# Trend in Gastric Cancer Mortality in Kazakhstan

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## Abstract

**Objective:** The aim is to study the trends in gastric cancer (GC) mortality in Kazakhstan. Methods: Data on those who died from GC and on the annual population were obtained from the Bureau of National Statistics of the Agency for Strategic Planning and Reforms of the Republic of Kazakhstan. A retrospective study was carried out for the period 2009-2018 using descriptive and analytical methods of oncoepidemiology. The extensive, crude and agespecific mortality rates are determined according to the generally accepted methodology used in sanitary statistics. Results: GC mortality in Kazakhstan is considered to be decreasing. It was determined that during the studied period 19,672 died of this cancer. The mean of death was 67.8 with 95% CI of 67.6 to 68.0. The highest mortality rates per 100,000 in the entire population were found in the age groups 75-79 years  $(145.9\pm24.1)$ , 80-84 years  $(161.0\pm11.0)$ , and 85+ years (116.5±16.4). Trends in age-related mortality rates had a pronounced tendency to increase in 70-74 years (T=+4.3%, R<sup>2</sup>=0.1924) and to decrease in the age of up to 30 (T=-8.7%, R<sup>2</sup>=0.2426). The average annual standardized mortality rate was 13.2 per 100,000, and in trends tended to decrease (T=-5.8%; R<sup>2</sup>=0.9763). In all regions, there is a decrease in mortality, except for the city of Astana. During categorization mortality rates were determined on the basis of standardized indicators: low - up to 12.9, average - from 12.9 to 15.1, high - above 15.1 per 100,000 for the entire population. Conclusion: The mortality rates from GC tend to decrease, while the downward trends and the degree of their approximation are expressed in almost all regions. The study of regional mortality has theoretical and practical significance for monitoring and evaluating the effectiveness of early detection and treatment. Health authorities should take into account the results obtained when organizing antitumor measures.

Keywords: Gastric cancer - mortality - trends - geographical variation - Kazakhstan

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## Introduction

According to the GLOBOCAN 2020 database, stomach cancer is considered the fifth most common cancer (1,089,103 new cases) and the fourth leading cause of death (768,793 deaths) from cancer all over the world (Sung et al., 2021). Age-standardized rates of morbidity and mortality from stomach cancer were 11.1 and 7.7 per 100,000 people (Ferlay et al., 2020A). Gastric cancer is one of the leading causes of death in recent decades (Veisani and Delpisheh, 2016). The death rates from stomach cancer on a global scale are steadily decreasing (Rawla and Barsouk, 2019), but regional differences are obvious. High-risk regions include East Asia, Eastern Europe, Central and South America (Luo et al., 2017). In most countries, there are trends towards a decrease in the incidence and mortality from stomach cancer over the past decade, especially among male patients and persons aged 40 years and older. However, in some countries, including Sweden, Ecuador and the UK, there has been an increase in the incidence of stomach cancer in people younger than 40 years (Wong et al., 2021). Despite the favorable trends in mortality reduction worldwide, in some countries the decline is less noticeable. In a number

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of large European countries, the death rate from stomach cancer is decreasing by about 3% per year. Similar declining trends were observed in Japan and Korea (Thrift and El-Serag, 2020). Recent studies have found that Asia has the highest number of new cases of stomach cancer, stomach cancer-related deaths, and age-standardized morbidity and mortality rates (Yang et al., 2021). Stomach cancer is associated with a high burden of morbidity and mortality, especially in low- and middle-income countries (Sierra et al., 2016).

The main cause of stomach cancer is chronic H. pylori infection, which accounts for approximately 90% of cases of distal stomach cancer worldwide (Plummer et al., 2015). The prevalence of *H. pylori* infection among adults exceeds 50% in many industrialized countries (Peleteiro et al., 2014). A diet high in salt and a small amount of vegetables and lifestyle factors (smoking, coffee and alcohol consumption) account for 33% to 50% of all cases of stomach cancer (Chan and Wong, 2021). GC is a heterogeneous disease in which every cancer patient has their own genetic and molecular profile (Matsuoka and Yashiro, 2018). Database studies have documented the incidence of gastric cancer among patients with precancerous gastric lesions in Western countries (Song et al., 2015). Early detection of precancerous lesions, such as atrophic gastritis, intestinal metaplasia and dysplasia, using esophagogastroduodenoscopy and subsequent endoscopic or surgical resection help reduce the progression of malignant neoplasm (Li et al., 2016) and, consequently, the incidence and mortality associated with gastric cancer.

