Excess deaths associated with long-term exposure to ambient NO\textsubscript{2} in China

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Abstract

World Health Organization updated the target of annual mean NO\textsubscript{2} from 40 \(\mu\text{g m}^{-3}\) to 10 \(\mu\text{g m}^{-3}\) in 2021 based on new evidences that showed statistically independent effects of long-term exposure to ambient NO\textsubscript{2} and mortality. We estimate the excess deaths associated with long-term exposure to ambient NO\textsubscript{2} (DAAN) from non-accidental disease (NAD), cardiovascular disease (CVD) and respiratory disease (RD) in China in 2013–2020 using a counterfactual analytic framework adopted by Global Burden Disease. We use relative risk (RR) values based on a meta-analysis, and assume a linear concentration-response (C-R) function and a threshold value of 10 \(\mu\text{g m}^{-3}\). DAAN from NAD vary in 279 (95\% Cl: 189–366) to 339 (95\% Cl: 231–442) thousand in 2013–2020, comparable to excess deaths attributed to long-term exposure to ambient O\textsubscript{3} in China. DAAN from NAD changes by \(-43\%\)–\(+220\%\) using different RR values, C-R function shapes, and threshold values. DAAN from RD reduces while those from CVD increases significantly in 2013–2020. DAAN from RD account for \(\sim\)10\% of total DAAN. We found that the reduction of NO\textsubscript{2} concentration and baseline mortality of NAD offsets the adverse effects of population growth and aging in 2013–2017. In 2017–2020, the contribution from air pollution reduction surpasses the adverse effects of population growth and aging in most regions. We suggest that continuing the reduction rate of NO\textsubscript{2} emissions in 2013–2020 would offset the effects of population growth and aging in 2020–2030. Faster reduction of NO\textsubscript{2} sources is required to reduce DAAN in Liaoning, Shanxi, Shanghai, and Anhui, where DAAN from NAD, CVD and RD increased in 2013–2020. Our results should be interpreted with caution because the causality support of long-term exposure to ambient NO\textsubscript{2} on mortality from toxicological studies is not firm yet, and NO\textsubscript{2} is possibly just a marker of traffic-related pollutants.

1. Introduction

Nitrate dioxide (NO\textsubscript{2}), a primary traffic pollutant, is an important precursor of nitric acid and ozone (Seinfeld 2016). To reduce fine particle (PM\textsubscript{2.5}) concentration, China started to control NO\textsubscript{x} emissions in the twelfth Five Year Plan (Ma et al 2019). Selective catalytic reduction systems were installed in this period, growing from a penetration of about 18% in 2011 to 86% in 2015 (Liu et al 2016). In 2011, China switched national emission standard for cars from the China III to China IV (Wu et al 2017). In 2013, China issued the toughest ever air pollution control policies and Action Plan of Air Pollution Prevention and Control (Council 2013, Zhang et al 2019) to reduce anthropogenic emissions and control PM\textsubscript{2.5} pollution. Following this plan, a Three year Action Plan to Win the Battle against the Blue Sky was issued, and NO\textsubscript{x} emissions were required to reduce 15\% in 2015–2020 (Council 2018). As a result, NO\textsubscript{x} column decreased at a rate of 6.2\% yr\textsuperscript{-1} after 2011, following a 17.7\% increase before 2011 (de Foy et al 2016, Georgoulia et al 2019, Huang et al 2022).

The World Health Organization (WHO) analysis in 2005 showed association between traffic related pollution and mortality, but was unable
to separate the contribution from PM$_{2.5}$ and NO$_2$ (WHO 2005). Since then, a growing body of evidence has reported independent association of long-term exposure to ambient NO$_2$ and non-accidental disease (NAD) mortality and cause-specific mortality, such as cardiovascular disease (CVD) and respiratory disease (RD). Based on a meta-analysis, Huangfu and Atkinson (2020) suggested positive association between long-term NO$_2$ exposure and mortality with relative risk (RR) of 1.02 (95% CI: 1.01–1.04) for NAD. Larger RR values were found for chronic obstructive pulmonary disease (COPD), RD and acute lower respiratory infection mortality: 1.03 (95% CI: 1.00–1.05), 1.03 (95% CI: 1.01–1.04) and 1.06 (95% CI: 1.02–1.10) per 10 µg m$^{-3}$, respectively. New evidence thereafter did not alter the overall associations, but RR for COPD and RD mortality were updated to 1.03 (95% CI: 1.01–1.04) and 1.03 (95% CI: 1.01–1.05) based on the WHO analysis in 2021 (WHO 2021). Based on this evidence, WHO updated the target of annual mean NO$_2$ concentration from 40 µg m$^{-3}$ to 10 µg m$^{-3}$ (WHO 2021). Huang et al (2021) incorporated six new studies since Huangfu and Atkinson (2020), and also suggested an independent effect of long-term exposure to ambient NO$_2$ on mortality from NAD, CVD and RD.

