**European’ health indicators and pancreatic cancer mortality between 2004 and 2019.**

**A mediation analysis of eurostat data and Global Burden of Disease Study 2019**

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**Introduction**

The number of cancer cases is estimated to double in the next decade, primarily due to the rapid societal and economic transitions [PMID: 22658655]. Such changes are clearly illustrated by pancreatic cancer where the rise is consequent on changes in risk factors including smoking, alcohol consumption, obesity, and physical inactivity at both the patient and country levels [PMID: 22658655; 33058868]. Such risk factors are compounded by increasing life expectancy that increases exposure to potential risk factors [PMID: 33058868; 31648972; 3266039; 30207593].

In addition to patient and socioeconomic-specific risk factors, incidence and mortality are contingent on access to and the provision of high-quality health care [PMID: 30195398]. Even in highly or very-highly developed European countries, for a considerable proportion of the population health care needs remain unmet for various reasons, including waiting lists and financial barriers [https://tinyurl.com/486skw4f]. By linking geographical and temporal patterns of pancreatic cancer incidence and mortality with matching levels of health care characteristics can help tailor initiatives aimed at reducing the burden of this neoplasm. These health care facilities have both direct and indirect effects in determining incidence and, most importantly, mortality of pancreatic cancer. For instance, increased life expectancy, achieved through improved living conditions via a health system improvement, may increase a populations age and thereby increase the risk of developing pancreatic cancer. The total effect may lead to the unwarranted conclusion that improving the health system results in increased incidence.

 It is, therefore, important to consider and isolate the presence of direct and indirect correlations. In mediation analysis, some or all of the total effect of exposure on an outcome operates through one or more mediators, which are both an effect of the exposure and a cause of the outcome. Mortality over the total population is inevitably affected by incidence, and both can be affected by health care-related features. When a mediator is hypothesized, as in the present case, the direct effect is finally formed by subtracting the indirect effect of the mediator from the total effect of the exposure on the outcome.

We aimed to draw attention to how certain health care indicators across European countries correlate with pancreatic cancer incidence and mortality. To do so, we matched data from the Global Burden of Disease study (GBD) 2019 with health care indicators derived from the statistical office of the European Union (eurostat) and applied mediation analysis to estimate direct and indirect effects of health care funding

**Methods**

**Global Burden of Disease (GBD) data**

The GBD 2019 database contains statistical data of 369 diseases and injuries and 87 risk factors from 204 countries and territories [PMID: 33069326]. Briefly, GBD data derived from censuses, household surveys, civil registration and vital statistics, disease registries, health service use, disease notifications and other sources. Cause-specific death rates were calculated using the Cause of Death Ensemble model and were adjusted to match the total all-cause deaths calculated as part of the GBD population, fertility, and mortality estimates. A Bayesian meta-regression modelling tool ensured consistency between incidence, prevalence and cause-specific mortality for most causes. Uncertainty intervals (UIs) were generated for every metric using the 25th and 975th ordered 1,000 draw values of the posterior distribution. In the GBD 2019 database pancreatic cancer was recorded through ICD-9 codes 157-157.9 and ICD-10 codes C25-C25.9, Z85.07.

Data used in the present study were extracted from the Global Health Data Exchange website (<https://vizhub.healthdata.org/gbd-results/>) and included the total population, incidence and mortality of pancreatic cancer for each year from 2004 through 2019 by country. Incidence and mortality were age-standardized. An age-standardized rate is a weighted average of the age-specific rates, where the weights are the proportions of a standard population in the corresponding age groups, so that specific rates within different populations can be compared without confounding by the different age of the populations [PMID: 30496106].

**Eurostat’ health care indicators**

The following indicators were extracted from the eurostat’ database available at <https://ec.europa.eu/eurostat/web/main/data/database> (last access 15 January 2023):