Reducing stomach cancer mortality also requires early identification of patients at high risk of developing stomach cancer and the development of treatment strategies aimed at slowing or preventing the progression of stomach cancer (Tsai et al., 2017). Since patients with early gastric cancer are usually asymptomatic, the frequency of early diagnosis of gastric cancer is low. Thus, in most patients (>70%) stomach cancer is detected in the late stages (Tan, 2019). The CONCORD program, which covered 71 countries, found that most cases of stomach cancer are diagnosed at late stages and the overall 5-year survival rate in most countries is less than 30% (Allemani et al., 2018). Thanks to the progress achieved in medicine and a deeper understanding of the pathogenesis of stomach cancer, approaches to the prevention of stomach cancer and the development of targeted therapy have emerged (Obermannová and Lordick, 2016). However, despite the development of radiation therapy, chemotherapy and immunotherapy, surgical resection remains the most effective method of treating stomach cancer (Chang et al., 2016; Das, 2017). It is more cost-effective to detect and treat stomach cancer in the early stages using endoscopic resection rather than surgical resection (Kim et al., 2016; Lee et al., 2017).

This study of gastric cancer mortality by age group and its geographical variability throughout Kazakhstan is the first in recent years.

## **Materials and Methods**

#### Registration of cancer mortality

Data on those who died from stomach cancer and on the annual population (taking into account age and gender) were obtained from the Bureau of National Statistics of the Agency for Strategic Planning and Reforms of the Republic of Kazakhstan. In this case, the registration of death is carried out in the civil registration authorities at the place of residence of the deceased or at the place of his death on the basis of a medical death certificate. Data on population mortality for the period from 2009 to 2018 were obtained for 14 regions and cities of republican significance - Almaty and Astana (now the city of Nur-Sultan) using the International Disease Code 10, code C16.

## Statistical analysis

The main method used in the study of mortality was a retrospective study using descriptive and analytical methods of epidemiology. Age-standardized mortality rates (ASRs) were calculated for eighteen different age groups (0-4, 5-9, ..., 80-84, and 85+) and ten calendar periods from 2009 to 2018 (1-year intervals). ASRs standardized to the world population proposed by World Health Organization (Ahmad et al., 2001) with recommendations from the National Cancer Institute (1976) were estimated for each studied year.

The extensive, crude rate (CR) and age-specific mortality rates (ASMR) are determined according to the generally accepted methodology used in sanitary statistics. The annual averages (M, P), mean error (m), Student criterion, 95% confidence interval (95% CI), and average annual upward/downward rates (T%) were calculated. Mortality rates are calculated per 100,000 of the corresponding population by age and gender annually. We have not given the basic calculation formulas in this article, as they are described in detail in methodological recommendations and textbooks on biomedical statistics (Merkov and Polyakov, 1974; Glanz, 1999; dos Santos Silva, 1999). Trends in mortality rates was studied for 10 years, while the trends of mortality were determined by the least squares method. To calculate the average annual growth rate and/or growth rate of the dynamic series, the geometric mean equal to the root of the power of n from the product of the annual growth rate indicators was used.

Viewing and processing of the data was carried out using the Microsoft 365 software package (Excel, Word, PowerPoint), in addition, online statistical calculators were used (https://medstatistic.ru/calculators/averagestudent. html), where Student criterion was calculated when comparing the average values.

#### Ethics approval

Because this study involved the analysis of publicly available administrative data and did not involve contacting individuals, consideration and approval by an ethics review board was not required. At the same time, the submitted data is in accordance with the Law of the Republic of Kazakhstan No. 257-IV of March 19, 2010 "About State statistics" (http://adilet.zan.kz/rus/docs/ Z100000257), the information in the summary report is confidential and can only be used for statistical purposes in accordance with the Principles of the World Medical Association (WMA, 2013). This research was carried out within the framework of Rustem Taszhanov's dissertation work.

