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**Response:** Thank you, we have carefully revised our manuscript.

## 3 SCIENTIFIC QUALITY

Please resolve all issues in the manuscript based on the peer review report and make a point-by-point response to each of the issues raised in the peer review report. Note, authors must resolve all issues in the manuscript that are raised in the peer-review report(s) and provide point-by-point responses to each of the issues raised in the peer-review report(s); these are listed below for your convenience:

**Response:** Authors are thankful to the Editors and the Reviewers for their careful reading of our manuscript. Their helpful comments have helped us improve our manuscript.

Reviewer #1:

**Scientific Quality:** Grade C (Good)

**Language Quality:** Grade B (Minor language polishing)

**Conclusion:** Minor revision

**Specific Comments to Authors:** In this manuscript, the Authors analyzed data concerning pancreatic cancer extracted from WHO databases (GLOBOCAN 2020) reported on the number of new diagnosis, the incidence of and the mortality for pancreatic cancer worldwide in 2020, according to sex, to WHO regions, and to countries. In addition, they also analyzed global and national trends in incidence and mortality of pancreatic cancer in the period between 1990 and 2017, according to sex and age class. Overall, they found that the highest incidence and mortality for pancreatic cancer were observed in the European region, while the lowest in the south East Asia Region. In addition, they found a pattern of increasing incidence and mortality for pancreatic cancer in the majority of countries included in this analysis, with minimal exceptions. The manuscript is well written and readable, the statistical analysis is adequately performed.

My comments: Abstract, methods: I suggest to mention that an analysis of pancreatic cancer incidence and mortality during 2020 was performed.

**Answer:**

Thank you very much for your valuable comments. Correction was made in the revised manuscript (in Abstract – Methods).

Data source (page 9): similar to the above comment: please mention that the first analysis of incidence and mortality for pancreatic cancer shown in the manuscript regards the year 2020.

**Answer:**

Thank you very much for your helpful comments. Correction was made in the revised manuscript (in section Materials and Methods – Data source).

Results: - I strongly believe that dividing this chapter in paragraphs (concerning: year 2020 results; patterns in incidence trends; pattern in mortality trends; pattern in trends according to age classes) may improve readability of the manuscript.

**Answer:**

Thank you very much for your valuable comments. Correction was made in the revised manuscript (in section Results).

- It would be interesting to investigate how patterns in incidence and mortality trends change according to age classes: is pancreatic cancer becoming more common because its incidence is increasing among younger or older age class or both?

**Answer:**

Thank you for this valuable comment. Correction was made in the revised manuscript; in the section Discussion we added new sentences, which read as follows:

"Although in countries where there is a significant trend of increasing incidence of pancreatic cancer this increase was recorded at the age of 50 and older, of particular concern is the significant trend of increasing incidence of pancreatic cancer in the youngest group (30-49 years), which is registered in our study mainly in developed countries (United Kingdom, USA, Australia, France, Israel, Italy, and Bulgaria). Also, although the trend of increasing mortality from pancreatic cancer was recorded at the age of 50 and above, the significant trend of increasing mortality from pancreatic cancer among the youngest group (30 to 49 years) in women is particularly worrying, mainly in developed countries such as the USA, France, Germany, Spain, and Brazil, and in males in Chile, China, Brazil and El Salvador. Although there is no unified definition, some authors defined the onset of pancreatic cancer at an age of 50 or younger as early-onset pancreatic cancer<sup>[48,49]</sup>. Similar to our results, one study found a significantly increasing trend in incidence of pancreatic cancer among persons younger than 40 years only in women in 4 high-income countries (Canada, the United Kingdom, France and the Netherlands)<sup>[27]</sup>. Despite the fact that some studies suggest an association with cigarette smoking, genetic factors, obesity and metabolic disorders, the reasons for the increasing trends in incidence and mortality of early-onset pancreatic cancer are still not well understood<sup>[50-52]</sup>. Population data on tobacco use from 12 European countries revealed that in both men and women, smoking prevalence was the highest among young adults aged 25-44 years, and decreased with increasing age<sup>[50]</sup>. Results of 2 prospective US cohort studies indicated that established risk factors were more strongly associated with earlier-onset pancreatic cancer (ie among those aged  $\leq 60$  years), while association attenuated among elderly<sup>[51]</sup>. The question of whether the frequency of performing diagnostic and therapeutic procedures, as well as

autopsies at a younger age has an impact on the trend in incidence and mortality from earlier-onset pancreatic cancer should also be clarified in future research<sup>[53]</sup>.”.

**Note:** six new references were added in the list of references in the corrected manuscript:

- **Raimondi S**, Maisonneuve P, L  hr JM, Lowenfels AB. Early onset pancreatic cancer: evidence of a major role for smoking and genetic factors. *Cancer Epidemiol Biomarkers Prev* 2007; **16**: 1894-1897 [PMID: 17855711 DOI: 10.1158/1055-9965.EPI-07-0341]
- **Piciucchi M**, Capurso G, Valente R, Larghi A, Archibugi L, Signoretti M, Stigliano S, Zerboni G, Barucca V, La Torre M, Cavallini M, Costamagna G, Marchetti P, Ziparo V, Delle Fave G. Early onset pancreatic cancer: risk factors, presentation and outcome. *Pancreatology* 2015; **15**: 151-155 [PMID: 25708929 DOI: 10.1016/j.pan.2015.01.013]
- **Gallus S**, Lugo A, Liu X, Behrakis P, Boffi R, Bosetti C, Carreras G, Chatenoud L, Clancy L, Contente X, Dobson R, Effertz T, Filippidis FT, Fu M, Geshanova G, Gorini G, Keogan S, Ivanov H, Lopez MJ, Lopez-Nicolas A, Precioso J, Przewozniak K, Radu-Loghin C, Ruprecht A, Semples S, Soriano JB, Starchenko P, Trapero-Bertran M, Tigova O, Tzortzi AS, Vardavas C, Vyzikidou VK, Colombo P, Fernandez E; TackSHS Project Investigators. Who Smokes in Europe? Data From 12 European Countries in the TackSHS Survey (2017-2018). *J Epidemiol* 2021; **31**: 145-151 [PMID: 32249267 DOI: 10.2188/jea.JE20190344]
- **Yuan C**, Kim J, Wang QL, Lee AA, Babic A; PanScan/PanC4 I-III Consortium, Amundadottir LT, Klein AP, Li D, McCullough ML, Petersen GM, Risch HA, Stolzenberg-Solomon RZ, Perez K, Ng K, Giovannucci EL, Stampfer MJ, Kraft P, Wolpin BM. The age-dependent association of risk factors with pancreatic cancer. *Ann Oncol* 2022; S0923-7534(22)00672-X [PMID: 35398288 DOI: 10.1016/j.annonc.2022.03.276]
- **McWilliams RR**, Maisonneuve P, Bamlet WR, Petersen GM, Li D, Risch HA, Yu H, Fontham ET, Lockett B, Bosetti C, Negri E, La Vecchia C, Talamini R, Bueno de Mesquita HB, Bracci P, Gallinger S, Neale RE, Lowenfels AB. Risk Factors for Early-Onset and Very-Early-Onset Pancreatic Adenocarcinoma: A Pancreatic Cancer Case-Control Consortium (PanC4) Analysis. *Pancreas* 2016; **45**: 311-316 [PMID: 26646264 DOI: 10.1097/MPA.0000000000000392]
- **LaPelusa M**, Shen C, Arhin ND, Cardin D, Tan M, Idrees K, Geevarghese S, Chakravarthy B, Berlin J, Eng C. Trends in the Incidence and Treatment of Early-Onset Pancreatic Cancer. *Cancers (Basel)* 2022; **14**: 283 [PMID: 35053447 DOI: 10.3390/cancers14020283]

**Discussion:** Page 17: the authors report results from previous studies on trends of pancreatic cancer incidence between 1970 and 1990, however such data are not adequately connected with results from the current study. Please improve it.

**Answer:**

Thank you for this valuable comment. Correction was made in the revised manuscript, in the section Discussion we added new sentences, which read as follows:

”Our study showed unfavorable trends in pancreatic cancer incidence rates in both males and females in many countries in the world in the last three decades. The incidence was noticeably increasing throughout European countries, the United States of America, Australia,

and Japan, while stable trends in incidence were noted in Canada, Sweden and Ireland. One previous study showed that pancreatic cancer incidence rates gradually increased in males and females among all ages in the USA, Canada, the Netherlands, Australia, New Zealand from the mid-1990s until 2014<sup>[31]</sup>. In the same study, a decreasing trend of pancreatic cancer incidence in males was noticed only in Iceland and Croatia, while in women there was a significant increasing trend in the incidence of pancreatic cancer in most of the countries from the 1990s onwards<sup>[31]</sup>. The pancreatic cancer incidence in both sexes in China increased continuously from 1990 to 2019<sup>[32]</sup>. The observed increasing trends in pancreatic cancer incidence could be attributed to population growth and ageing, as well as changes in the prevalence of risk factors for cancer<sup>[6,33,34]</sup>. Global Burden of Disease study demonstrated that there was a link between increasing trends in incidence for pancreatic cancer and increases in development status at the national level in period 1990-2017<sup>[6]</sup>. Also, one previous study indicated that increasing trends in pancreatic cancer incidence in both sexes were correlated with socioeconomic development (measured by Human Development Index and Gross Domestic Product per capita)<sup>[35]</sup>. In the 1980s, a rapid social and economic transition from the lifestyle that characterized socialistic countries (such as countries of the former Eastern Bloc, etc) to an industrialized westernized lifestyle took place<sup>[36-38]</sup>; it is hypothesized that, with a lag phase, undergoing different states of social and economic transition has contributed to the sharply increasing trends of pancreatic cancer incidence that have been observed in east and south European countries, China, Brazil since 2000s. Based the results of the Czech MONICA and post-MONICA studies, cigarette smoking prevalence declined significantly only in males (from 45.0% in 1985 to 23.9% in 2016/17), while there was no change in the prevalence of smoking in females (from 20.9% to 25.9%) over the analyzed period<sup>[38]</sup>. Throughout the entire 30-year survey period, for both sexes a significantly decreased prevalence of dyslipidemia and the consumption of meat and fat was observed, with increase in vegetable oils intake and fresh fruit and vegetable, whereas a significant increase in body mass index was observed in males only<sup>[38]</sup>. Both the incidence and mortality trends of pancreatic cancer significantly increased in China during the last decades, which could be due to the rise of the prevalence of overweight to 28.1%, diabetes to 11.2%, and smoking to 28.1% of adults: namely, China consumes about 40% of the world's total cigarettes, and that predominantly among men, with a large increase in consumption over the past decades<sup>[32,39]</sup>. A large-scale nationwide cohort study in the Republic of Korea, which included 9,514,171 adults during a median follow-up period of 7.3 years, indicated that diabetes and alcohol use were associated with an increased risk of pancreatic cancer<sup>[40]</sup>. On the other hand, the influence of the improvement of medical imaging on the diagnosis of pancreatic cancer, that is, on the increasing trends of the incidence of pancreatic cancer during the last decades cannot be ruled out<sup>[41]</sup>.”.