* *Current health care expenditure* [HLTH\_SHA11\_HC]: quantifies the economic resources, in terms of purchasing power standard (PPS) per inhabitant, dedicated to all health functions [TOT\_HC], excluding capital investment, and primarily concerns goods and services that are consumed by resident units, irrespective of where that consumption takes place. It includes both curative, inpatient and rehabilitative cares. Imports of healthcare goods and services for final use are included.
* *Health care expenditure by function* [HLTH\_SHA11\_HC]: quantifies the economic resources, in terms of PPS per inhabitant, dedicated to specific health functions. Among those available, the following were selected: curative cares [HC1], inpatient curative care [HC11], preventive care [HC6], outpatient curative care [HC13], and long-term care [HC3].
* *Hospitals beds by type of care* [HLTH\_RS\_BDS]: included available beds [HBEDT], curative care beds [HBEDT\_CUR] and long-term care beds [HBEDT\_LT] in all hospitals and reported as per 1000 inhabitants.
* *Medical technology* [HLTH\_RS\_EQUIP]: quantifies the number of computed tomography scanners [CT\_SCAN], magnetic resonance imaging units [MRI], PET scanners [PET\_SCAN] and radiation therapy equipment [RAD], reported as per 100.000 inhabitants.
* *Health personnel* [HLTH\_RS\_PRS1 and HLTH\_RS\_PRSNS]: practising [PRACT] medical doctors [OC221], nurses [OC2221\_3221] and health care assistants and home-based personal care workers [OC5321\_5322] reported as per 1,000 inhabitants.
* *Physicians by medical specialty* [HLTH\_RS\_SPEC]: gastroenterology [MED\_GAS], oncology [MED\_ONC], radiology [MED\_RAD], general surgery [SURG\_GEN] were selected and reported as per 100.000 inhabitants.
* *Unmet needs for medical examination* [HLTH\_SILC\_08]: because of expense, travel limitations or waiting lists [TOOEFW] expressed in percentage [PC]

**Mediation analysis**

Correlations among eurostat indicators, incidence and mortality were analysed through mediation analysis. Mediation refers to the transmission of the effect of an independent variable on a dependent variable through one or more other variables. In the present analysis, the dependent variable was mortality, and incidence was a single mediator.

An example is reported in **Figure 1.** If the median age of the population was tested against mortality,a positive correlation was found (total effect), thus meaning that mortality of the population was due to the aging of the population itself. However, an increased median age also correlated with an increased incidence (indirect effect) which in turn had an expected strong correlation with mortality (indirect effect). The true effect of the population’s median age on mortality, once the mediator is considered, is obtained by subtracting from the total effect the indirect effects. In this example, median age had no direct effect over mortality, and the observation was completely due to the presence of the mediator.

**Statistical analysis**

The epidemiologic trends in incidence and mortality in different countries were calculated using the Annual Percent Change (APC) by joinpoint regression analysis, with log-transformation and automatic selection of the best fitting model. This was performed using Joinpoint Regression Program, Version 4.9.1.0. April, 2022; Statistical Research and Applications Branch, National Cancer Institute. Mediation analysis was performed using the Structural Equation Modeling (SEM) command of Stata 17.0 (StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC) with robust clustering and weighting for each country’ population applied to regressions to assure reliability of results.

**Results**

**Incidence and mortality**

Data from the GBD study showed that the average APC (AAPC) of incidence, between 2004 and 2019 was +0.6% (95%CI: 0.4, 0.7; p= 0.001), being an increment for most of the selected European countries (**Figure 2**). The AAPC of mortality in the same time-period was +0.3% (95%CI: 0.2, 0.5; p= 0.001) and again most countries showed an increase over time (**Figure 2**). Incidence and mortality were strongly positively correlated (β= 0.839; 95%CI: 0.700, 0.977; p= 0.001).

**Eurostat’ health care indicators**

 **Table 1** reports the details of the eurostat indicators used. All indicators showed high variability. As an example, the current health expenditure ranged from 630 Euros per PPS per capita in Romania in 2011 to 4,920 Euros in Switzerland in 2019. The quantity of CT scans also varied, from 0.3 per 1,000 inhabitants in Romania in 2007 to 4.8 per 1,000 people in Iceland in 2018. The number of practising medical doctors ranged between 1.2 per 1,000 inhabitants in Albania in 2006 to 5.3 in Austria in 2019. And of final note the unmet need for medical examination ranged between 0.1% of respondents up to 16.4% (Türkiye 2006).

**Current health expenditure**

Total correlations, as well as indirect and direct correlations resulting from mediation analysis among eurostat indicators, pancreatic cancer mortality and incidence are detailed in **Table 2**. The current health expenditure showed no apparent (total) correlation with mortality (p= 0.228) but showed a positive correlation with incidence (β= 0.606; p= 0.049). Once the effect of incidence as a mediator was considered, the current health expenditure had an inverse correlation (direct effect) with mortality (β= -0.150; p= 0.048). The same was observed for the health expenditure on inpatient cares (β = -0.483; p= 0.003) and similar correlations were observed for the expenditure on all curative cares (β= -0.485; p= 0.003) and on outpatient curative cares (β = -0.820; p= 0.009). No indirect or direct correlations were seen among health expenditure on preventive cares and incidence nor mortality.