## Results

During 10 years (2009-2018) 19,672 people died of GC, of these, there are 12,638 (64.2%) men and 7,034 (35.8%) women. The distribution of age groups by the number of deaths from GC showed that the groups aged 50 to 84 years were the most frequent -17,419 (88.5%) and a significant proportion of deaths from GC by age groups (both sexes) characterized by a high proportion of deaths was detected at the age of over 50 years (namely in the groups of 60-64 years – 14.3%, 65-69 years – 15.6%, 70-74 years – 15.3% and 75-79 years – 16.5%) (Table 1). The proportion of deaths from GC among the male and female population by age group was similar to that for both sexes.

The average age of those who died from GC in trend increased slightly from  $68.2\pm0.3$  years (95% CI=67.7-68.6) in 2009 to  $68.1\pm0.3$  years (95%CI=67.6-68.7), and average annual rate of growth made T=+0.03. An average age of the dead made  $67.8\pm0.1$  years (95%CI=67.6-68.0) (Table 1).

The highest mortality rates per 100,000 in the entire population were found in the age groups 75-79 years ( $145.9\pm24.1$ ), 80-84 years ( $161.0\pm11.0$ ), and 85+ years ( $116.5\pm16.4$ ) (Figure 1).

GC mortality had an upward trend only in two studied age groups: 70-74 years (T=+4.3%) and in the age of 80-84 years (T=+1.8%). In other age groups, the leveled GC mortality was decreasing, with the most pronounced annual average downward rates in the age groups of up to 30 (T=-8.7%), 55-59 years (T=-8.5%), and 60-64 years (T=-8.4%) (Table 1).

Age-specific mortality rates per 100,000 from gastric cancer had regional peculiarities: trimodal growth was observed in groups of 65-69, 75-79, 85+ years in West

Kazakhstan region (respectively 88.7, 126.5, 120.7) (Figure 2A). Bimodal growth with peaks in the groups of 65-69 and 80-84 years was observed in East Kazakhstan (respectively 97.2, 158.4) (Figure 2A) and in North Kazakhstan (respectively 89.4, 110.3) regions (Figure 2B), in the groups of 70-74 and 80-84 years was observed in Karaganda region (respectively 88.8, 86.4) (Figure 2A). In other regions there was a unimodal increase in mortality (Figure 2A and 2B).

Crude rates of GC mortality (Figure 3) tended to decrease from 14.0 $\pm$ 0.3 (95%CI=13.4-14.6) (2009) to 8.9 $\pm$ 0.2 (95%CI=8.4-9.3) in 2018 per 100,000, the average was 11.6 $\pm$ 0.6 per 100,000 (95%CI=8.4-9.3). The average annual rate of mortality decline by GC was significant T=-4.9% (R<sup>2</sup>=0.9800). Age - standardized mortality rate for the country was 13.2 $\pm$ 0.8 per 100,000 population (T=-5.8%; R<sup>2</sup>=0.9763). The standardized mortality rate for the study period in the male population was 22.7 $\pm$ 1.3 per 100,000 (T=-5.5%; R2=0.9468), while this indicator in the female population was almost 3 times less and amounted to 7.7 $\pm$ 0.5 per 100,000 (T=-6.6%; R<sup>2</sup>=0.9443).

Based on the calculated average annual CMR and ASMR GC indicators, the cartograms were compiled. The levels of GC CMR per 100,000 based on the following criteria were determined: low – up to 10.6, average – from 10.6 to 13.5, high – above 13.5. As a result, the following groups of regions were revealed (Figure 4A):

1. Regions with the lowest indicators (up to 10.6 per 100,000): South Kazakhstan (7.8), Mangystau (8.3), Astana city (9.3), Almaty (9.6), Atyrau (9.9).

2. Regions with average indicators (from 10.6 to 13.5 per 100,000): Kyzylorda (10.9), Almaty city (11.1), Aktobe (11.7), Kostanay (11.8), Zhambyl (11.8), West Kazakhstan (12.4), Karaganda (13.5).

3. Regions with high indicators (13.5 and above per 100,000): North Kazakhstan (15.3), East Kazakhstan (16.3), Pavlodar (16.4), Akmola (16.9).

