | | | 1 | | |
| Respiratory disorder, unspecified | J98.9 | | | | | | | | | | | | | 5 | 2 | 1 |
| End stage | | 1 | 10 | 6 | 26 | 1 | 1 | 1 | 1 | 1 | 3 | 9 | 4 | 11 | 4 | 2 |
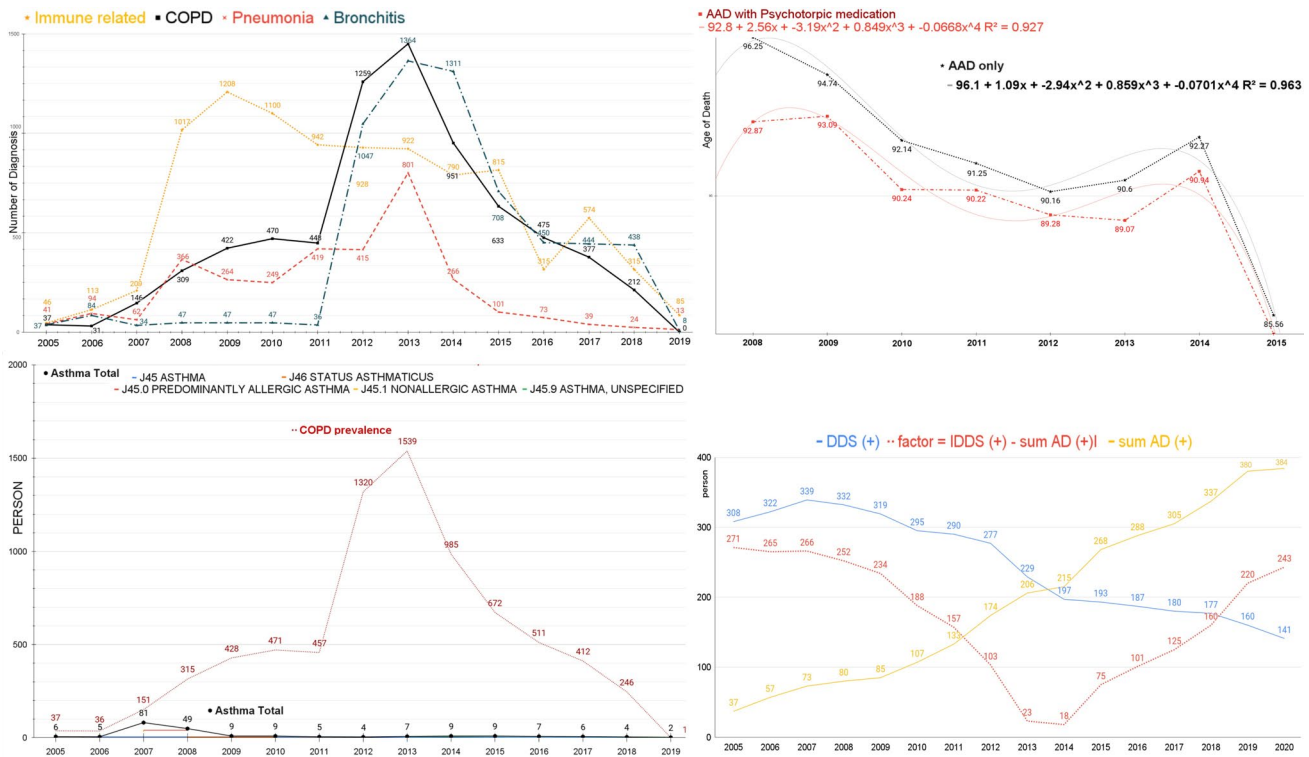
**Fig. 3** Bronchitis, COPD, and pneumonia after the endemic of viral respiratory diseases. (1) The initial step in the cellular entry of viral respiratory disease (VRD) is binding the spike protein to cell surface receptors. This allows the fusion of the virus to the cell surface through cellular proteases such as TMPRSS2 and furin to be involved in priming the spike protein. Virions are taken up into endosomes, where the virus may be cleaved and possibly activated by the cysteine protease. The virus uses endogenous cellular machinery to replicate itself inside the cell (Muniyappa and Gubbi 2020). Pathogen-associated molecular patterns (PAMPs) or danger-associated molecular patterns (DAMPs) induced by the virus may affect respiratory symptoms. The prevalence of viral respiratory diseases showed a sharp increase from 2008, followed by COPD and bronchitis, increasing in 2012 and decreasing from 2014. Pneumonia increased sharply in 2013 compared to previous years. (2) The expectancy of Hansen's disease (HD) patients with Alzheimer's disease (AD) taking AChEIs or memantine with psychotropic medicines at Sorok Island. The mean ages of death decrease. The mean ages of deaths without taking additional psychotropic drugs are black. The life expectancy trends of HD patients taking other psychotropic medications (red) decreased. The life expectancy trends of HD patients taking anti-Alzheimer's disease drugs (AAD) were decreased on Sorok Island (black), and those taking AAD with psychotropic medicines (red) were reduced more (Lee 2022b). (3) We reviewed the prevalence of asthma patients from the ICD-10 codes ASTHMA (J45), PREDOMINANTLY ALLERGIC ASTHMA (J45.0), NONALLERGIC ASTHMA (J45.1), ASTHMA, UNSPECIFIED (J45.9), and STATUS ASTHMATICUS (J46). (4) We calculated that all Hansen's disease patients were taking dapsone, and all the individuals diagnosed with Alzheimer's disease (AD)[*] were taking anti-Alzheimer's disease (AAD)[**]. Then, we subtracted one from the other, processed the data as an absolute value, and illustrated these data graphically. Our results were strongly negatively correlated with COPD and bronchitis, not pneumonia

with dementia and COPD (Mahan and Blaszczyk 2016). Virus infection and interferon treatment decreased the M2 muscarinic receptor gene expression on the parasympathetic nerve endings by causing the release of IFN-gamma, which inhibits M2 receptor gene expression (Jacoby et al. 1998). Acetylcholine excess appears to inhibit acetylcholine receptors for interferon production against virus invasion. The genesis of acetylcholine receptor needs interferon (Balasa et al. 1997). The muscarinic and nicotinic acetylcholine receptors play critical roles in regulating immune function (Kawashima et al. 2012). This study elucidates the correlation between donepezil and acetylcholine and suggests that acetylcholine excess negatively affects acetylcholine receptor gene expression.

An asthma component might facilitate the identification of COPD patients with no previous diagnosis of obstructive lung disease. The prevalence of asthma–COPD overlap syndrome was only 6% of the COPD patients who fulfilled both criteria (Baarnes et al. 2017). Our study also corresponds to previous results. Asthma and lung function trajectories did not lead to COPD.

The molecule neuropilin-1 (NRP1) plays an important and complex role in the secondary CD8 T-cell response to control viral infections and tumors (Hwang et al. 2019). We can divide innate lymphoid cells (ILCs) into three groups based on distinct cytokine secretion profiles and dependent transcription factors. Group 3 ILCs (ILC3s) are present in smokers and patients with COPD.

ILC3s with NRP1 produce higher levels of cytokines than ILC3s without NRP1 (Shikhagaie et al. 2017). NRP1^{+} ILC3s play a potential role in inflammation and vascularization (Meininger et al. 2020). Dapsone might control the NRP1-ILC inflammatory pathway with the IFN1 or cGAS-STING cascade pathways through acetylation-deacetylation.

## Conclusion

This study provides theoretical clinical data to limit acetylcholine excess during the VRD pandemic for bronchitis, COPD, and pneumonia.

## Declarations

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