Although increasing epidemiological evidences show probable independent association of long-term exposure to ambient NO$_2$ and mortality, support from chamber and toxicological evidences are not as robust (WHO Regional Office for Europe 2013, EPA 2016). Sub-chronic animal studies showed adverse effects of NO exposure on blood viscosity, red blood cell rigidity, protein expression, and lung tissue (Brandsma et al 2008, Zhu et al 2012). Mixture studies also showed statistically significant changes in lung function, inflammation, and oxidative stress (Mauderly et al 2011, Mcdonald et al 2012). In vitro genotoxicity test in human cells showed deoxyribonucleic acid fragmentation and increased micronuclei at 0.1 ppm NO$_2$ (Koehler et al 2011). The NO$_2$ concentration used in these toxicological experiments are at ppm level, thus the degree to which the conclusion applies at ambient concentrations is less clear. These scattered findings do not support a firm causal conclusion of the effects of long-term NO$_2$ exposure on mortality.

To the best knowledge of the authors, very few studies have estimated the excess deaths associated with long-term exposure to ambient NO$_2$ (DAAN) in China because the annual mean NO$_2$ concentration (≈20 µg m$^{-3}$ in 2013–2020) was well below the WHO recommended target (40 µg m$^{-3}$) before the 2021 update. Zhang et al (2021) estimated DAAN based on result of a cohort in China, and showed that DAAN in China was 1.65 million in 2018, comparable to the excess deaths attributed to long-term exposure to ambient PM$_{2.5}$. However, due to the high RR value from one cohort, the estimated DAAN by Zhang et al (2021) is possibly biased high.

In this study, we estimate DAAN from NAD, CVD and RD in China following the framework adopted by global burden of disease (GBD) using RR values from a meta-analysis. We investigated the contributions from different factors: NO$_2$ concentration changes, population growth, population age structure changes, and baseline mortality changes. We also tested the sensitivity of estimated DAAN to RR values, C-R function shapes and threshold values. We analyze the results in China and the key regions: North China Plain (NCP), Yangtze River Delta (YRD), Pearl River Delta (PRD) and FenWei Plain (FWP, see region definition in figure S1) and in two periods: Action Plan of Air Pollution Prevention and Control in 2013–2017 and Three year Action Plan to Win the Battle against the Blue Sky in 2017–2020.

2. Method

2.1. Data

We obtain the annual mean NO$_2$ concentrations with horizontal resolution of 10 km in China during 2013–2020 from an assimilated dataset developed based on multiple data sources, including ground-based observations, satellite remote sensing products, atmospheric reanalysis, chemical transport model simulations and other ancillary data (Wei and Li 2021). The cross-validation coefficient of determination for daily NO$_2$ was 0.84 and the root-mean-square error was 7.99 µg m$^{-3}$. Population distribution data with a spatial resolution of 1 km in 2013–2020 was from WorldPop (Available at www.worldpop.org/geodata/listing?id=78), and was re-gridded to 10 km resolution, the same grids with NO$_2$ concentration data. We adjusted the population data on province scale by survey data from Chinese National Statistical Yearbook (National Bureau of Statistics of China 2021). Age structure of 0–14, 15–64 and >65 on provincial level was from Chinese National Statistical Yearbook in 2013–2020. Data of age structure every five years was from a national scale census data (National Bureau of Statistics 2012, available at: www.stats.gov.cn/tjjs/pkjv/kpc/6rp/index.htm). Baseline mortality from NAD, CVD and RD were from the National Center for Chronic and Non-communicable Disease Control and Prevention (NCNCD, Available at: http://ncncd.chinacdc.cn/jcysj/siyinjcx/syfxbg/202101/t20210118_223798.htm).