Note: Eight new references were added in the list of references in the corrected manuscript:

- **Lucas AL**, Malvezzi M, Carioli G, Negri E, La Vecchia C, Boffetta P, Bosetti C. Global Trends in Pancreatic Cancer Mortality From 1980 Through 2013 and Predictions for 2017. *Clin Gastroenterol Hepatol* 2016; **14**: 1452-1462.e4 [PMID: 27266982 DOI: 10.1016/j.cgh.2016.05.034]

- **Tsai HJ**, Chang JS. Environmental Risk Factors of Pancreatic Cancer. *J Clin Med* 2019; **8**: 1427 [PMID: 31510046 DOI: 10.3390/jcm8091427]
- **Shkolnikov VM**, Churilova E, Jdanov DA, Shalnova SA, Nilssen O, Kudryavtsev A, Cook S, Malyutina S, McKee M, Leon DA. Time trends in smoking in Russia in the light of recent tobacco control measures: synthesis of evidence from multiple sources. *BMC Public Health* 2020; **20**: 378 [PMID: 32293365 DOI: 10.1186/s12889-020-08464-4]
- **Psota M**, Bandosz P, Gonçalvesová E, Avdičová M, Bucek Pšenková M, Studenčan M, Pekarčíková J, Capewell S, O'Flaherty M. Explaining the decline in coronary heart disease mortality rates in the Slovak Republic between 1993-2008. *PLoS One* 2018; **13**: e0190090 [PMID: 29320517 DOI: 10.1371/journal.pone.0190090]
- **Cífková R**, Bruthans J, Wohlfahrt P, Krajčoviechová A, Šulc P, Jozífová M, Eremiášová L, Pudil J, Linhart A, Widimský J Jr, Filipovský J, Mayer O Jr, Škodová Z, Poledne R, Stávek P, Lánská V. 30-year trends in major cardiovascular risk factors in the Czech population, Czech MONICA and Czech post-MONICA, 1985 - 2016/17. *PLoS One* 2020; **15**: e0232845 [PMID: 32392239 DOI: 10.1371/journal.pone.0232845]
- **Liu S**, Zhang M, Yang L, Li Y, Wang L, Huang Z, Wang L, Chen Z, Zhou M. Prevalence and patterns of tobacco smoking among Chinese adult men and women: findings of the 2010 national smoking survey. *J Epidemiol Community Health* 2017; **71**: 154-161 [PMID: 27660401 DOI: 10.1136/jech-2016-207805]
- **Park JH**, Han K, Hong JY, Park YS, Park JO. Association between alcohol consumption and pancreatic cancer risk differs by glycaemic status: A nationwide cohort study. *Eur J Cancer* 2022; **163**: 119-127 [PMID: 35065369 DOI: 10.1016/j.ejca.2021.12.027]
- **Defossez G**, Uhry Z, Delafosse P, Dantony E, d'Almeida T, Plouvier S, Bossard N, Bouvier AM, Molinié F, Woronoff AS, Colonna M, Grosclaude P, Remontet L, Monnereau A; French Network of Cancer Registries (FRANCIM). Cancer incidence and mortality trends in France over 1990-2018 for solid tumors: the sex gap is narrowing. *BMC Cancer* 2021; **21**: 726 [PMID: 34167516 DOI: 10.1186/s12885-021-08261-1]

In the subsequent paragraph of the discussion, concerning trends of incidence and mortality among males and females, is a repetition of results previously exposed in related chapter.

**Answer:**

Thank you for this valuable comment. Correction was made in the revised manuscript, and those paragraphs in section Discussion completely reconstructed, as follows:

"Our study showed unfavorable trends in pancreatic cancer incidence rates in both males and females in many countries in the world in the last three decades. The incidence was noticeably increasing throughout European countries, the United States of America, Australia, and Japan, while stable trends in incidence were noted in Canada, Sweden and Ireland. One previous study showed that pancreatic cancer incidence rates gradually increased in males and females among all ages in the USA, Canada, the Netherlands, Australia, New Zealand from the mid-1990s until 2014<sup>[31]</sup>. In the same study, a decreasing trend of pancreatic cancer incidence in males was noticed only in Iceland and Croatia, while in women there was a significant increasing trend in the incidence of pancreatic cancer in most of the countries from the 1990s onwards<sup>[31]</sup>. The pancreatic cancer incidence in both sexes in China increased continuously

from 1990 to 2019<sup>[32]</sup>. The observed increasing trends in pancreatic cancer incidence could be attributed to population growth and ageing, as well as changes in the prevalence of risk factors for cancer<sup>[6,33,34]</sup>. Global Burden of Disease study demonstrated that there was a link between increasing trends in incidence for pancreatic cancer and increases in development status at the national level in period 1990-2017<sup>[6]</sup>. Also, one previous study indicated that increasing trends in pancreatic cancer incidence in both sexes were correlated with socioeconomic development (measured by Human Development Index and Gross Domestic Product per capita)<sup>[35]</sup>. In the 1980s, a rapid social and economic transition from the lifestyle that characterized socialistic countries (such as countries of the former Eastern Bloc, etc) to an industrialized westernized lifestyle took place<sup>[36-38]</sup>; it is hypothesized that, with a lag phase, undergoing different states of social and economic transition has contributed to the sharply increasing trends of pancreatic cancer incidence that have been observed in east and south European countries, China, Brazil since 2000s. Based the results of the Czech MONICA and post-MONICA studies, cigarette smoking prevalence declined significantly only in males (from 45.0% in 1985 to 23.9% in 2016/17), while there was no change in the prevalence of smoking in females (from 20.9% to 25.9%) over the analyzed period<sup>[38]</sup>. Throughout the entire 30-year survey period, for both sexes a significantly decreased prevalence of dyslipidemia and the consumption of meat and fat was observed, with increase in vegetable oils intake and fresh fruit and vegetable, whereas a significant increase in body mass index was observed in males only<sup>[38]</sup>. Both the incidence and mortality trends of pancreatic cancer significantly increased in China during the last decades, which could be due to the rise of the prevalence of overweight to 28.1%, diabetes to 11.2%, and smoking to 28.1% of adults: namely, China consumes about 40% of the world's total cigarettes, and that predominantly among men, with a large increase in consumption over the past decades<sup>[32,39]</sup>. A large-scale nationwide cohort study in the Republic of Korea, which included 9,514,171 adults during a median follow-up period of 7.3 years, indicated that diabetes and alcohol use were associated with an increased risk of pancreatic cancer<sup>[40]</sup>. On the other hand, the influence of the improvement of medical imaging on the diagnosis of pancreatic cancer, that is, on the increasing trends of the incidence of pancreatic cancer during the last decades cannot be ruled out<sup>[41]</sup>.

Pancreatic cancer mortality rates across the countries showed an increasing trend in both sexes. A decreasing trend, on the other hand, was found in both sexes only in Canada and Mexico, and a level-off was observed in Denmark, Norway, Sweden, Panama, Republic of Moldova, and Venezuela. With the exception of some developing countries (Latvia, Kyrgyzstan, Mauritius, Turkmenistan, Nicaragua and Colombia), in all other populations the magnitude of the increase in mortality from pancreatic cancer was higher in women. While the increased trends of pancreatic cancer mortality have long been observed in developed countries (such as the United States of America, Japan, Germany, France, Italy, Spain)<sup>[33]</sup>, in recent years a precipitous increase has also been reported in developing countries (such as Kyrgyzstan, Turkmenistan, Bulgaria, Serbia, etc)<sup>[42,43]</sup>. Some of these changes have been associated with western lifestyle and environmental factors which are linked to an increased risk of pancreatic cancer occurrence (including smoking, diabetes, alcohol consumption, obesity, physical inactivity, high-energy food intake, etc)<sup>[8,22,23,27,35,38,44]</sup>. International patterns in incidence and mortality trends of pancreatic cancer in the last three decades mostly reflect different phases of

the smoking epidemic across countries, and among males and females<sup>[26]</sup>. In support of that, our study indicated that mortality rates from pancreatic cancer showed a slower rise among women and a drop among men in China in the last decade (from 1998 to 2012), which could be affected by reduced prevalence of tobacco consumption<sup>[44,45]</sup>. Also, significantly decreasing trends in pancreatic cancer mortality in both sexes in Mexico (especially since 2008) can partially be attributed to changes in smoking patterns which are resulting from new tobacco tax/laws which were implemented in Mexico in 2007/2008<sup>[46]</sup>. Unfortunately, due to the silent nature of disease, late diagnosis, and limited treatment options, and the metastatic potential of pancreatic cancer cells, and its poor prognosis, most pancreatic cancers are diagnosed at an advanced stage, which is not amenable to treatment<sup>[42,43]</sup>. Differences in the international patterns in incidence and mortality trends of pancreatic cancer in the last three decades could be pertinent to impel continuous efforts to identify novel risk factors (particularly the modifiable risk factors) and implement policies for more effective pancreatic cancer control<sup>[34]</sup>. Global inequalities in standard medical practices (prevention/diagnosis/therapy) and their impact on pancreatic cancer mortality have not yet been systematically explored<sup>[47]</sup>.”.