**Hospital beds**

As reported in **Table 2**, a higher number of hospital beds (all available) correlated positively with mortality (β= 0.476; p= 0.001), but this correlation was completely mediated by the increased incidence (β= 0.570; p= 0.001) consequent to increased beds itself, so that the direct effect of this indicator on mortality was absent (p= 0.827). A similar correlation (p= 0.779) was observed when curative beds were considered, for which the total effect on mortality (β= 0.840; p= 0.001) was completely due to the increased incidence related to the increase of this indicator (β= 0.831; p= 0.001). Long-term curative beds had no direct or indirect correlations with incidence or mortality.

**Medical technology**

As also reported in **Table 2**, the number of available CT scans correlated with incidence (β= 0.886; p= 0.016) and when the effect of this mediator was considered, this was inversely correlated with mortality (β = -0.250; p= 0.001), so that the total effect was negligible (p= 0.077). The same was observed for MR units, that is, the higher the number of units per inhabitants the higher the incidence (β= 0.954; p= 0.008), but the lower the mortality (β = -0.360; p= 0.001) with a final negligible total effect (p= 0.108). Similar correlations were observed also for PET scanners (β = -1.470; p= 0.011) and for radiation therapy equipment (β= -0.383; p= 0.003)

**Health personnel and unmet need for medical examination**

 As reported in **Table 3**, the number of practising medical doctors positively correlated with the incidence (β= 0.791; p= 0.048). The direct correlation with mortality, through incidence as mediator, was inverse (β = -0.362; p= 0.002) so that the total effect was absent (p= 0.378). Practising nurses, assistant and home-based care workers showed no correlation with incidence or mortality. Medical specialties were not related with incidence or mortality. Of final note, that higher the reported unmet needs for medical examination, lower the incidence (β= -0.219; p= 0.035); however, this indicator was not correlated with mortality (p= 0.386)

**Discussion**

More than a decade ago, data from the Global Cancer Observatory (GLOBOCAN) projected that rapid societal and economic development will result in an increase in the number of new cancer cases linked to lifestyle in many countries [ref]. An ageing population, the higher prevalence of obesity, diabetes, and alcohol consumption in more economically and socially developed societies [ref], can explain the rise of incidence of pancreatic cancer. However, incidence reflects the rate at which new cases of disease are being added to the population, so that the provision of good medical care that is able to offer timely and accurate diagnosis contribute to this cancer indicator.

After diagnosis is made the lethality of the tumour also depends on health care quality, finally determining the mortality over the total population. In the current study, we combined information about how medical resources are supported in European countries and cancer indicators.

Current statistics from the GBD-2019 study confirms the initial prediction, with an estimated AAPC of incidence of +0.6% between 2004 and 2019. As the incidence increased, so did mortality, albeit at a slower rate of +0.3% per year. The health expenditure showed a positive correlation with incidence and an inverse correlation with mortality and this was especially true for expenditure for curative and inpatient care (**Table 2**). Correlations with incidence are partly due to the decline in competing causes of premature death, such as communicable or more prevalent diseases, but are also due to improvement in accurate diagnosis. Once that incidence is benchmarked, as obtained by the present mediation analysis, the correlation of health expenditure with mortality can be considered as direct and mainly driven by expenditure on inpatient and outpatient curative services. That is, higher health care expenditure causes an increase in pancreatic cancer incidence due to a decrease of other causes of early death and improved diagnostic ability, but also leads to a considerable reduction in the lethality of the tumour itself. From the opposite point of view, interpretation of cancer indicators across European countries must consider that they are largely determined by economic spending. 🡨 I was wondering whether further highlight this source of bias of population statistics. Similar considerations can be applied to the availability of hospital beds, and of CT scan and MR units (**Table 2**).