The levels of GC ASMR per 100,000 population based on the following criteria were determined: low – up to 12.9, average – from 12.9 to 15.1, high – above 15.1. As a result, the following groups of regions were determined (Figure 4B):



Figure 1. Age Distribution of GC Mortality in Kazakhstan, 2009-2018

Table 1. Number Age	and Age-Specific	Mortality Rat	e of GC in	Kazakhstan,	2009-2018	Ma	ale				Fema	Female
		per 100,000	Т, %	$\mathbb{R}^2$		per 100,000	т, %	1	$\mathbb{R}^2$	R <sup>2</sup>	R <sup>2</sup> per 100,000	R <sup>2</sup> per 100,000 T, %
<30	59 (0.3)	$0.1{\pm}0.0$	-8.7	0.2426	28 (0.2)	$0.1{\pm}0.0$	-11.9		0.2777	0.2777 31 (0.4)	0.2777 31 (0.4) 0.1±0.0	0.2777 31 (0.4) 0.1±0.0 -6.1
30-34	118 (0.6)	$0.9{\pm}0.2$	-3.0	0.0322	41 (0.3)	$0.6{\pm}0.1$	-1.5		0.0057	0.0057 77 (1.1)	0.0057 77 (1.1) 1.2±0.2	0.0057 77 (1.1) 1.2±0.2 -3.7
35-39	214 (1.1)	$1.8 {\pm} 0.1$	-5.9	0.5630	105 (0.8)	$1.8 \pm 0.2$	-9.1		0.6071	0.6071 109 (1.5)	0.6071 109 (1.5) 1.8±0.2	0.6071 109 (1.5) 1.8±0.2 -2.9
40-44	416 (2.1)	$3.8 {\pm} 0.4$	-7.6	0.6087	234 (1.9)	4.4±0.5	-6.9		0.4357	0.4357 182 (2.6)	0.4357 182 (2.6) 3.2±0.3	0.4357 182 (2.6) 3.2±0.3 -8.4
45-49	637 (3.2)	$6.0 \pm 0.4$	-5.4	0.6683	434 (3.4)	8.5±0.6	-5.5		0.5439	0.5439 203 (2.9)	0.5439 203 (2.9) 3.6±0.4	0.5439 203 (2.9) 3.6±0.4 -5.3
50-54	1210 (6.2)	$12.2 \pm 1.0$	-7.3	0.8480	782 (6.2)	$17.0{\pm}1.4$	-7.5		0.8414	0.8414 428 (6.1)	0.8414 428 (6.1) 8.0±0.7	0.8414 428 (6.1) 8.0±0.7 -7.0
55-59	2048 (10.4)	25.7±2.2	-8.5	0.9457	1457 (11.5)	$41.1 \pm 3.9$	-9.2		0.9476	0.9476 591 (8.4)	0.9476 591 (8.4) 13.3±1.1	0.9476 591 (8.4) 13.3±1.1 -7.3
50-64	2810 (14.3)	$48.9 \pm 4.4$	-8.4	0.8843	2012 (15.9)	82.7±7.2	-7.9		0.8292	0.8292 798 (11.3)	0.8292 798 (11.3) 24.1±2.6	0.8292 798 (11.3) 24.1±2.6 -9.9
65-69	3063 (15.6)	82.6±9.0	-3.7	0.1213	2152 (17.0)	145.5±15.5	-3.2		0.0948	0.0948 911 (13.0)	0.0948 911 (13.0) 41.2±5.2	0.0948 911 (13.0) 41.2±5.2 -5.0
70-74	3000 (15.3)	94.8±9.2	+4.3	0.1924	1950 (15.4)	166.8±15.5	+4.3		0.2061	0.2061 1050 (14.9)	0.2061 1050 (14.9) 52.7±5.7	0.2061 1050 (14.9) 52.7±5.7 +4.7
15-79	3245 (16.5)	$145.9\pm24.1$	-17.8	0.9164	1926 (15.2)	$255.1{\pm}40.1$	-16.1		0.8790	0.8790 1319 (18.8)	0.8790 1319 (18.8) 90.2±15.9	0.8790 1319 (18.8) 90.2±15.9 -20.2
30-84	2043 (10.4)	$161.0{\pm}11.0$	+1.8	0.0671	1116 (8.8)	300.8±25.6	+2.6		0.0932	0.0932 927 (13.2)	0.0932 927 (13.2) 102.9±6.0	0.0932 927 (13.2) 102.9±6.0 +0.0
85+	809 (4.1)	$116.5 \pm 16.4$	-13.4	0.8260	401 (3.2)	240.7±36.5	-14.5		0.8076	0.8076 408 (5.8)	0.8076 408 (5.8) 77.7±11.5	0.8076 408 (5.8) 77.7±11.5 -14.5
CR	19672 (100.0)	$11.6 {\pm} 0.6$	-4.9	0.9800	12638 (100.0)	15.4±0.7	-4.4		0.9356	0.9356 7034 (100.0)	0.9356 7034 (100.0) 8.0±0.5	0.9356 7034 (100.0) 8.0±0.5 -5.9
ASR	I	$13.2 \pm 0.8$	-5.8	0.9763	I	22.7±1.29	-5.5		0.9468	0.9468 –	0.9468 – 7.7±0.53	0.9468 – 7.7±0.53 –6.6
Average Age	I	$67.8 \pm 0.1$	+0.03	0.0325	I	$67.3 \pm 0.1$	+0.1		0.2809	0.2809 -	0.2809 – 68.7±0.2	0.2809 - 68.7±0.2 -0.1