**Note:** Thirteen new references were added in the list of references in the corrected manuscript:

- **Lucas AL**, Malvezzi M, Carioli G, Negri E, La Vecchia C, Boffetta P, Bosetti C. Global Trends in Pancreatic Cancer Mortality From 1980 Through 2013 and Predictions for 2017. *Clin Gastroenterol Hepatol* 2016; **14**: 1452-1462.e4 [PMID: 27266982 DOI: 10.1016/j.cgh.2016.05.034]
- **Tsai HJ**, Chang JS. Environmental Risk Factors of Pancreatic Cancer. *J Clin Med* 2019; **8**: 1427 [PMID: 31510046 DOI: 10.3390/jcm8091427]
- **Shkolnikov VM**, Churilova E, Jdanov DA, Shalnova SA, Nilssen O, Kudryavtsev A, Cook S, Malyutina S, McKee M, Leon DA. Time trends in smoking in Russia in the light of recent tobacco control measures: synthesis of evidence from multiple sources. *BMC Public Health* 2020; **20**: 378 [PMID: 32293365 DOI: 10.1186/s12889-020-08464-4]
- **Psota M**, Bandosz P, Gonçalvesová E, Avdičová M, Bucek Pšenková M, Studenčan M, Pekarčíková J, Capewell S, O'Flaherty M. Explaining the decline in coronary heart disease mortality rates in the Slovak Republic between 1993-2008. *PLoS One* 2018; **13**: e0190090 [PMID: 29320517 DOI: 10.1371/journal.pone.0190090]
- **Cífková R**, Bruthans J, Wohlfahrt P, Krajčoviechová A, Šulc P, Jozífová M, Eremiášová L, Pudil J, Linhart A, Widimský J Jr, Filipovský J, Mayer O Jr, Škodová Z, Poledne R, Stávek P, Lánská V. 30-year trends in major cardiovascular risk factors in the Czech population, Czech MONICA and Czech post-MONICA, 1985 - 2016/17. *PLoS One* 2020; **15**: e0232845 [PMID: 32392239 DOI: 10.1371/journal.pone.0232845]
- **Liu S**, Zhang M, Yang L, Li Y, Wang L, Huang Z, Wang L, Chen Z, Zhou M. Prevalence and patterns of tobacco smoking among Chinese adult men and women: findings of the 2010 national smoking survey. *J Epidemiol Community Health* 2017; **71**: 154-161 [PMID: 27660401 DOI: 10.1136/jech-2016-207805]
- **Park JH**, Han K, Hong JY, Park YS, Park JO. Association between alcohol consumption and pancreatic cancer risk differs by glycaemic status: A nationwide cohort study. *Eur J Cancer* 2022; **163**: 119-127 [PMID: 35065369 DOI: 10.1016/j.ejca.2021.12.027]

- **Defossez G**, Uhry Z, Delafosse P, Dantony E, d'Almeida T, Plouvier S, Bossard N, Bouvier AM, Molinié F, Woronoff AS, Colonna M, Grosclaude P, Remontet L, Monnereau A; French Network of Cancer Registries (FRANCIM). Cancer incidence and mortality trends in France over 1990-2018 for solid tumors: the sex gap is narrowing. *BMC Cancer* 2021; **21**: 726 [PMID: 34167516 DOI: 10.1186/s12885-021-08261-1]
- **Saad AM**, Turk T, Al-Husseini MJ, Abdel-Rahman O. Trends in pancreatic adenocarcinoma incidence and mortality in the United States in the last four decades; a SEER-based study. *BMC Cancer* 2018; **18**: 688 [PMID: 29940910 DOI: 10.1186/s12885-018-4610-4]
- **Seoane-Mato D**, Nuñez O, Fernández-de-Larrea N, Pérez-Gómez B, Pollán M, López-Abente G, Aragonés N. Long-term trends in pancreatic cancer mortality in Spain (1952-2012). *BMC Cancer* 2018; **18**: 625 [PMID: 29866063 DOI: 10.1186/s12885-018-4494-3]
- **GBD 2019 Risk Factors Collaborators**. Global burden of 87 risk factors in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet* 2020; **396**: 1223-1249 [PMID: 33069327 DOI: 10.1016/S0140-6736(20)30752-2]
- **Zhang K**, Tartarone A, Pérez-Ríos M, Novello S, Mariniello A, Roviello G, Zhang J. Smoking burden, MPOWER, future tobacco control and real-world challenges in China: reflections on the WHO report on the global tobacco epidemic 2021. *Transl Lung Cancer Res* 2022; **11**: 117-121 [PMID: 35242633 DOI: 10.21037/tlcr-22-27]
- **Hernández-Garduño E**. The impact of tobacco tax/law implementation on pancreatic cancer mortality in Mexico, 1999-2015. *Ecancermedicalscience* 2018; **12**: ed85 [PMID: 30483361 DOI: 10.3332/ecancer.2018.ed85]

Instead, the authors should try to interpret such results, comparing them with results previously published.

**Answer:**

Thank you for this valuable comment. Correction was made in the revised manuscript, and section Discussion was completely reconstructed, and now reads as follows:

"Since the risk of pancreatic cancer occurrence increases linearly with age and the average age at the time of diagnosis of pancreatic cancer is 70<sup>[2-6]</sup>, significant geographic differences in pancreatic cancer incidence and mortality rates could be explained by differences in life expectancy at birth by region: although improving continuously in all regions in the past decades, life expectancy at birth in 2019 was the highest in countries in Northern America and Europe, and the lowest in South Asia and Africa<sup>[21]</sup>. Also, the Global Burden of Disease study showed the association of age-standardized incidence and mortality rates for pancreatic cancer with development status at the national level (measured by the Socio-demographic Index, that composes the total fertility rate among women under the age of 25, mean education for individuals aged 15 and older, and income per capita) in 2017<sup>[6]</sup>. Based on the current evidence, international variations in incidence rates of pancreatic cancer are mainly attributed to exposure to environmental factors, particularly tobacco smoking, obesity, diabetes mellitus, alcohol consumption<sup>[6,22,23]</sup>. Additionally, the migrant effect among Japanese in Hawaii<sup>[24]</sup> and the discrepancies in pancreatic cancer incidence in Chinese populations<sup>[25]</sup>, which share similar genetics, but have lived in different regions, indicate that cancer development was mainly determined by environmental factors. Based on the WHO 2015 estimates, the prevalence of



tobacco smoking was the highest in countries in the European region (35% in Greece, equally 33% in the Russian Federation and Serbia), intermediate (about 20%) in Western Pacific and Eastern Mediterranean, and the lowest (nearly 10%) in Africa and Americas<sup>[26]</sup>. Based on the results of the Global Burden of Disease Study, pancreatic cancer deaths worldwide were primarily attributable to smoking (25.9% in males, 16.1% in females), high fasting plasma glucose (9.3% in males, 8.6% in females), and high body-mass index (5.0% in males, 7.4% in females) in 2017<sup>[6]</sup>. In both sexes together in 2017, fraction of pancreatic cancer age-standardized deaths attributable to smoking was the highest in central Europe (28.2% of all pancreatic cancer deaths), while the highest fraction attributable to high fasting plasma glucose was observed in Oceania (16.6%), and the highest fraction attributable to high body mass index was observed in high-income North America (10.2%)<sup>[6]</sup>. Similarly, the correlation analysis of risk factors for pancreatic cancer for 48 countries showed that higher incidence and mortality rates among men were significantly associated with higher prevalence of smoking, alcohol drinking, physical inactivity, obesity and high cholesterol levels<sup>[27]</sup>. At the same time, pancreatic cancer rates among women were linked with higher prevalence of smoking, alcohol drinking and high cholesterol. On the other hand, the correlation analysis indicated absence of association between the prevalence of diabetes mellitus and the incidence and mortality for pancreatic cancer. Contrary, a recent meta-analysis involving 23 cohort studies indicated that diabetes mellitus was associated with a 52% excess risk for pancreatic cancer<sup>[28]</sup>. However, the issue of the validity of a cancer certificate always exists and the impact of variations in data quality on incidence rates cannot be ruled out, especially for pancreatic and other cancers with poorer prognosis and in older age groups<sup>[29,30]</sup>. Pancreatic cancer incidence rates in the world in 2020 indicate the possibility that there is an underestimation of the incidence rates in many countries, mainly in developing countries<sup>[2]</sup>. Namely, many countries reported the incidence rate that was equal to the mortality rate of pancreatic cancer in 2020, while in few countries the mortality rate was higher than the incidence rate<sup>[2]</sup>. Besides, in many countries cancer registries were not populational, but sometimes reported data only from urban / metropolitan area.