2.2. DAAN estimate

We estimated DAAN in China in 2013–2020 in each 10 km grid using comparative risk assessment
framework, widely used in health impact assessment conducted by GBD (Collaborators 2020) and WHO (WHO 2021). DAAN can be calculated as:

$$\text{DAAN}_d = \sum_{a,d} \text{POPl} \times \text{AgeSa}_a \times \text{MortR}_{a,d,t} \times \left[ 1 - \frac{1}{\text{RR}_{d,t}} \right]$$

where $\text{DAAN}_d$ is excess deaths associated with long-term exposure to ambient $\text{NO}_2$ in a given year $t$, $\text{POPl}_d$ refers to total population in year $t$; $\text{AgeSa}_a$ is the proportion of population with age $a$ in year $t$; $\text{MortR}_{a,d,t}$ is the baseline mortality rate of disease $d$ for population with age $a$ in year $t$; $\text{RR}_{d,t}$ is the RR of disease $d$ in year $t$. We assume a linear C-R function following WHO (2021):

$$\text{RR}_{d,t} = a_d \Delta \text{c}_t + b_d$$

$$\Delta \text{c}_t = \begin{cases} 0, & \text{c}_t \leq \text{c}_0 \\ \text{c}_t - \text{c}_0, & \text{c}_t > \text{c}_0 \end{cases}$$

where $a_d$ and $b_d$ are the exposure-response factor for disease $d$, estimated from RR values per $10 \ \mu g m^{-3}$ from epidemiological study. In this study, we use global overall RR values of NAD, RD and CVD from a recent meta-analysis (Huang et al. 2021). The RR for all-cause mortality was 1.06 (95% Cl: 1.04–1.08) per 10 ppb increase in annual $\text{NO}_2$ concentration and 1.11 (95% Cl: 1.07–1.16), 1.05 (95% Cl: 1.02–1.08) for mortality from CVD and RD, respectively. $\text{c}_t$ is the annual mean $\text{NO}_2$ concentration in each grid in year $t$. $\text{c}_0$ is the theoretical minimum risk exposure level. We use $10 \ \mu g m^{-3}$ as suggested by WHO air quality guidelines in the 2021 update (WHO 2021).

2.3. Decompose effects of different factors on changes of DAAN

We decomposed the contributions of $\text{NO}_2$ concentrations, population, age structure, and baseline mortality to changes of DAAN in China (table S1). In the BASE experiment, DAAN is estimated using parameter values in each year in 2013–2020. The contribution of different factors is estimated by sequentially fixing parameter values in the 2013 levels in the mortality equation. For example, to investigate the contribution from $\text{NO}_2$ concentration changes, we vary $\text{NO}_2$ concentration in each year and fixed values of population, age structure and baseline mortality as the 2013 level in Experiment CON. Thus, the trend of DAAN in this experiment reflects the contribution from $\text{NO}_2$ concentration changes. See setting of other experiments in table S1.

2.4. Sensitivity tests

We tested the sensitivity of DAAN from NAD to RR values (Test 1), shapes of C-R function (Test 2) and threshold values (Test 3). Base and sensitivity experimental setup are shown in table S2. We summarized RR values in recent meta-analysis and cohort studies in table S3. Based on four cohort studies, Huang et al. (2021) showed that the RR values in Asia for NAD, CVD and RD mortality were 1.13 (95% CI: 0.83–1.54), 1.39 (95% CI: 1.02–1.88) and 1.16 (95% CI: 1.00–1.34) per 10 ppb $\text{NO}_2$ increase, much larger than the global overall associations in BASE experiment. Although the cohort study in Canada showed much larger RR for NAD (table S3), the RR values from cohort studies published in 2021–2022 are within the range of studies included in the meta-analysis from Huang et al. (2021). We present results of meta-analysis of studies before June 2022 in a separate paper (Chen et al., in preparation). For the sensitivity analysis purpose in this study, we change the RR value for NAD to 1.02 (95% Cl: 1.01, 1.04) per $10 \ \mu g m^{-3}$ from (WHO 2021) and 1.06 (95% Cl: 0.92, 1.27) per $10 \ \mu g m^{-3}$ in Asia from Huang et al. (2021) in Test 1.