Of note is that health expenditure on preventive services had no correlation with incidence or mortality. Pancreatic cancer, unlike other cancers such as colorectal, cervical, or breast cancer, cannot be detected through screening at a population level. Therefore, the findings of no effect of preventive care expenditure on incidence or mortality was expected. On the opposite, one interesting finding was that higher the number of practising medical doctors the higher the incidence, and the lower the mortality (**Table 3**). Additionally, no specific medical specialization showed a correlation with these two cancer indicators. These correlations suggest that general medical doctors are fundamental in recognizing the clinical signs of pancreatic cancer onset, and their presence is pivotal to plan subsequent diagnosis. The observation that higher the unmet need for medical examination decreased incidence supports this observation (that is, a patient cannot receive a diagnosis if unmet needs are too high). Once that diagnosis is made, eventually earlier, most patients would need outpatient curative and supportive cares during cancer natural history, such as adequate nutrition, pain management, biliary and duodenal obstruction management, and advance care planning in order to increase both length and quality of life [ref]. These factors explain why outpatient care and the ability of medical practitioners to adequately treat patients at home for complications related to the disease or comorbidities can eventually improve survival, reducing pancreatic cancer lethality.

The current study has merits, providing one of the few extensive analyses of the correlation between healthcare resource allocation and the incidence and mortality of pancreatic cancer but comes with limitations intrinsic to its nature. In fact, there may be an ecological fallacy when interpreting correlations observed but this is an unavoidable bias that we tried to handle through mediation analysis and the application of robust standard errors. Additionally, even if recent data were used, a lead time between registration of indicators and the development of pancreatic cancer may exist so that some of them may no longer impact on the outcomes considered. However, our results are consistent one with the other, and there are plausible reasons for the observed associations. Finally, it must be acknowledged that the relationship among healthcare indicators, incidence, and mortality is complicated and cannot be described exclusively by one element, as defined by the idea of intersectionality, where none alone can provide a thorough understanding of the issue [ref].

In conclusion, the incidence of pancreatic cancer has been consistently rising in Europe in recent years, while the rate of mortality appears to be increasing at a slower pace. Despite all countries included in the analysis being categorized as having high or very high human development, substantial disparities still exist. Economic investment in comprehensive healthcare services, advanced diagnostic technologies, and outpatient care could potentially contribute to enhancing the prognosis of this fatal disease.

**Authors’ contributions:** A. Cucchetti developed the original idea, performed the analyses and wrote the manuscript; C.A. Pacilio and S.Crippa collected the data and interpreted results; G. Capurso and P. Johnson helped in manuscript preparation; C. Fabbri, M. Falconi and G. Ercolani provided important intellectual content and administrative support.

**Table 1.** Summary and description of health care factors potentially related to incidence and mortality of pancreatic cancer.

|  |  |  |  |
| --- | --- | --- | --- |
| **Indicators** | **eurostat data code** | **# of data** | **Median (min, max)** |
| **Health expenditures,** (per PPS/inhabitant, Euro) | HLTH\_SHA11\_HC |  |  |
| Current health care expenditure (1K) | TOT\_HC | 344 | 2.80 (0.63, 4.92) |
| Curative care (1K) | HC1 | 304 | 1.38 (0.27, 2.43) |
| Preventive care  | HC6 | 321 | 68.3 (6.5, 150.7) |
| Inpatient curative care | HC11 | 303 | 689 (164, 1148)  |
| Outpatient curative care | HC13 | 326 | 634 (61, 1282) |
| Long-term care | HC3 | 344 | 433 (38, 1361) |
| **Hospitals beds by type of care**, (per 1000 inhabitants) | HLTH\_RS\_BDS |  |  |
| All available beds | HBEDT | 561 | 4.5 (2.1, 8.6) |
| Curative beds | HBEDT\_CUR | 505 | 3.4 (1.9, 6.5) |
| Long-term care beds | HBEDT\_LT | 372 | 0.5 (0.0, 3.2) |
| **Medical technology,** (per 100K inhabitants) | HLTH\_RS\_EQUIP |  |  |
| CT scan | CT\_SCAN | 454 | 1.7 (0.3, 4.8) |
| Magnetic Resonance units | MRI | 421 | 1.1 (0.2, 3.5) |
| PET scanners | PET\_SCAN | 397 | 0.1 (0.0, 0.5) |
| Radiation therapy equipment | RAD | 380 | 0.5 (0.2, 1.8) |
| **Health personnel,** (per 1000 inhabitants) | HLTH\_RS\_PRS / NS |  |  |
| Practising medical doctors | OC221 | 444 | 3.4 (1.2, 5.3) |
| Practising nurses | OC2221\_3221 | 428 | 7.8 (3.2, 17.9) |
| Assistants & home-based care workers | OC5321\_5322 | 355 | 7.6 (0.0, 22.0) |
| **Physicians by medical specialty,** (per 100K inhabitants) | HLTH\_RS\_SPEC |  |  |
| Gastroenterology | MED\_GAS | 313 | 3.4 (0.0, 8.5) |
| Oncology | MED\_ONC | 287 | 2.4 (0.2, 8.0) |
| Radiology | MED\_RAD | 332 | 9.8 (2.4, 31.2) |
| General Surgery | SURG\_GEN | 333 | 13.5 (3.8, 30.0) |
| **Unmet needs for medical examination,** (%) | HLTH\_SILC\_08 |  |  |
| Because too far / expensive / waiting list | TOOEFW | 407 | 2.1 (0.1, 16.4) |