Our study showed unfavorable trends in pancreatic cancer incidence rates in both males and females in many countries in the world in the last three decades. The incidence was noticeably increasing throughout European countries, the United States of America, Australia, and Japan, while stable trends in incidence were noted in Canada, Sweden and Ireland. One previous study showed that pancreatic cancer incidence rates gradually increased in males and females among all ages in the USA, Canada, the Netherlands, Australia, New Zealand from the mid-1990s until 2014<sup>[31]</sup>. In the same study, a decreasing trend of pancreatic cancer incidence in males was noticed only in Iceland and Croatia, while in women there was a significant increasing trend in the incidence of pancreatic cancer in most of the countries from the 1990s onwards<sup>[31]</sup>. The pancreatic cancer incidence in both sexes in China increased continuously from 1990 to 2019<sup>[32]</sup>. The observed increasing trends in pancreatic cancer incidence could be attributed to population growth and ageing, as well as changes in the prevalence of risk factors for cancer<sup>[6,33,34]</sup>. Global Burden of Disease study demonstrated that there was a link between increasing trends in incidence for pancreatic cancer and increases in development status at the national level in period 1990-2017<sup>[6]</sup>. Also, one previous study indicated that increasing trends in pancreatic cancer incidence in both sexes were correlated with socioeconomic development

(measured by Human Development Index and Gross Domestic Product per capita)<sup>[35]</sup>. In the 1980s, a rapid social and economic transition from the lifestyle that characterized socialistic countries (such as countries of the former Eastern Bloc, etc) to an industrialized westernized lifestyle took place <sup>[36-38]</sup>; it is hypothesized that, with a lag phase, undergoing different states of social and economic transition has contributed to the sharply increasing trends of pancreatic cancer incidence that have been observed in east and south European countries, China, Brazil since 2000s. Based the results of the Czech MONICA and post-MONICA studies, cigarette smoking prevalence declined significantly only in males (from 45.0% in 1985 to 23.9% in 2016/17), while there was no change in the prevalence of smoking in females (from 20.9% to 25.9%) over the analyzed period<sup>[38]</sup>. Throughout the entire 30-year survey period, for both sexes a significantly decreased prevalence of dyslipidemia and the consumption of meat and fat was observed, with increase in vegetable oils intake and fresh fruit and vegetable, whereas a significant increase in body mass index was observed in males only<sup>[38]</sup>. Both the incidence and mortality trends of pancreatic cancer significantly increased in China during the last decades, which could be due to the rise of the prevalence of overweight to 28.1%, diabetes to 11.2%, and smoking to 28.1% of adults: namely, China consumes about 40% of the world's total cigarettes, and that predominantly among men, with a large increase in consumption over the past decades<sup>[32,39]</sup>. A large-scale nationwide cohort study in the Republic of Korea, which included 9,514,171 adults during a median follow-up period of 7.3 years, indicated that diabetes and alcohol use were associated with an increased risk of pancreatic cancer<sup>[40]</sup>. On the other hand, the influence of the improvement of medical imaging on the diagnosis of pancreatic cancer, that is, on the increasing trends of the incidence of pancreatic cancer during the last decades cannot be ruled out<sup>[41]</sup>.

Pancreatic cancer mortality rates across the countries showed an increasing trend in both sexes. A decreasing trend, on the other hand, was found in both sexes only in Canada and Mexico, and a level-off was observed in Denmark, Norway, Sweden, Panama, Republic of Moldova, and Venezuela. With the exception of some developing countries (Latvia, Kyrgyzstan, Mauritius, Turkmenistan, Nicaragua and Colombia), in all other populations the magnitude of the increase in mortality from pancreatic cancer was higher in women. While the increased trends of pancreatic cancer mortality have long been observed in developed countries (such as the United States of America, Japan, Germany, France, Italy, Spain)<sup>[33]</sup>, in recent years a precipitous increase has also been reported in developing countries (such as Kyrgyzstan, Turkmenistan, Bulgaria, Serbia, etc)<sup>[42,43]</sup>. Some of these changes have been associated with western lifestyle and environmental factors which are linked to an increased risk of pancreatic cancer occurrence (including smoking, diabetes, alcohol consumption, obesity, physical inactivity, high-energy food intake, etc)<sup>[8,22,23,27,35,38,44]</sup>. International patterns in incidence and mortality trends of pancreatic cancer in the last three decades mostly reflect different phases of the smoking epidemic across countries, and among males and females<sup>[26]</sup>. In support of that, our study indicated that mortality rates from pancreatic cancer showed a slower rise among women and a drop among men in China in the last decade (from 1998 to 2012), which could be affected by reduced prevalence of tobacco consumption<sup>[44,45]</sup>. Also, significantly decreasing trends in pancreatic cancer mortality in both sexes in Mexico (especially since 2008) can partially be attributed to changes in smoking patterns which are resulting from new tobacco

tax/laws which were implemented in Mexico in 2007/2008<sup>[46]</sup>. Unfortunately, due to the silent nature of disease, late diagnosis, and limited treatment options, and the metastatic potential of pancreatic cancer cells, and its poor prognosis, most pancreatic cancers are diagnosed at an advanced stage, which is not amenable to treatment<sup>[42,43]</sup>. Differences in the international patterns in incidence and mortality trends of pancreatic cancer in the last three decades could be pertinent to impel continuous efforts to identify novel risk factors (particularly the modifiable risk factors) and implement policies for more effective pancreatic cancer control<sup>[34]</sup>. Global inequalities in standard medical practices (prevention/diagnosis/therapy) and their impact on pancreatic cancer mortality have not yet been systematically explored<sup>[47]</sup>.

In our study, significantly less favorable pancreatic cancer incidence trends in the young age group (30-49 years) were observed in women compared to men in all countries. Both older age groups (50-69 and 70+ years), for both men and women, generally showed similar trends in the incidence of pancreatic cancer. Other studies have reported similar results<sup>[29,30]</sup>. Similar to incidence, significantly less favorable trends in mortality of pancreatic cancer in the young age group (30-49 years) were observed in women compared to men in all countries. In both older age groups (50-69 and 70+ years), both men and women generally showed similarly increasing trends in the mortality of pancreatic cancer. It is particularly promising that in males in young age group (30-49 years) pancreatic cancer mortality trends were falling in most of the countries. Some studies also reported an increasing trend in mortality for pancreatic cancer in the past decade, especially among women and those 50 years or older in some countries<sup>[24,28]</sup>. Although in countries where there is a significant trend of increasing incidence of pancreatic cancer this increase was recorded at the age of 50 and older, of particular concern is the significant trend of increasing incidence of pancreatic cancer in the youngest group (30-49 years), which is registered in our study mainly in developed countries (United Kingdom, USA, Australia, France, Israel, Italy, and Bulgaria). Also, although the trend of increasing mortality from pancreatic cancer was recorded at the age of 50 and above, the significant trend of increasing mortality from pancreatic cancer among the youngest group (30 to 49 years) in women is particularly worrying, mainly in developed countries such as the USA, France, Germany, Spain, and Brazil, and in males in Chile, China, Brazil and El Salvador. Although there is no unified definition, some authors defined the onset of pancreatic cancer at an age of 50 or younger as early-onset pancreatic cancer<sup>[48,49]</sup>. Similar to our results, one study found a significantly increasing trend in incidence of pancreatic cancer among persons younger than 40 years only in women in 4 high-income countries (Canada, the United Kingdom, France and the Netherlands)<sup>[27]</sup>. Despite the fact that some studies suggest an association with cigarette smoking, genetic factors, obesity and metabolic disorders, the reasons for the increasing trends in incidence and mortality of early-onset pancreatic cancer are still not well understood<sup>[50-52]</sup>. Population data on tobacco use from 12 European countries revealed that in both men and women, smoking prevalence was the highest among young adults aged 25-44 years, and decreased with increasing age<sup>[50]</sup>. Results of 2 prospective US cohort studies indicated that established risk factors were more strongly associated with earlier-onset pancreatic cancer (ie among those aged  $\leq 60$  years), while association attenuated among elderly<sup>[51]</sup>. The question of whether the frequency of performing diagnostic and therapeutic procedures, as well as

autopsies at a younger age has an impact on the trend in incidence and mortality from earlier-onset pancreatic cancer should also be clarified in future research<sup>[53]</sup>.

However, certain comparisons of trends may not be feasible due to the unavailability or incompleteness of data in the registries from some countries. Additionally, some factors may contribute to difficulties in international comparisons, including differences in quality of data (such as variations in medical certification, the coding process, accuracy, coverage and completeness of death certification, frequency and registry of autopsies)<sup>[2]</sup>. But, and besides that, the observed disparities in trends for pancreatic cancer incidence and mortality across the countries can help generate hypotheses of pancreatic cancer etiology, enable the identification of unknown risk factors, as well as to evaluate preventive/therapy measures. Therefore, the assessment of the patterns in trends in incidence and mortality for pancreatic cancer in the world based on available data from registries that did not cover all countries (primarily without all African countries and many Asian countries) is difficult, does not allow for accurate interpretation or valid generalization.

Along with either increasing or stable current incidence and mortality trends of pancreatic cancer in many countries, with the aging population and the increase in prevalence of certain risk factors (cigarette smoking, overweight/obesity, diabetes, alcohol use), and taking into consideration that screening for pancreatic cancer is currently not recommended, it would be difficult to expect that the UN-SDG's goal of reducing mortality from cancers (hence pancreatic cancer) by one-third by 2030 can be achieved<sup>[8]</sup>. Additionally, pancreatic cancer survival is still consistently low<sup>[20]</sup>. Since the COVID-19 pandemic began there has been concern regarding the possible delay in the diagnosis/treatment of pancreatic cancer patients, as indicated by a recent study in Portugal<sup>[54]</sup> about the pancreatic cancer having been diagnosed at a later stage during the pandemic, which is a matter that should be elucidated in future research. In summary, the marked international differences in rates and trends in incidence and mortality of pancreatic cancer indicate the need for introducing a more effective public health approach to prevention and improvements in diagnostic and treatment practices worldwide.“

Note: Twenty-three new references were added in the list of references in the corrected manuscript:

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- **Liu Z**, Shi O, Cai N, Jiang Y, Zhang K, Zhu Z, Yuan H, Fang Q, Suo C, Franceschi S, Zhang T, Chen X. Disparities in Cancer Incidence among Chinese Population versus Migrants to Developed Regions: A Population-Based Comparative Study. *Cancer Epidemiol Biomarkers Prev* 2019; **28**: 890-899 [30944147 DOI: 10.1158/1055-9965.EPI-18-0827]
- **Huang J**, Lok V, Ngai CH, Zhang L, Yuan J, Lao XQ, Ng K, Chong C, Zheng ZJ, Wong MCS. Worldwide Burden of, Risk Factors for, and Trends in Pancreatic Cancer. *Gastroenterology* 2021; **160**: 744-754 [PMID: 33058868 DOI: 10.1053/j.gastro.2020.10.007]
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- of 22 cohort studies. *Int J Cancer* 2017; **140**: 1781-1788 [PMID: 28063165 DOI: 10.1002/ijc.30599]
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  - **Tsai HJ**, Chang JS. Environmental Risk Factors of Pancreatic Cancer. *J Clin Med* 2019; **8**: 1427 [PMID: 31510046 DOI: 10.3390/jcm8091427]
  - **Shkolnikov VM**, Churilova E, Jdanov DA, Shalnova SA, Nilssen O, Kudryavtsev A, Cook S, Malyutina S, McKee M, Leon DA. Time trends in smoking in Russia in the light of recent tobacco control measures: synthesis of evidence from multiple sources. *BMC Public Health* 2020; **20**: 378 [PMID: 32293365 DOI: 10.1186/s12889-020-08464-4]
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  - **Cífková R**, Bruthans J, Wohlfahrt P, Krajčoviechová A, Šulc P, Jozífová M, Eremiášová L, Pudil J, Linhart A, Widimský J Jr, Filipovský J, Mayer O Jr, Škodová Z, Poledne R, Stávek P, Lánská V. 30-year trends in major cardiovascular risk factors in the Czech population, Czech MONICA and Czech post-MONICA, 1985 - 2016/17. *PLoS One* 2020; **15**: e0232845 [PMID: 32392239 DOI: 10.1371/journal.pone.0232845]
  - **Liu S**, Zhang M, Yang L, Li Y, Wang L, Huang Z, Wang L, Chen Z, Zhou M. Prevalence and patterns of tobacco smoking among Chinese adult men and women: findings of the 2010 national smoking survey. *J Epidemiol Community Health* 2017; **71**: 154-161 [PMID: 27660401 DOI: 10.1136/jech-2016-207805]
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  - **Saad AM**, Turk T, Al-Husseini MJ, Abdel-Rahman O. Trends in pancreatic adenocarcinoma incidence and mortality in the United States in the last four decades; a SEER-based study. *BMC Cancer* 2018; **18**: 688 [PMID: 29940910 DOI: 10.1186/s12885-018-4610-4]
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- **Hernández-Garduño E**. The impact of tobacco tax/law implementation on pancreatic cancer mortality in Mexico, 1999-2015. *Ecancermedicalscience* 2018; **12**: ed85 [PMID: 30483361 DOI: 10.3332/ecancer.2018.ed85]
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- **Piciocchi M**, Capurso G, Valente R, Larghi A, Archibugi L, Signoretti M, Stigliano S, Zerboni G, Barucca V, La Torre M, Cavallini M, Costamagna G, Marchetti P, Ziparo V, Delle Fave G. Early onset pancreatic cancer: risk factors, presentation and outcome. *Pancreatology* 2015; **15**: 151-155 [PMID: 25708929 DOI: 10.1016/j.pan.2015.01.013]
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The section “strength and limitations” should be improved: strength points should be looked more in deep.

**Answer:**

Thank you for this valuable comment. Correction was made in the revised manuscript (in section Discussion, subsection Strengths and limitation), which now reads as follows:

"This study analyzed both incidence and mortality figures of pancreatic cancer for 185 WHO member states for 2020. Also, our study analyzed international patterns in trends of incidence and mortality of pancreatic cancer in the last three decades by sex and by age groups. One of the major strengths of our study is the use of the GLOBOCAN database, the large population-based datasets, whereby the trends analysis was conducted only for countries with quality of data that was classified as high or medium quality level. Finally, the described international patterns and trends in pancreatic cancer incidence and mortality over time may be useful in generating hypotheses about risk factors for pancreatic cancer."

**In addition, means of mitigation for limitations should be hypothesized.**

**Answer:**

Thank you for this valuable comment. Correction was made in the revised manuscript (in section Discussion, subsection Strengths and limitation), and now reads as follows:

"Possible modes of mitigation for the above mentioned limitations include greater diagnostic accuracy of pancreatic cancer, better quality of death certification, implementation of mandatory population-based cancer registry, further reduction of the proportion of uncertain causes of death, introduction of registration of autopsies (eg part of pancreatic cancer cases diagnosed at autopsy was missing on the death certificates), provision of survival data for pancreatic cancer patients, as well as the improvements and availability of pancreatic cancer treatment across countries<sup>[55-57]</sup>. Based on accurate assessment of epidemiological characteristics of pancreatic cancer, policymakers could provide a better planning for funding, access to more effective treatment and care strategies, scientific and clinical advances in development of effective screening tests, improving early diagnosis and improving survival<sup>[55]</sup>."

Note: Three new references were added in the list of references in the corrected manuscript:

- **Laugesen K**, Ludvigsson JF, Schmidt M, Gissler M, Valdimarsdottir UA, Lunde A, Sørensen HT. Nordic Health Registry-Based Research: A Review of Health Care Systems and Key Registries. *Clin Epidemiol* 2021; **13**: 533-554 [PMID: 34321928 DOI: 10.2147/CLEP.S314959]
- **Gupta N**, Yelamanchi R. Pancreatic adenocarcinoma: A review of recent paradigms and advances in epidemiology, clinical diagnosis and management. *World J Gastroenterol* 2021; **27**: 3158-3181 [PMID: 34163104 DOI: 10.3748/wjg.v27.i23.3158]
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**Reviewer #2:**

**Scientific Quality:** Grade C (Good)

**Language Quality:** Grade B (Minor language polishing)

**Conclusion: Major revision**  
**Specific Comments to Authors:**

For join point calculation, how many maximum number of join points has been set? And reason for so?

**Answer:**

Thank you for your valuable comments. In our manuscript we have already written that the maximum number of joinpoints has been set to 4.

We indicate that the default maximum number of joinpoints based on the following recommendations: at least seven data points should be observed in order to consider allowing a joinpoint, while there should be, on average, at least two data points between consecutive joinpoints (please see:

<https://surveillance.cancer.gov/help/joinpoint/setting-parameters/method-and-parameters-tab/number-of-joinpoints>).

The revised manuscript (section Methods, subsection Statistical analysis) now reads as follows:

"The analysis starts with a minimum of zero joinpoints (i.e. a straight line) and tests whether a change in the trend was statistically significant by testing more joinpoints up to the maximum of four joinpoints (five segments)<sup>[16]</sup>. ... Grid Search method was selected<sup>[17]</sup>."

Note: One new reference was added in the list of references in the corrected manuscript:

- **Lerman PM.** Fitting segmented regression models by grid search. *Appl Stat* 1980; **29**: 77-84 [doi:10.2307/2346413]

Authors should provide line diagram of join point analysis for 6 WHO regions in main text and individual countries in supplementary material in result section

**Answer:**

Thank you for your valuable comments.

With regard to the 6 WHO regions, we have shown data for 2020, because the GLOBOCAN databases provide data for trends only in 60 countries, i.e. there is no data for other countries so therefore a joinpoint analysis for 6 WHO regions is unfortunately not possible due to the lack of data (please see: <https://gco.iarc.fr/>, data for trends in 6 WHO regions are therefore not available).

Line diagram of joinpoint analysis for individual countries provided in supplementary material in Supplementary Figure 1 and Supplementary Figure 2. Consequently, correction was made in the revised manuscript (in section Methods, subsection Statistical analysis), and now reads as follows:

"A line diagram of joinpoint analysis for individual countries provides information about the number of the joinpoints for the trends in incidence and mortality of pancreatic cancer by sex, by describing of Annual Percent Change (APC) and the corresponding 95%CI."

Also, correction was made in the revised manuscript (in section Results, subsection Patterns in pancreatic cancer incidence trends), and now reads as follows:

"In some of the most developed countries (such as the United Kingdom, Sweden) in both sexes a significantly increasing trends in pancreatic cancer incidence rates were observed in the last decade, which followed a previous period characterized by a declining incidence trend (Supplementary Figure 1). In contrast to that, after 2 decades of continuous growth, a downward trend of pancreatic cancer incidence rates in both sexes happened in the more recent decade in Denmark."



And, correction was made in the revised manuscript (in section Results, subsection Pattern in pancreatic cancer mortality trends), and now reads as follows:

"In some of the most developed countries (such as the United States of America, the United Kingdom, Germany) a significantly increasing trends in pancreatic cancer mortality rates were observed since the 1990s (Supplementary Figure 2).".

Author should not only discuss only about the change over the complete interval, but they should also discuss about at which year, the trend changes at least for the 6 WHO regions.

**Answer:**

Thank you for your valuable comments. Please see our answer to your previous comment. Once again, unfortunately, due to the lack of data in the GLOBOCAN database it is not possible to do a joinpoint analysis of trends for the 6 WHO regions.

Authors shall discuss trends of various risk factors of pancreatic cancer incidence/mortality by WHO regions and for selected countries which shows significant decreasing or increasing trends in last few decades.

**Answer:**

Thank you for your valuable comments.

Due to the above-mentioned reasons, it was not possible to perform an analysis of trends by regions, so therefore it is not possible to discuss trends of various risk factors of pancreatic cancer incidence/mortality by WHO regions.

In the revised manuscript we have entered data which refer to discussion of trends of various risk factors of pancreatic cancer incidence/mortality for selected countries which show significant decreasing or increasing trends in the last few decades.