Few studies have assessed the shape of the C-R function of long-term exposure to ambient $\text{NO}_2$ and mortality. A linear C-R function was detected starting from a very low exposure level (Hanigan et al. 2019, Qian et al. 2021). WHO also assumed a linear C-R relationship (WHO 2021). Brunekreef et al. (2021) observed linear to supralinear associations between $\text{NO}_2$ exposure and NAD mortality. In Test 2, we change the C-R function to log-linear as follows:

$$\text{RR}_{d,t} = \exp(\beta_d \Delta \text{c}_t)$$

where $\beta_d$ is the exposure-response factor of disease $d$, estimated from RR value of 1.03 (95% Cl: 1.02, 1.04) per $10 \ \mu g m^{-3}$ in BASE experiment.

Based on the association of low level $\text{NO}_2$ exposure and NAD mortality, WHO suggested annual mean $\text{NO}_2$ concentration of $10 \ \mu g m^{-3}$ (WHO 2021). The lowest level of exposure measured (the 5th percentile of the exposure distribution) vary significantly among studies from $-2.7$ to $38.1 \ \mu g m^{-3}$ (WHO 2021). In Test 3, we change the threshold values to 5 and $15 \ \mu g m^{-3}$ and kept the other setting as those in BASE experiment to test the influences of threshold values on DAAN estimates (table S3).

3. Results and discussions

3.1. Excess deaths associated with long-term exposure to ambient $\text{NO}_2$ in China

DAAN from NAD in China vary in 279 (95% Cl: 189–366) to 339 (95% Cl: 231–442) thousand and show no significant trend in 2013–2020 (figure 1). These estimates are much smaller than that from Zhang et al. (2021) that based on a cohort study including 30,843 adults from 25 provincial regions in China (1.65 million). The larger estimate from the latter is mainly attributed to larger RR values:
Excess deaths associated with long-term exposure to ambient NO\textsubscript{2} (thousand) from NAD, CVD and RD in China in 2013–2020.

Figure 1. Excess deaths associated with long-term exposure to ambient NO\textsubscript{2} (thousand) from NAD, CVD and RD in China in 2013–2020.

1.127 (95% CI: 1.04, 1.22) per 10 \(\mu\)g m\(^{-3}\), 4.2 times of the RR value in BASE experiment in this study. We find that DAAN is comparable to excess deaths attributed to long-term exposure to ambient O\textsubscript{3} (181–579 thousand, Maji and Namdeo 2021), and is much lower than those attributed to long-term exposure to ambient PM\(_{2.5}\) (1.8–2.0 million, Liu et al. 2021).

In 2013–2017, during the implementation period of Action Plan of Air Pollution Prevention and Control, DAAN from NAD decreased by 2%. In 2017–2020, China implemented Three year Action Plan to Win the Battle against the Blue Sky, and DAAN from NAD decreased by 11%.

DAAN from RD reduces significantly by 12 thousand \((p < 0.01)\) while those from CVD increase significantly by 19 thousand \((p < 0.1)\) in 2013–2020. As a result, the relative contribution of DAAN from RD decreases from 10% in 2013 to 7% in 2020. DAAN from CVD (266–299 thousand) is larger than excess deaths attributed to long-term exposure to ambient O\textsubscript{3}; (112–233 thousand, Seltzer et al. 2018, Maji and Namdeo 2021). In contrast, DAAN from RD are 20–32 thousand, smaller than those for O\textsubscript{3} (73–316 thousand, Malley et al. 2017, Seltzer et al. 2018, Chowdhury et al. 2020, Maji and Namdeo 2021).

These comparisons suggest that long-term exposure to ambient NO\textsubscript{2} shows possibly larger effects on excess deaths from CVD and smaller effects on excess deaths from RD compared to long-term exposure to ambient O\textsubscript{3}. In 2013–2017 and 2017–2020, the reduction rates of DAAN from RD are similar (~20%). In contrast, DAAN from CVD changes marginally in 2013–2017, but increase by 5% in 2017–2020.