PPS: purchasing power standard

Median values are weighted on the basis of total population of each country

**Table 2.** Results from mediation analysis highlighting total correlations betweenhealth expenditure, hospital beds and medical technology extracted from Eurostat and mortality *(c)*, their correlations with ***incidence*** *(a)* and the controlled direct effect of these indicators on ***mortality*** mediated by incidence *(c’)*.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Mortality – total effect *(c)*** |  | **Incidence *(a)*** |  | **Direct effect on mortality *(c’)*** |
| **Exposure**, (unit of measure of increase) | **β-coeff (95%CI)** | **P** |  | **β-coeff (95%CI)** | **P** |  | **β-coeff (95%CI)** | **P** |
| **Health expenditures**, (per PPS/inhabitant, Euro) |  |  |  |  |  |  |  |  |
| Current health care expenditure (1K) | 0.340 (-0.214, 0.895) | 0.228 |  | 0.606 (0.035, 1.248) | **0.049** |  | -0.150 (-0.320, -0.020) | **0.048** |
| Curative care (1K) | 0.554 (-0.552, 1.661) | 0.326 |  | 1.237 (-0.063, 2.538) | 0.062 |  | -0.485 (-0.799, -0.169) | **0.003** |
| Preventive care | 0.885 (-0.548, 2.318) | 0.226 |  | 1.468 (-0.392, 3.329) | 0.122 |  | -0.300 (-0.744, 0.142) | 0.183 |
| Inpatient curative care | 1.832 (-0.674, 4.339) | 0.152 |  | 3.208 (0.457, 5.958) | **0.022** |  | -0.912 (-1.544, -0.281) | **0.005** |
| Outpatient curative care | -0.008 (-1.856, 1.840) | 0.994 |  | 1.025 (-1.516, 3.565) | 0.429 |  | -0.820 (-1.433, -0.207) | **0.009** |
| Long-term care  | 1.229 (-0.577, 3.036) | 0.182 |  | 1.837 (-0.198, 3.872) | 0.077 |  | -0.218 (-0.826, 0.389) | 0.481 |
| **Hospitals beds by type of care**, (per 1000/p) |  |  |  |  |  |  |  |  |
| All available beds  | 0.476 (0.263, 0.690) | **0.001** |  | 0.570 (0.306, 0.833) | **0.001** |  | 0.012 (-0.098, 0.123) | 0.827 |
| Curative beds  | 0.840 (0.742, 0.937) | **0.001** |  | 0.831 (0.391, 1.272) | **0.001** |  | -0.027 (-0.217, 0.163) | 0.779 |
| Long-term care beds | 0.366 (-0.576, 1.308) | 0.446 |  | 0.472 (-0.443, 1.389) | 0.312 |  | -0.098 (-0.511, 0.315) | 0.641 |
| **Medical technology**, (per 100K/p) |  |  |  |  |  |  |  |  |
| CT scans  | 0.552 (-0.061, 1.164) | 0.077 |  | 0.886 (-167, 1,605) | **0.016** |  | -0.250 (-0.390, -0.110) | **0.001** |
| Magnetic Resonance units  | 0.521 (-0.115, 1.159) | 0.108 |  | 0.954 (0.250, 1.658) | **0.008** |  | -0.360 (.0.506, -0.213) | **0.001** |
| Gamma cameras | 0.617 (-0.681, 1.915) | 0.351 |  | 0.895 (-0.610, 2.399) | 0.244 |  | -0.241 (-0.601, 0.118) | 0.189 |
| PET scanners | 1.159 (-1.999, 4.319) | 0.472 |  | 2.778 (-0.158, 5.715) | 0.064 |  | -1.470 (-2.596, -0.344) | **0.011** |
| Radiation therapy equipment | 1.161 (-0.669, 2.992) | 0.214 |  | 1.651 (-0.394, 3.696) | 0.114 |  | -0.383 (-0.736, -0.031) | **0.033** |

Regression models weighted for population (millions of inhabitants) and clustered for countries.