Section Discussion was completely reconstructed, as follows:

" Our study showed unfavorable trends in pancreatic cancer incidence rates in both males and females in many countries in the world in the last three decades. The incidence was noticeably increasing throughout European countries, the United States of America, Australia, and Japan, while stable trends in incidence were noted in Canada, Sweden and Ireland. One previous study showed that pancreatic cancer incidence rates gradually increased in males and females among all ages in the USA, Canada, the Netherlands, Australia, New Zealand from the mid-1990s until 2014<sup>[31]</sup>. In the same study, a decreasing trend of pancreatic cancer incidence in males was noticed only in Iceland and Croatia, while in women there was a significant increasing trend in the incidence of pancreatic cancer in most of the countries from the 1990s onwards<sup>[31]</sup>. The pancreatic cancer incidence in both sexes in China increased continuously from 1990 to 2019<sup>[32]</sup>. The observed increasing trends in pancreatic cancer incidence could be attributed to population growth and ageing, as well as changes in the prevalence of risk factors for cancer<sup>[6,33,34]</sup>. Global Burden of Disease study demonstrated that there was a link between increasing trends in incidence for pancreatic cancer and increases in development status at the national level in period 1990-2017<sup>[6]</sup>. Also, one previous study indicated that increasing trends in pancreatic cancer incidence in both sexes were correlated with socioeconomic development (measured by Human Development Index and Gross Domestic Product per capita)<sup>[35]</sup>. In the

1980s, a rapid social and economic transition from the lifestyle that characterized socialistic countries (such as countries of the former Eastern Bloc, etc) to an industrialized westernized lifestyle took place [36-38]; it is hypothesized that, with a lag phase, undergoing different states of social and economic transition has contributed to the sharply increasing trends of pancreatic cancer incidence that have been observed in east and south European countries, China, Brazil since 2000s. Based the results of the Czech MONICA and post-MONICA studies, cigarette smoking prevalence declined significantly only in males (from 45.0% in 1985 to 23.9% in 2016/17), while there was no change in the prevalence of smoking in females (from 20.9% to 25.9%) over the analyzed period[38]. Throughout the entire 30-year survey period, for both sexes a significantly decreased prevalence of dyslipidemia and the consumption of meat and fat was observed, with increase in vegetable oils intake and fresh fruit and vegetable, whereas a significant increase in body mass index was observed in males only[38]. Both the incidence and mortality trends of pancreatic cancer significantly increased in China during the last decades, which could be due to the rise of the prevalence of overweight to 28.1%, diabetes to 11.2%, and smoking to 28.1% of adults: namely, China consumes about 40% of the world's total cigarettes, and that predominantly among men, with a large increase in consumption over the past decades[32,39]. A large-scale nationwide cohort study in the Republic of Korea, which included 9,514,171 adults during a median follow-up period of 7.3 years, indicated that diabetes and alcohol use were associated with an increased risk of pancreatic cancer[40]. On the other hand, the influence of the improvement of medical imaging on the diagnosis of pancreatic cancer, that is, on the increasing trends of the incidence of pancreatic cancer during the last decades cannot be ruled out[41].

Pancreatic cancer mortality rates across the countries showed an increasing trend in both sexes. A decreasing trend, on the other hand, was found in both sexes only in Canada and Mexico, and a level-off was observed in Denmark, Norway, Sweden, Panama, Republic of Moldova, and Venezuela. With the exception of some developing countries (Latvia, Kyrgyzstan, Mauritius, Turkmenistan, Nicaragua and Colombia), in all other populations the magnitude of the increase in mortality from pancreatic cancer was higher in women. While the increased trends of pancreatic cancer mortality have long been observed in developed countries (such as the United States of America, Japan, Germany, France, Italy, Spain)[33], in recent years a precipitous increase has also been reported in developing countries (such as Kyrgyzstan, Turkmenistan, Bulgaria, Serbia, etc)[42,43]. Some of these changes have been associated with western lifestyle and environmental factors which are linked to an increased risk of pancreatic cancer occurrence (including smoking, diabetes, alcohol consumption, obesity, physical inactivity, high-energy food intake, etc)[8,22,23,27,35,38,44]. International patterns in incidence and mortality trends of pancreatic cancer in the last three decades mostly reflect different phases of the smoking epidemic across countries, and among males and females[26]. In support of that, our study indicated that mortality rates from pancreatic cancer showed a slower rise among women and a drop among men in China in the last decade (from 1998 to 2012), which could be affected by reduced prevalence of tobacco consumption[44,45]. Also, significantly decreasing trends in pancreatic cancer mortality in both sexes in Mexico (especially since 2008) can partially be attributed to changes in smoking patterns which are resulting from new tobacco tax/laws which were implemented in Mexico in 2007/2008[46]. Unfortunately, due to the silent

nature of disease, late diagnosis, and limited treatment options, and the metastatic potential of pancreatic cancer cells, and its poor prognosis, most pancreatic cancers are diagnosed at an advanced stage, which is not amenable to treatment<sup>[42,43]</sup>. Differences in the international patterns in incidence and mortality trends of pancreatic cancer in the last three decades could be pertinent to impel continuous efforts to identify novel risk factors (particularly the modifiable risk factors) and implement policies for more effective pancreatic cancer control<sup>[34]</sup>. Global inequalities in standard medical practices (prevention/diagnosis/therapy) and their impact on pancreatic cancer mortality have not yet been systematically explored<sup>[47]</sup>.

In our study, significantly less favorable pancreatic cancer incidence trends in the young age group (30-49 years) were observed in women compared to men in all countries. Both older age groups (50-69 and 70+ years), for both men and women, generally showed similar trends in the incidence of pancreatic cancer. Other studies have reported similar results<sup>[29,30]</sup>. Similar to incidence, significantly less favorable trends in mortality of pancreatic cancer in the young age group (30-49 years) were observed in women compared to men in all countries. In both older age groups (50-69 and 70+ years), both men and women generally showed similarly increasing trends in the mortality of pancreatic cancer. It is particularly promising that in males in young age group (30-49 years) pancreatic cancer mortality trends were falling in most of the countries. Some studies also reported an increasing trend in mortality for pancreatic cancer in the past decade, especially among women and those 50 years or older in some countries<sup>[24,28]</sup>. Although in countries where there is a significant trend of increasing incidence of pancreatic cancer this increase was recorded at the age of 50 and older, of particular concern is the significant trend of increasing incidence of pancreatic cancer in the youngest group (30-49 years), which is registered in our study mainly in developed countries (United Kingdom, USA, Australia, France, Israel, Italy, and Bulgaria). Also, although the trend of increasing mortality from pancreatic cancer was recorded at the age of 50 and above, the significant trend of increasing mortality from pancreatic cancer among the youngest group (30 to 49 years) in women is particularly worrying, mainly in developed countries such as the USA, France, Germany, Spain, and Brazil, and in males in Chile, China, Brazil and El Salvador. Although there is no unified definition, some authors defined the onset of pancreatic cancer at an age of 50 or younger as early-onset pancreatic cancer<sup>[48,49]</sup>. Similar to our results, one study found a significantly increasing trend in incidence of pancreatic cancer among persons younger than 40 years only in women in 4 high-income countries (Canada, the United Kingdom, France and the Netherlands)<sup>[27]</sup>. Despite the fact that some studies suggest an association with cigarette smoking, genetic factors, obesity and metabolic disorders, the reasons for the increasing trends in incidence and mortality of early-onset pancreatic cancer are still not well understood<sup>[50-52]</sup>. Population data on tobacco use from 12 European countries revealed that in both men and women, smoking prevalence was the highest among young adults aged 25-44 years, and decreased with increasing age<sup>[50]</sup>. Results of 2 prospective US cohort studies indicated that established risk factors were more strongly associated with earlier-onset pancreatic cancer (ie among those aged  $\leq 60$  years), while association attenuated among elderly<sup>[51]</sup>. The question of whether the frequency of performing diagnostic and therapeutic procedures, as well as autopsies at a younger age has an impact on the trend in incidence and mortality from earlier-onset pancreatic cancer should also be clarified in future research<sup>[53]</sup>.

However, certain comparisons of trends may not be feasible due to the unavailability or incompleteness of data in the registries from some countries. Additionally, some factors may contribute to difficulties in international comparisons, including differences in quality of data (such as variations in medical certification, the coding process, accuracy, coverage and completeness of death certification, frequency and registry of autopsies)<sup>[2]</sup>. But, and besides that, the observed disparities in trends for pancreatic cancer incidence and mortality across the countries can help generate hypotheses of pancreatic cancer etiology, enable the identification of unknown risk factors, as well as to evaluate preventive/therapy measures. Therefore, the assessment of the patterns in trends in incidence and mortality for pancreatic cancer in the world based on available data from registries that did not cover all countries (primarily without all African countries and many Asian countries) is difficult, does not allow for accurate interpretation or valid generalization.“.