DAAN from NAD in NCP, YRD, PRD and FWP account for 55% of the national total in 2013 and the percentage increases to 59% in 2020. DAAN from NAD increases from 85 to 90 thousand in YRD, but decreases from 92 to 77 thousand in NCP in 2013–2020 \((p < 0.05, \text{figure } S2)\). DAAN from NAD in PRD and FWP show no trends. Thus, the relative contribution from YRD increases from 22% to 27% in 2013–2020 and YRD became the largest contributor. For cause-specific mortality, the relative contributions from the four regions are similar to those for NAD mortality. Similar as the trend of national DAAN from RD, DAAN from RD in NCP decrease by 3 thousand significantly \((p < 0.01)\). In contrast, DAAN from RD in YRD, PRD and FWP showed no significant trends. Similar as the trend of national total DAAN from CVD, DAAN from CVD increase by 16 thousand in YRD \((p < 0.05)\) and by 5 thousand \((p < 0.01)\) in FWP in 2013–2020. In contrast, DAAN from RD and CVD in other regions show no statistically significant trends.

The spatial distribution of DAAN from NAD in 2013, 2020 and the difference between the two years is shown in figure 2. Except for the four key regions, large DAAN is also seen in Sichuan, Chongqing, and cities in middle China. The area of large excess deaths is smaller in 2020 than that in 2013. The differences of DAAN from NAD in 2020 and 2013 are negative in a large part of NCP, PRD, Hubei, and Sichuan, but are positive in part of YRD and Liaoning. The spatial distribution of DAAN from CVD is similar as those of DAAN from NAD. However, the difference of DAAN from CVD in 2020 and 2013 are different from that of DAAN from NAD. Most of the increase of DAAN from CVD are in Liaoning, Shanxi, Henan, Anhui, and Shanghai, while most of the decrease of DAAN from CVD are in part of Hebei, Shandong, and Guangdong. Spatial distribution of DAAN from RD is distinctively different from distributions of DAAN from NAD and CVD. Large DAAN from RD is centered in a few large cities. Strong decrease of DAAN from RD spread in a large part of China: Beijing, Hebei, Henan, Shandong, Jiangsu, Sichuan, Guangdong, and Shaanxi. In summary, difference of DAAN from NAD, CVD and RD in 2020 and 2013 are positive in Liaoning, Shanxi, Shanghai, and Anhui, and are negative in Beijing, south Hebei, west Shandong, and south Guangdong.

3.2. Factors that control the variations of DAAN

Contribution from NO\textsubscript{2} concentration reduction to DAAN from NAD in 2017–2020 \((-27 \text{ thousand yr}^{-1})\) is much larger than that in 2013–2017 \((-10 \text{ thousand yr}^{-1}, \text{figure } 3)\). This is in general agreement with NO\textsubscript{2} concentration changes in the two periods. Annual mean NO\textsubscript{2} concentration in China changes marginally in 2013–2017 \((20.2–21.3 \mu\text{g m}^{-3})\), but decrease by 12% in 2017–2020. Baseline mortality change is also beneficial to reduce DAAN from NAD (2013–2017: \(-7 \text{ thousand}; 2017–2020: \(-2 \text{ thousand}\)). In contrast, population growth and aging...
increase DAAN from NAD by 4 and 13–15 thousand yr$^{-1}$, respectively, in 2013–2020. Statistical Year Book showed that population grow at a rate of 0.4% yr$^{-1}$ in China. According to the national statistical yearbook, population with age of 15–64 decreases from 73.9% to 70.2% in 2013–2020 (by 5%), while population with age above 65 increases from 9.7% in 2013 to 12.9% in 2020 in China (by 33%). As a result, the reduction of NO$_2$ concentration and baseline mortality of NAD offset the adverse effects of population growth and aging in 2013–2017. In 2017–2020, the contribution from air pollution reduction surpasses the effects of population growth and aging.
Baseline mortality of CVD decreases in 2013–2017 but increases substantially in 2017–2020. The faster reduction of NO\(_2\) does not offset the effect of faster increase of baseline mortality of CVD in 2017–2020. Thus, DAAN from CVD increase by 5 thousand yr\(^{-1}\) in 2017–2020, larger than the change in 2013–2017 (1 thousand yr\(^{-1}\)). In contrast, baseline mortality of RD in China decreases faster in 2013–2017 than in 2017–2020. The slower decreasing in the latter is offset by the faster decrease of NO\(_2\) concentration, thus DAAN from RD in the two periods are similar.