**Regions:** 1. Akmola, 2. Aktobe, 3. Almaty, 4. Atyrau, 5. East-Kazakhstan, 6. Zhambyl, 7. West-Kazakhstan, 8. Karaganda

Figure 2A. Age-Specific Mortality Rate of Gastric Cancer in Kazakhstan, 2009-2018

1. Regions with the lowest indicators (up to 12.9 per 100,000): Kostanay (9.98), Almaty city (11.5), Almaty (11.7), North Kazakhstan (12.1), Karaganda (12.3), West Kazakhstan (12.9).

2. Regions with average indicators (from 12.9 to 15.1 per 100,000): South Kazakhstan (13.5), East Kazakhstan (13.8), Atyrau (14.6), Aktobe (14.8), Pavlodar (14.9).

3. Regions with high indicators (15.1 per 100,000 and above): Mangystau (15.6), Akmola (15.6), Zhambyl

(16.3), Astana city (16.6), Kyzylorda (17.9).

Analyzing the average annual growth rates of standardized indicators, it was found that there was a downward trend in all regions (the minimum indicator was in Atyrau (T=-3.3%; R<sup>2</sup>=0.1764), and in South Kazakhstan (T=-3.9%; R<sup>2</sup>=0.6031), the maximum in West Kazakhstan (T=-10.5%; R<sup>2</sup>=0.8109)), except for the city of Astana (T=+1.9%; R<sup>2</sup>=0.1794) (Figure 5A).

In all regions, there is a decrease in the age-



Figure 2B. Age-Specific Mortality Rate of Gastric Cancer in Kazakhstan, 2009-2018

standardized indicator, while the downward trends and the degree of their approximation are expressed in almost all regions, which suggests that this trend will be stable in the coming years.

# Discussion

In our country, there is a clear decrease in mortality from stomach cancer, but at the same time, the mortality



Figure 3. Dynamics of GC Mortality in Kazakhstan, 2009-2018



**Regions:** 1. Akmola, 2. Aktobe, 3. Almaty, 4. Atyrau, 5. East-Kazakhstan, 6. Zhambyl, 7. West-Kazakhstan, 8. Karaganda, 9. Kostanay, 10. Kyzylorda, 11. Mangystau, 12. Pavlodar, 13. North-Kazakhstan, 14. South-Kazakhstan

Figure 4. Cartogram of Gastric Cancer mortality in Kazakhstan, 2009-2018



Regions: 1. Akmola, 2. Aktobe, 3. Almaty, 4. Atyrau, 5. East-Kazakhstan, 6. Zhambyl, 7. West-Kazakhstan, 8. Karaganda

Figure 5A. Trends of Age-Standardized Mortality Rates of Gastric Cancer in Kazakhstan, 2009-2018.

rate remains as high as ever. In Kazakhstan, as in the whole world, the majority of the deceased are men (64.2%). The same results were found in Tianjin – 67.1% (Zheng et al., 2020) and in Brazil – 64.9% (Braga et al., 2019). The rates of decline by region in Kazakhstan were different. This geographical structure may reflect a different distribution of risk factors for stomach cancer, such as the prevalence of *H. pylori*, poor eating habits, in addition to

the socio-economic situation of the population.