**Note:** Nineteen new references were added in the list of references in the corrected manuscript:

- **Lucas AL**, Malvezzi M, Carioli G, Negri E, La Vecchia C, Boffetta P, Bosetti C. Global Trends in Pancreatic Cancer Mortality From 1980 Through 2013 and Predictions for 2017. *Clin Gastroenterol Hepatol* 2016; **14**: 1452-1462.e4 [PMID: 27266982 DOI: 10.1016/j.cgh.2016.05.034]
- **Tsai HJ**, Chang JS. Environmental Risk Factors of Pancreatic Cancer. *J Clin Med* 2019; **8**: 1427 [PMID: 31510046 DOI: 10.3390/jcm8091427]
- **Shkolnikov VM**, Churilova E, Jdanov DA, Shalnova SA, Nilssen O, Kudryavtsev A, Cook S, Malyutina S, McKee M, Leon DA. Time trends in smoking in Russia in the light of recent tobacco control measures: synthesis of evidence from multiple sources. *BMC Public Health* 2020; **20**: 378 [PMID: 32293365 DOI: 10.1186/s12889-020-08464-4]
- **Psota M**, Bandosz P, Gonçalvesová E, Avdičová M, Bucek Pšenková M, Studenčan M, Pekarčíková J, Capewell S, O'Flaherty M. Explaining the decline in coronary heart disease mortality rates in the Slovak Republic between 1993-2008. *PLoS One* 2018; **13**: e0190090 [PMID: 29320517 DOI: 10.1371/journal.pone.0190090]
- **Cífková R**, Bruthans J, Wohlfahrt P, Krajčoviechová A, Šulc P, Jozífová M, Eremiášová L, Pudil J, Linhart A, Widimský J Jr, Filipovský J, Mayer O Jr, Škodová Z, Poledne R, Stávek P, Lánská V. 30-year trends in major cardiovascular risk factors in the Czech population, Czech MONICA and Czech post-MONICA, 1985 - 2016/17. *PLoS One* 2020; **15**: e0232845 [PMID: 32392239 DOI: 10.1371/journal.pone.0232845]
- **Liu S**, Zhang M, Yang L, Li Y, Wang L, Huang Z, Wang L, Chen Z, Zhou M. Prevalence and patterns of tobacco smoking among Chinese adult men and women: findings of the 2010 national smoking survey. *J Epidemiol Community Health* 2017; **71**: 154-161 [PMID: 27660401 DOI: 10.1136/jech-2016-207805]
- **Park JH**, Han K, Hong JY, Park YS, Park JO. Association between alcohol consumption and pancreatic cancer risk differs by glycaemic status: A nationwide cohort study. *Eur J Cancer* 2022; **163**: 119-127 [PMID: 35065369 DOI: 10.1016/j.ejca.2021.12.027]
- **Defossez G**, Uhry Z, Delafosse P, Dantony E, d'Almeida T, Plouvier S, Bossard N, Bouvier AM, Molinié F, Woronoff AS, Colonna M, Grosclaude P, Remontet L, Monnereau A; French Network of Cancer Registries (FRANCIM). Cancer incidence and

- mortality trends in France over 1990-2018 for solid tumors: the sex gap is narrowing. *BMC Cancer* 2021; **21**: 726 [PMID: 34167516 DOI: 10.1186/s12885-021-08261-1]
- **Saad AM**, Turk T, Al-Husseini MJ, Abdel-Rahman O. Trends in pancreatic adenocarcinoma incidence and mortality in the United States in the last four decades; a SEER-based study. *BMC Cancer* 2018; **18**: 688 [PMID: 29940910 DOI: 10.1186/s12885-018-4610-4]
  - **Seoane-Mato D**, Nuñez O, Fernández-de-Larrea N, Pérez-Gómez B, Pollán M, López-Abente G, Aragonés N. Long-term trends in pancreatic cancer mortality in Spain (1952-2012). *BMC Cancer* 2018; **18**: 625 [PMID: 29866063 DOI: 10.1186/s12885-018-4494-3]
  - **GBD 2019 Risk Factors Collaborators**. Global burden of 87 risk factors in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet* 2020; **396**: 1223-1249 [PMID: 33069327 DOI: 10.1016/S0140-6736(20)30752-2]
  - **Zhang K**, Tartarone A, Pérez-Ríos M, Novello S, Mariniello A, Roviello G, Zhang J. Smoking burden, MPOWER, future tobacco control and real-world challenges in China: reflections on the WHO report on the global tobacco epidemic 2021. *Transl Lung Cancer Res* 2022; **11**: 117-121 [PMID: 35242633 DOI: 10.21037/tlcr-22-27]
  - **Hernández-Garduño E**. The impact of tobacco tax/law implementation on pancreatic cancer mortality in Mexico, 1999-2015. *Ecancermedicalscience* 2018; **12**: ed85 [PMID: 30483361 DOI: 10.3332/ecancer.2018.ed85]
  - **Raimondi S**, Maisonneuve P, Löhr JM, Lowenfels AB. Early onset pancreatic cancer: evidence of a major role for smoking and genetic factors. *Cancer Epidemiol Biomarkers Prev* 2007; **16**: 1894-1897 [PMID: 17855711 DOI: 10.1158/1055-9965.EPI-07-0341]
  - **Piciocchi M**, Capurso G, Valente R, Larghi A, Archibugi L, Signoretti M, Stigliano S, Zerboni G, Barucca V, La Torre M, Cavallini M, Costamagna G, Marchetti P, Ziparo V, Delle Fave G. Early onset pancreatic cancer: risk factors, presentation and outcome. *Pancreatology* 2015; **15**: 151-155 [PMID: 25708929 DOI: 10.1016/j.pan.2015.01.013]
  - **Gallus S**, Lugo A, Liu X, Behrakis P, Boffi R, Bosetti C, Carreras G, Chatenoud L, Clancy L, Continente X, Dobson R, Effertz T, Filippidis FT, Fu M, Geshanova G, Gorini G, Keogan S, Ivanov H, Lopez MJ, Lopez-Nicolas A, Precioso J, Przewozniak K, Radu-Loghin C, Ruprecht A, Sempile S, Soriano JB, Starchenko P, Trapero-Bertran M, Tigova O, Tzortzi AS, Vardavas C, Vyzikidou VK, Colombo P, Fernandez E; TackSHS Project Investigators. Who Smokes in Europe? Data From 12 European Countries in the TackSHS Survey (2017-2018). *J Epidemiol* 2021; **31**: 145-151 [PMID: 32249267 DOI: 10.2188/jea.JE20190344]
  - **Yuan C**, Kim J, Wang QL, Lee AA, Babic A; PanScan/PanC4 I-III Consortium, Amundadottir LT, Klein AP, Li D, McCullough ML, Petersen GM, Risch HA, Stolzenberg-Solomon RZ, Perez K, Ng K, Giovannucci EL, Stampfer MJ, Kraft P, Wolpin BM. The age-dependent association of risk factors with pancreatic cancer. *Ann Oncol* 2022; S0923-7534(22)00672-X [PMID: 35398288 DOI: 10.1016/j.annonc.2022.03.276]
  - **McWilliams RR**, Maisonneuve P, Bamlet WR, Petersen GM, Li D, Risch HA, Yu H, Fontham ET, Lockett B, Bosetti C, Negri E, La Vecchia C, Talamini R, Bueno de Mesquita HB, Bracci P, Gallinger S, Neale RE, Lowenfels AB. Risk Factors for Early-Onset and Very-Early-Onset Pancreatic Adenocarcinoma: A Pancreatic Cancer Case-Control

Consortium (PanC4) Analysis. *Pancreas* 2016; **45**: 311-316 [PMID: 26646264 DOI: 10.1097/MPA.0000000000000392]

- **LaPelusa M**, Shen C, Arhin ND, Cardin D, Tan M, Idrees K, Geevarghese S, Chakravarthy B, Berlin J, Eng C. Trends in the Incidence and Treatment of Early-Onset Pancreatic Cancer. *Cancers (Basel)* 2022; **14**: 283 [PMID: 35053447 DOI: 10.3390/cancers14020283]

Author needs to clarify if the data of Incidence/ mortality of few years of any country is not available, have they completely removed the country for trend analysis or they have interpolated those estimates. As mentioned here” The trends analyses included only countries with data of pancreatic cancer incidence/mortality available in the observed period (from 1991 or later) continuously, provided that there has been data for at least 15 years in a row continuously. Countries with “missing” values in any year of trend analysis were excluded from the analysis.”, a further clarification is required i.e., if the data is available for 15 years in a row continuously, but few years are missing. What they have done further to that country data?

**Answer:**

Thank you very much for your helpful comments.

The analysis included every country which had data for at least 15 years continuously in any part of the observed period. If a country did not meet this condition to have data continuously for 15 or more years, that country was excluded from the analysis. No data interpolation was done.

Mention the joint point regression equation in the statistical analysis of materials and method section.

**Answer:**

Thank you for your valuable comments. Correction was made in the revised manuscript (in section Methods, subsection Statistical analysis), and now reads as follows:

”The resulting regression equation is:  $y = a + bx$ , where  $y = \ln(\text{rate})$  and  $x = \text{calendar year}$ , with slope  $a$  and y-intercept  $b$ , whereby Annual Percent Change (APC) is estimated as  $100 \times (eb - 1)$ .”.

As the data of incidence and mortality are taken for different intervals for different countries, author should mention this also in their limitations.

**Answer:**

Thank you very much for your valuable comments. In the revised manuscript (in section Discussion, subsection Strengths and limitation), a new sentence was added, as follows:

”Therefore, the data of incidence and mortality are taken for different intervals for some countries, which makes it much more difficult to compare trends across countries.”.

The author shall provide some suggestions or recommendations to policymakers for future planning

**Answer:**

Thank you for this valuable comment. Correction was made in the revised manuscript (in section Discussion, subsection Strengths and limitation), and now reads as follows:

”Possible modes of mitigation for the above mentioned limitations include greater diagnostic accuracy of pancreatic cancer, better quality of death certification, implementation of mandatory population-based cancer registry, further reduction of the proportion of uncertain

causes of death, introduction of registration of autopsies (eg part of pancreatic cancer cases diagnosed at autopsy was missing on the death certificates), provision of survival data for pancreatic cancer patients, as well as the improvements and availability of pancreatic cancer treatment across countries<sup>[55-57]</sup>. Based on accurate assessment of epidemiological characteristics of pancreatic cancer, policymakers could provide a better planning for funding, access to more effective treatment and care strategies, scientific and clinical advances in development of effective screening tests, improving early diagnosis and improving survival<sup>[55]</sup>.”.

Note: Three new references were added in the list of references in the corrected manuscript:

- **Laugesen K**, Ludvigsson JF, Schmidt M, Gissler M, Valdimarsdottir UA, Lunde A, Sørensen HT. Nordic Health Registry-Based Research: A Review of Health Care Systems and Key Registries. *Clin Epidemiol* 2021; **13**: 533-554 [PMID: 34321928 DOI: 10.2147/CLEP.S314959]
- **Gupta N**, Yelamanchi R. Pancreatic adenocarcinoma: A review of recent paradigms and advances in epidemiology, clinical diagnosis and management. *World J Gastroenterol* 2021; **27**: 3158-3181 [PMID: 34163104 DOI: 10.3748/wjg.v27.i23.3158]
- **Fest J**, Ruiter R, van Rooij FJ, van der Geest LG, Lemmens VE, Ikram MA, Coebergh JW, Stricker BH, van Eijck CH. Underestimation of pancreatic cancer in the national cancer registry - Reconsidering the incidence and survival rates. *Eur J Cancer* 2017; **72**: 186-191 [PMID: 28033529 DOI: 10.1016/j.ejca.2016.11.026]

Note: Reference list and order was appropriately updated in line with comments according to their order in the text.

