Analysis of Mortality from Asbestos-Related Diseases in Brazil Using Multiple Health Information Systems, 1996–2017

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ABSTRACT

Background: In Brazil, asbestos was intensively used from the 1960s until its ban in 2017. Mesothelioma, asbestosis, and pleural plaques are typical asbestos-related diseases (ARD-T). To create an ARD-T national database, death records from 1996–2017 were retrieved from several health information systems (HIS).

Methods: All national HIS containing coded diagnoses (ICD-10) and death information were obtained. Linkage was performed to create a single database of ARD-T death records, either as underlying or contributory causes, in adults aged 30 years and older.

Results: A total of 3,057 ARD-T death records were found, 2,405 (76.4%) of which being malignant mesotheliomas (MM). Pleural MM (n = 1,006; 41.8%) and unspecified MM (n = 792; 32.9%) prevailed. Male to female MM ratio (M:F) was 1.4:1, and higher ratios were found for non-malignant ARD-T: 3.5:1 for asbestosis and 2.4:1 for pleural plaques. Male crude annual mesothelioma mortality (CMmm x1,000,000) was 0.98 in 1996 and 2.26 in 2017, a 131.1% increment, while for females it was 1.04 and 1.25, a 20.2% increase, correspondingly. The small number of deaths with asbestosis and pleural plaques records precluded conclusive interpretations.

Conclusions: Even with the linkage of several HIS, ARD-T in death records remained in low numbers. MM mortality in men was higher and showed a rapid increase and, along with non-malignant ARD-T, higher M:F ratios suggested a predominant pattern of work-related exposure. The monitoring of workplace and environmental asbestos exposure needs to be improved, as well as the workers surveillance, following the recent Brazilian ban.

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1. Introduction

Malignant mesothelioma (MM), along with two other non-malignant respiratory illnesses, asbestosis and pleural plaques, diseases typically related to asbestos-related diseases exposure (ARD-T) [1]. Mainly because efficient exposure control is unfeasible, a worldwide asbestos ban has been recommended [2]. Currently, under effect in 67 countries [3], it was adopted in Brazil only in 2017. MM is a rare lethal cancer known for the long latency between the beginning of exposure and the occurrence of the disease [4], although this period can be shorter when the asbestos concentration reaches 100 f/mL year or more [5]. An immediate full asbestos elimination is unplausible, given its physical properties and its global scale usage [6]. In addition, new cases of ARD-T and other asbestos-related illnesses will continue to appear long after occupational exposure cessation, as a result from environmental contamination, long latency, and irreversible past exposure status.

In Brazil, despite the growth of workers’ health care in the national public health system (SUS), media attention, and the increased awareness of the hazardous effect of asbestos on health, the number of notified or registered ARD-T cases in health information systems (HIS) remains far below estimates from other
Asbestos consumer countries. Asbestos is the major global work-related carcinogen, responsible for the largest number of recorded work-related cancers [7]. Therefore, many countries have created national or regional MM registries following well-defined protocols, usually fed by multiple information systems [8]. The National Registry of Mesotheliomas in Italy (ReNaM) launched in 2002, at the end of 2016 contained 27,356 case records of MM, mostly from pleura (93.0%), either among men (94.1%) or women (90.3%). Overall, male deaths prevailed (71.7%), particularly among elderly individuals over 65 years of age (71.9%), but there were no significant sex differences across age groups [9]. In the USA, from 1999 to 2015, mesothelioma was recorded as the underlying cause of death in 93.9% out of 45,221 death certificates with MM records. Consistently with other study findings, death cases were likely to be males (79.8%), aged 64 years or older (80.4%), and to have a diagnosis of MM unspecified (77.5%), while pleural MM accounted for only 7.4% of records [10]. From 1994 to 2008, worldwide MM deaths summed 92,253 records mainly unspecified MM (43.1%), followed by pleural (41.3%) and peritoneal MM (4.5%) [11].

The non-malignant ARD-T group comprises, among other illnesses, asbestosis, a pulmonary interstitial fibrosis associated with high exposure levels [12] and pleural thickening. Pleural plaques are the most common non-malignant ARD that are characterized by the thickening of the parietal pleura; they are an exceptional cause of death, whereas diffuse thickening can rarely be associated with ventilatory impairment and respiratory failure [13]. Pleural thickening may occur with exposures of varying intensity [14].

In Brazil, the small number of recorded ARD in vital statistics and its work-relatedness and the few studies addressing the subject limit the understanding of the burden of diseases caused by asbestos. Based on death certificates from 1996 to 2010, 976 MM records were found, mostly classified as “other anatomic places” (43%), followed by those from pleura (35.1%), showing a male to female ratio (M:F) of 1.4 while the number of deaths increased from 44 in 1996 to 85 in 2010 [15]. Considering another reference period, 2000 to 2012, a study reported 929 MM as the underlying cause of death and an increasing mortality rate in the state of São Paulo [16]. Both studies make the case of potential underdiagnosis and/or underreporting, given the small number of deaths. Mortality data from non-malignant ARDs are also scarce in Brazil. From a cohort of Brazilian former asbestos-cement workers, a nine-fold increase in SMR for asbestosis was estimated [17]. An ecological study in Brazilian municipalities with high asbestos consumption showed increased standardized risk ratios for deaths with records of asbestosis and pleural plaques in men and for asbestosis in women when compared to all others [18].