Mortality is declining worldwide, but mortality rates remain high for both sexes and unequal across geographical regions. The high mortality rates can be explained by the lack of preventive health policy, the lack of national screening measures for early detection and timely treatment of this neoplasm. 75.3% (819,944 people) of new cases and 74.8% (575,206 people) of



**Regions:** 9. Kostanay, 10. Kyzylorda, 11. Mangystau, 12. Pavlodar, 13. North-Kazakhstan, 14. South-Kazakhstan

Figure 5B. Trends of Age-Standardized Mortality Rates of Gastric Cancer in Kazakhstan, 2009-2018.

deaths from stomach cancer are Asian residents (Ferlay et al., 2020). The highest incidence rates per 100,000 were found in such countries as Mongolia (32.5), Japan (31.6), the Republic of Korea (27.9), Tajikistan (23.4), China (20.6). At the same time, the highest mortality rates per 100,000 were in Mongolia (24.6), Tajikistan (19.7), Bhutan (15.9), China (15.9), Kyrgyzstan (15.7) (Ferlay et al., 2020). Differences in morbidity and mortality from

stomach cancer can be explained by risk factors, such as the prevalence of Helicobacter pylori infection, alcohol consumption, smoking (Karimi et al., 2014); and may also depend on specific demographic, socio-economic and genetic characteristics of the population. Since the death rate from stomach cancer is directly related to the level of medical care (Choi et al., 2017), stomach cancer in countries with higher health care costs per capita has better

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clinical outcomes, and this is mainly due to improved quality of treatment (Yang et al., 2021). Although, of course, the rate of death from stomach cancer depends on many factors, such as early detection, universal screening, the general level of medicine, and so on. For example, a reduction in mortality and an increase in survival in Japan (0.45; 95%CI: 0.31-0.59) (Hamashima et al., 2015), Korea (the risk of GC-specific death - 0.58; 95% CI, 0.36 to 0.94 and survival rate - 2.24; 95% CI, 1.61 to 3.11) (Kim et al., 2018) and China (0.72; 95% CI: 0.54-0.97) (Chen et al., 2016) are associated with their endoscopic screening program. In general, in Asian countries endoscopic screening was associated with a 40% reduction in gastric cancer mortality (0.60; 95% CI, 0.49-0.73) (Zhang et al., 2018).

The downward trend in stomach cancer mortality may be related to an improved understanding of stomach cancer. Ongoing research on this topic helps to efficiently identify high-risk groups to prevent stomach cancer, choose the optimal strategy for effective treatment of the disease and reduce mortality by controlling the progression of the disease. H. pylori eradication therapy reduces the incidence of secondary gastric cancer in patients who have undergone endoscopic resection of the mucous membrane in early gastric cancer (0.53;95%CI: 0.44–0.64), demonstrating the preventive effect of *H. pylori* eradication therapy against stomach cancer (Sugimoto et al., 2020). One of the proofs of this statement can be considered a decrease in the number of deaths (by about 9.2%) from stomach cancer in a few years after the increase in eradication therapy in Japan, which remained stable for several decades (Tsuda et al., 2017).

Understanding the trend of deaths from stomach cancer stratified by geographical regions will help to assess the efficacy of health policies implemented for the prevention and control of stomach cancer, identify obstacles to access to treatment for stomach cancer and, finally, optimize the allocation of health resources to improve the results of treatment of patients with stomach cancer. The burden of gastric cancer mortality will be a priority of our next studies.

## **Author Contribution Statement**

RT, ZT, AB, KK, NS – Collection and preparation of data, primary processing of the material and their verification. RT, KI, ZB, TK, VM – Statistical processing and analysis of the material, writing the text of the article (material and methods, results). RT, GN, SO, SK, FD, ZA, KR – Writing the text of the article (introduction, discussion). NI, RT, GI, US, IK – Concept, design and control of the research, approval of the final version of the article. All authors approved the final version of the manuscript.

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#### Conflict of interest

The authors declare that there is no conflict of interest

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