We hope that those sentences are the answers to your comments. Again, we appreciate all of your valuable comments, kind suggestions and detailed advice. A major revision of the paper has been carried out and we believe the manuscript has been significantly improved. Thank you for taking the time and energy to help us improve the manuscript.

#### 4 LANGUAGE POLISHING REQUIREMENTS FOR REVISED MANUSCRIPTS SUBMITTED BY AUTHORS WHO ARE NON-NATIVE SPEAKERS OF ENGLISH

As the revision process results in changes to the content of the manuscript, language problems may exist in the revised manuscript. Thus, it is necessary to perform further language polishing that will ensure all grammatical, syntactical, formatting and other related errors be resolved, so that the revised manuscript will meet the publication requirement (Grade A).

**Authors are requested to send their revised manuscript to a professional English language editing company or a native English-speaking expert to polish the manuscript further. When the authors submit the subsequent polished manuscript to us, they must provide a new language certificate along with the manuscript.**

Once this step is completed, the manuscript will be quickly accepted and published online. Please visit the following website for the professional English language editing companies we recommend:  
<https://www.wjgnet.com/bpg/gerinfo/240>.

**Response:** Our revised manuscript was checked for clarity by a colleague whose native language is English.

## 5 ABBREVIATIONS

In general, do not use non-standard abbreviations, unless they appear at least two times in the text preceding the first usage/definition. Certain commonly used abbreviations, such as DNA, RNA, HIV, LD50, PCR, HBV, ECG, WBC, RBC, CT, ESR, CSF, IgG, ELISA, PBS, ATP, EDTA, and mAb, do not need to be defined and can be used directly.

The basic rules on abbreviations are provided here:

**(1) Title:** Abbreviations are not permitted. Please spell out any abbreviation in the title.

**(2) Running title:** Abbreviations are permitted. Also, please shorten the running title to no more than 6 words.

**(3) Abstract:** Abbreviations must be defined upon first appearance in the Abstract. Example 1: Hepatocellular carcinoma (HCC). Example 2: *Helicobacter pylori* (*H. pylori*).

**(4) Key Words:** Abbreviations must be defined upon first appearance in the Key Words.

**(5) Core Tip:** Abbreviations must be defined upon first appearance in the Core Tip. Example 1: Hepatocellular carcinoma (HCC). Example 2: *Helicobacter pylori* (*H. pylori*)

**(6) Main Text:** Abbreviations must be defined upon first appearance in the Main Text. Example 1: Hepatocellular carcinoma (HCC). Example 2: *Helicobacter pylori* (*H. pylori*)

**(7) Article Highlights:** Abbreviations must be defined upon first appearance in the Article Highlights. Example 1: Hepatocellular carcinoma (HCC).

Example 2: *Helicobacter pylori* (*H. pylori*)

**(8) Figures:** Abbreviations are not allowed in the Figure title. For the Figure Legend text, abbreviations are allowed but must be defined upon first appearance in the text. Example 1: A: Hepatocellular carcinoma (HCC) biopsy sample; B: HCC-adjacent tissue sample. For any abbreviation that appears in



the Figure itself but is not included in the Figure Legend textual description, it will be defined (separated by semicolons) at the end of the figure legend. Example 2: BMI: Body mass index; US: Ultrasound.

**(9) Tables:** Abbreviations are not allowed in the Table title. For the Table itself, please verify all abbreviations used in tables are defined (separated by semicolons) directly underneath the table. Example 1: BMI: Body mass index; US: Ultrasound.

## 6 EDITORIAL OFFICE'S COMMENTS

Authors must revise the manuscript according to the Editorial Office's comments and suggestions, which are listed below:

### **(1) Science editor:**

This manuscript analyzed data concerning pancreatic cancer extracted from WHO databases (GLOBOCAN 2020) and reported on the number of new diagnoses, the incidence of and the mortality for pancreatic cancer worldwide in 2020, according to sex, WHO regions, and countries. However, In addition to modifying in accordance with the reviewer's comments, some other issues have to be addressed: The figures need further arranged and the resolution of the images needs to improve. The form of the table in the article should adopt the form of a three-line table. Please provide documents following the requirements in the journal's Guidelines for manuscript type and related ethics: Copyright License Agreement.

Language Quality: Grade B (Minor language polishing)

Scientific Quality: Grade C (Good)

**Response:** We are grateful to the Science Editor for their thorough reading of our manuscript. Thank you for your kind comments. We have addressed all of the points raised by the Reviewers, provided detailed point-by-point responses above and incorporated changes accordingly in our revised manuscript. We have arranged figures, revised tables and we are providing the necessary documents.

### **(2) Company editor-in-chief:**

I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Gastroenterology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. Please be sure to use Reference Citation Analysis (RCA) when revising the manuscript. RCA is an artificial intelligence technology-based open multidisciplinary citation analysis database. For details on the RCA, please visit the following web site:

<https://www.referencecitationanalysis.com/>. Please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file. Please authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content. In order to respect and protect the author's intellectual property rights and prevent others from misappropriating

figures without the author's authorization or abusing figures without indicating the source, we will indicate the author's copyright for figures originally generated by the author, and if the author has used a figure published elsewhere or that is copyrighted, the author needs to be authorized by the previous publisher or the copyright holder and/or indicate the reference source and copyrights. Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper). If the picture is 'original', the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2022. If an author of a submission is re-using a figure or figures published elsewhere, or that is copyrighted, the author must provide documentation that the previous publisher or copyright holder has given permission for the figure to be re-published; and correctly indicating the reference source and copyrights. For example, "Figure 1 Histopathological examination by hematoxylin-eosin staining (200 ×). A: Control group; B: Model group; C: Pioglitazone hydrochloride group; D: Chinese herbal medicine group. Citation: Yang JM, Sun Y, Wang M, Zhang XL, Zhang SJ, Gao YS, Chen L, Wu MY, Zhou L, Zhou YM, Wang Y, Zheng FJ, Li YH. Regulatory effect of a Chinese herbal medicine formula on non-alcoholic fatty liver disease. *World J Gastroenterol* 2019; 25(34): 5105-5119. Copyright ©The Author(s) 2019. Published by Baishideng Publishing Group Inc[6]". And please cite the reference source in the references list. If the author fails to properly cite the published or copyrighted picture(s) or table(s) as described above, he/she will be subject to withdrawal of the article from BPG publications and may even be held liable.

**Response:** We would like to thank the Company Editor-in-Chief for carefully reviewing our manuscript and relevant documents. We have revised the manuscript according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision. We are providing decomposable Figures organized into a single PowerPoint file. Also, we have checked the Tables. All figures are original.

## 7 STEPS FOR SUBMITTING THE REVISED MANUSCRIPT

### Step 1: Author Information

Please click and download the Format for authorship, institution, and corresponding author guidelines, and further check if the authors names and institutions meet the requirements of the journal.

### Step 2: Manuscript Information

Please check if the manuscript information is correct.

### Step 3: Abstract, Main Text, and Acknowledgements

**(1) Guidelines for revising the content:** Please download the guidelines for Original articles, Review articles, or Case Report articles for your specific manuscript type (Observational Study) at: <https://www.wjgnet.com/bpg/GerInfo/291>. Please further revise the content your manuscript according to the Guidelines and Requirements for Manuscript Revision.

**(2) Format for Manuscript Revision:** Please update the format of your manuscript according to the Guidelines and Requirements for Manuscript Revision and the Format for Manuscript Revision. Please

visit <https://www.wjgnet.com/bpg/GerInfo/291> for the article type-specific guidelines and formatting examples.

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**(4) Common issues in revised manuscript.** Please click and download the List of common issues in revised manuscripts by authors and comments (PDF), and revise the manuscript accordingly.

#### **Step 4: References**

Please revise the references according to the Format for References Guidelines, and be sure to edit the reference using the reference auto-analyser.

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#### **Step 5: Footnotes and Figure Legends**

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## **Step 7: Upload the Revision Files**

For all required accompanying documents (listed below), you can begin the uploading process via the F6Publishing system. Then, please download all the uploaded documents to ensure all of them are correct.

- (1) 76116-Answering Reviewers
- (2) 76116-Audio Core Tip
- (3) 76116-Biostatistics Review Certificate
- (4) 76116-Conflict-of-Interest Disclosure Form
- (5) 76116-Copyright License Agreement
- (6) 76116-Approved Grant Application Form(s) or Funding Agency Copy of any Approval Document(s)
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If your manuscript has no “Video” or “Supplementary Material”, you do not need to submit those two types of documents.

**Response:** The manuscript has been revised according to the STEPS FOR SUBMITTING REVISED MANUSCRIPT and relevant accompanying documents have been prepared and uploaded.

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**Response:** The Copyright License Agreement Form has been signed by all authors and uploaded.

## **9 CONFLICT-OF-INTEREST DISCLOSURE FORM**

Please click and download the fillable ICMJE Form for Disclosure of Potential Conflicts of Interest (PDF), and fill it in. The Corresponding Author is responsible for filling out this form. Once filled out

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**Response:** The ICMJE Form for Disclosure of Potential Conflicts of Interest was filled completely and uploaded.

We thank the Editors and the Reviewers for taking the time to thoroughly and carefully read our manuscript and we are grateful for the opportunity to revise our manuscript according to their very useful remarks.

We hope that those sentences are the answers to your comments. Again, we appreciate all of your valuable comments, kind suggestions and detailed advice. Thank you for taking the time and energy to help us improve the manuscript.