The path *(b)* of indirect effect was represented by the correlation between incidence and mortality (β =0.839; 95%CI: 0.700, 0.977; p=0.001)

**Table 3.** Results from mediation analysis highlighting total correlations betweenhealth personnel, physicians’ specialty and unmet needs extracted from Eurostat and mortality *(c)*, their correlations with ***incidence*** *(a)* and the controlled direct effect of these indicators on ***mortality*** mediated by incidence *(c’)*.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Mortality – total effect *(c)*** |  | **Incidence *(a)*** |  | **Direct effect on Mortality *(c’)*** |
| **Exposure**, (unit of measure of increase) | **β-coeff (95%CI)** | **P** |  | **β-coeff (95%CI)** | **P** |  | **β-coeff (95%CI)** | **P** |
| **Health personnel**, (per 1000/p) |  |  |  |  |  |  |  |  |
| Practising medical doctors  | 0.318 (-0.389, 1.026) | 0.378 |  | 0.791 (0.007, 1.574) | **0.048** |  | -0.362 (-0.593, -0.130) | **0.002** |
| Practising nurses  | .0.106 (-0.092, 0.305) | 0.293 |  | 0.188 (-0.059, 0.435) | 0.137 |  | -0.050 (-0.112, 0.012) | 0.115 |
| Assistants & home-based care workers | -0.038 (-0.117, 0.040) | 0.339 |  | -0.024 (-0.115, 0.068) | 0.612 |  | -0.018 (-0.046, 0.009) | 0.192 |
| **Physicians’ specialty**, (per 100K/p) |  |  |  |  |  |  |  |  |
| Gastroenterology | 0.166 (-0.259, 0.593) | 0.444 |  | 0.224 (-0.248, 0.697) | 0.353 |  | -0.011 (-0.097, 0.074) | 0.797 |
| Oncology  | 0.177 (-0.204, 0.559) | 0.363 |  | 0.238 (-0.188, 0.663) | 0.274 |  | -0.010 (-0.073, 0.054) | 0.765 |
| Radiology | 0.090 (-0.048, 0.228) | 0.202 |  | 0.096 (-0.064, 0.258) | 0.239 |  | 0.014 (-0.010, 0.039) | 0.255 |
| General Surgery | 0.138 (-0.027, 0.312) | 0.110 |  | 0.163 (-0.032, 0.357) | 0.101 |  | 0.011 (-0.021, 0.043) | 0.495 |
| **Medical examination’ unmet needs,** (per %) |  |  |  |  |  |  |  |  |
| Too far / expensive / waiting list | .0.166 (-0.368, 0.035) | 0.106 |  | -0.219 (-0.423, 0.016) | **0.035** |  | 0.021 (-0.027, 0.070) | 0.386 |

Regression models weighted for population (millions of inhabitants) and clustered for countries.

The path *(b)* of indirect effect was represented by the correlation between incidence and mortality (β =0.839; 95%CI: 0.700, 0.977; p=0.001)

**Figure 1.** Description of mediation analysis where population median age is the variable of interest, mortality is the analysed outcome and incident represents the mediator.



**Panel A**: The total effect (correlation) of increased median age of the population on mortality *(c)* showed a positive coefficient (β= 0.270; p= 0.001), apparently meaning that mortality of the population was due to the aging of the population itself.

**Panel B:** However, median age also correlated *(a)* with incidence (β= 0.334; p= 0.002) which in turn had a strong correlation *(b)* with mortality (β= 0.839; p= 0.001). The direct effect of population’ median age *(c’)* on mortality is obtained by subtracting from the total effect *(c)* the indirect effect *(a x b)*. In this example the direct effect was thus 0.270 – (0.334 x 0.839) = -0.010 (p= 0.711), meaning that median age had no direct effect over mortality, and that the observation was due to the presence of the mediator.

**Figure 2.** Average Annual Percent Change (AAPC) of incidence and mortality across 36 European countries between 2004 and 2019 resulting from the GBD study 2019.