DAAN from NAD decrease in NCP (p < 0.05), but increase in YRD (p < 0.1) in 2013–2020. The difference among the regions is mainly from NO\(_2\) concentration (figure S3). Annual mean NO\(_2\) concentrations decrease much faster in 2017–2020 than those in 2013–2017 in the four key regions (figure S4). Annual mean NO\(_2\) concentration reduction rate in NCP is the largest (2013–2017: −2.8% yr\(^{-1}\); 2017–2020: −4.9% yr\(^{-1}\)). In the other three regions, annual mean NO\(_2\) concentrations change marginally (−0.6−+0.9% yr\(^{-1}\)) in 2013–2017, but decrease fast in 2017–2020 (−3.0−−5.2% yr\(^{-1}\)). As a result, NO\(_2\) concentration reduction in NCP was more than offset the adverse effects from population growth and aging. In contrast, the contribution from NO\(_2\) concentration reduction is smaller than the contribution from population growth and aging in YRD. This suggests that larger NO\(_2\) reduction is required in YRD, PRD and FWP to offset the adverse effects from other factors. DAAN from CVD and RD are decomposed in figures S5 and S6. The relative contribution from different factors in key regions are similar to the national total.

Increase of DAAN from NAD, CVD, and RD in 2013–2020 in Liaoning, Shanxi, Shanghai, and Anhui is mainly attributed to the relatively faster population aging and relatively slower NO\(_2\) concentration reduction (figure 4). In the future, NO\(_2\) emission reduction in these regions should be enhanced to reduce DAAN. The negative trends of DAAN in Beijing, south Hebei, west Shandong, and south Guangdong are attributed to the fast NO\(_2\) concentration reduction and the beneficial effects from baseline mortalities, despite the large adverse effects from population aging.

3.3 Sensitivity of DAAN to relative risk, shape of C-R function and threshold values
We tested the sensitivity of DAAN to RR values, the shape of C-R functions and the threshold values (See sensitivity experimental setup in table S2). In Test 1, using the RR value in Asia from Huang et al (2021), DAAN from NAD and cause-specific diseases are 2.3 and 3.2 times of the estimates in BASE experiment. Using the RR values from WHO, DAAN from NAD is 20% smaller than that in BASE experiment. DAAN from NAD estimated using supralinear C-R function in Test 2 is 1.4–1.5 times of those estimated using the linear function in BASE experiment. In Test 3, using 15 and 5 µg m\(^{-3}\) as the threshold values would decrease and increase the estimated DAAN.
from NAD by 24%–34% and 27%–43%, respectively. The difference is getting larger and larger over years. Thus, threshold values might also affect the trends of DAAN. We find that different from the significant increasing trend in BASE experiment, estimated DAAN from CVD using $15 \, \mu g \, m^{-3}$ as threshold value show no statistically significant trend.

### 3.4. Future trends

#### 3.4.1. Trends of population growths and aging

China is not only the country with the largest population on earth, but also one of the countries with the fastest aging process. Total population is growing at a rate of 0.49% yr$^{-1}$ in 2008–2019 according to the national statistical yearbook. It is predicted that population growth would slow down in 2020–2030 with a rate of 0.17% yr$^{-1}$ and will start to decrease in 2030 (www.populationpyramid.net/china). In addition, the share of population aged 65 and older is predicted to increase from 12.9% in 2020 to 19%, 27% and 31% in 2030, 2040 and 2050, mainly due to decades of falling birth rates on the one hand and steeply rising life expectancy on the other (Luo et al. 2021).

In other words, proportion of population aged 65 and above grows at a rate of 0.61% yr$^{-1}$ in 2020–2030, larger than the increasing rate of 0.46% yr$^{-1}$ in 2013–2020. The combined effect of population growth and aging before 2030 is enhancing DAAN. We estimated that to offset these effects before 2030, annual mean NO$_2$ concentration is required to decrease by 1.6% yr$^{-1}$, comparable to the decreasing rate of 1.7% yr$^{-1}$ in 2013–2020 and slower than the decreasing rate of 4.0% yr$^{-1}$ in 2017–2020. Thus, if NO$_2$ concentration continues the decreasing trend as in 2017–2020, it is more than enough to offset the adverse effects of population growth and aging, assuming unchanged baseline mortality.

#### 3.4.2. Trends of baseline mortalities

Although age-standardized mortality of CVD changed marginally (Yu et al. 2019) or declined in China in 2002–2016 (Sun et al. 2017), mortality rate of CVD increases at rates of 4.4% and 7.5% yr$^{-1}$ in urban and rural regions in 2006–2016 owing to the lifestyle changes, urbanization and population aging (Ma et al. 2020). In 2016 mortality from CVD was the leading cause of deaths and accounted for 45% of the total deaths. In contrast, mortality rates of RD decrease by 5.0, 2.2 and 2.8% yr$^{-1}$ in East, Middle and West China in 2013–2020, in line with the decreasing trends in the last thirty years ($-3.6\% \, yr^{-1}$, Sun et al. 2017, Zhang et al. 2020). Although with the decreasing trend, mortality from RD account for 12% of total deaths in 2016 (Ma et al. 2020), ranking as the third major cause of deaths. It is predicted that mortality rate of CVD and RD would continue the increasing and decreasing trends in the next decade (Ma et al. 2020). Following these trends, relative contribution of DAAN from CVD (93% in 2020) would also increase. Thus, helping to create and promote healthy lifestyles in Chinese population should be a fundamental national policy for the prevention of DAAN from CVD (Zhao et al. 2019).

### 4. Conclusions and summary

We estimated DAAN in China in 2013–2020 at 10 km resolution following the framework of GBD. We used RR values for NAD, CVD and RD from a meta-analysis (Huang et al. 2021). We assume a linear C-R function and a threshold value of 10 $\mu g \, m^{-3}$ following WHO (WHO 2021). We found that DAAN from NAD was comparable to the excess deaths from long-term exposure to ambient O$_3$. DAAN from NAD show no trends in 2013–2020. We tested the sensitivity of estimated DAAN to the choice of RR values, C-R function shape and threshold values. Using RR value in Asia increased DAAN by 1.3–2.2 times. DAAN increases by 40%–50% with supralinear C-R function compared to linear function. $5 \, \mu g \, m^{-3}$ difference of threshold values would change estimated DAAN by 24%–43%.

DAAN from RD reduces while those from CVD increases significantly. Excess deaths from RD account for ~10% of the excess deaths from NAD. Considering the upcoming decreasing trend of mortality rate of RD and increasing trend of CVD mortality rate, importance of DAAN from CVD would increase in the future. Control of mortality rate from CVD is critical in reducing DAAN in the future.

We found that the reduction of NO$_2$ concentration and baseline mortality of NAD offset the effects of population growth and aging in 2013–2017. In 2017–2020, the contribution from air pollution reduction surpasses the effects of population growth and aging. DAAN from NAD, CVD, and RD in 2020 were larger than those in 2013 in Liaoning, Shanxi, Shanghai, and Anhui. Faster reduction of emissions from NO$_2$ sources in these regions are needed to offset the adverse effects from population growth and aging.

Population in China is predicted to continue the increasing and aging trend in 2020–2030. Annual mean NO$_2$ concentration is required to decrease by 1.6% yr$^{-1}$ to offset these effects. Mortality rate of CVD and RD would continue the increasing and decreasing trends in the next decade. As a result, relative contribution of DAAN from CVD would also increase. Thus, promoting healthy lifestyles in Chinese population is critical to prevent DAAN from CVD.

The above results should be interpreted with caution, because the causality relationship between long-term exposure to NO$_2$ and population mortality is not firmly established due to lack of sufficient toxicological evidences. More toxicological and controlled human exposure studies are needed to fill the current knowledge gap.
Data availability statement

The data generated and/or analysed during the current study are not publicly available for legal/ethical reasons but are available from the corresponding author on reasonable request.

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