More recently, our group showed a mean 33% increase in MM death records originally found in the mortality information system (SIM) from 2008 until 2014, by linking the SIM to other HIS [19]. These supposedly small numbers were the drivers that led to the Interdisciplinary Project on Occupational Exposure to Asbestos and Health Effects in Brazil. Starting in 2015, it aimed at investigating the burden of ARD-T with the use of data from multiple HIS. The objective of this study was to collect every coded ARD-T in death records in all available HIS, irrespective of being the underlying or the contributory cause, from adults aged 30 years or older between 1996 and 2017.

2. Methods

2.1. Data sources and ARD-T database

The five HIS used in the study were as follows: SIM; Hospital Information System of the Unified Health System (SIH-SUS); the Hospital and Outpatient Information Communication System of the private sector (CIH and CIHA); the Hospital Cancer Registry of the National Cancer Institute (INCA); and the Notifiable Diseases Information System (SINAN), which gathers data on work-related pneumoniosis and cancer since 2007. In addition, data from a repository of ARD cases from three specialized outpatient occupational respiratory diseases units — FUNDACENTRO, InCor/USP, and the Center for Occupational Health and Human Ecology Studies (CESTEH/FIOCRUZ) — were included. Except from the ARD repository, all databases were anonymous.

Completeness and consistency of recorded data were checked, and corrections or imputations were made when applicable. Variable formats and operational definitions were standardized. Since the five databases were anonymous and there was no common identifier, a probabilistic linkage technique was used. Detailed information can be found elsewhere [19]. This strategy was previously tested and presented feasibility and good performance for mesothelioma [20] and cancer of the larynx [21].

Descriptive variables were ICD-10 codes, sex, age ranges (30 to 50, 51 to 64, and over 64 years), skin color/ethnicity (white, black, brown, Asian, and Indigenous), and schooling (incomplete or complete primary school, secondary school, and incomplete or complete higher education). Absolute and relative frequencies of each variable by diagnosis and sex were estimated. Sex differences were measured using M:F ratio of the death numbers. When multiple ARD-T diagnoses were assigned to the same individual, one was selected for analysis, considering the most common, or in case of distinct ICD codes, the following order was adopted: C45x, J61, and J92.0. When pleural plaques were recorded with only three-digit (J92) it was assumed as J92.0.

Annual crude mesothelioma mortality x 1,000,000 inhabitants (CM\textsubscript{MM} x 1,000,000) was estimated for males and females, as well as the relative proportionate change over time. Resident-population projected estimates were drawn from the official country institute [22]. No statistical tests were applicable given the descriptive study purpose and the use of the total population.

2.2. Ethical aspects

The study protocol was registered in the National Council of Research Ethics, CONEP, and approved by the Research Ethics Committee of the Institute of Collective Health of the Federal University of Bahia - CAAE 36547514.0000.5030, Addendum No. 962 145 and 1 761 856.

3. Results

Records from all data sources were retrieved and linked. There were 3,057 deaths with ARD-T records either as underlying or contributory cause, mostly MM (n = 2,405; 76.4%), in a lower proportion for males (n = 1,404; 72.1%) compared to female (n = 1,001; 83.4%). Approximately three quarters of all MM deaths were coded as C45.0 pleural (n = 1,006/2,405; 41.8%) or C45.9 unspecified (n = 792/2,405; 32.9%). Non-malignant ARD-T deaths (n = 652) comprised records of asbestosis and pleural plaques mainly in males (n = 488; 74.8%). The number of male deaths exceeded the number of female deaths for ARD-T, an M:F average of 1.62:1, being 1.4:1 for MM and higher for asbestosis (M:F = 3.5:1) and pleural plaques (M:F = 2.4:1). Table 1 shows the results.

Table 2 shows that MM male deaths were likely to occur in the oldest age group 64 years or older (46.3%), except for MM of the pericardium, which was more prevalent in the 51–64 age group (41.4%). Among men, prevailed those with white skin color (70.4%) and complete or incomplete higher education (57.1%). Table 3 shows that women MM deaths had a similar distribution, except for a higher percentage of peritoneal MM (22.9%) compared with
Typical asbestos-related diseases (ARD-T) death records coded with ICD 10th revisions by specific diagnoses, Brazil, 1996–2017

| Typical asbestos-related diseases (ARD-T) | Total | Men | Women | Male-Female ratio |
|------------------------------------------|-------|-----|-------|------------------|
| All ARD-T                                 | 3,057 | 1,892 | 1,165 | 1.62             |
| All malignant (mesothelioma)              | 2,405 | 1,404 | 1,001 | 1.40             |
| C45.0 Pleura                               | 1,006 | 626   | 380   | 1.65             |
| C45.1 Peritoneum                          | 415   | 186   | 229   | 0.81             |
| C45.2 Pericardium                         | 42    | 29    | 13    | 2.23             |
| C45.7 Others                              | 150   | 87    | 63    | 1.38             |
| C45.9 Unspecified                         | 792   | 476   | 316   | 1.51             |
| All non-malignant                         | 652   | 488   | 164   | 2.98             |
| J61 Asbestos                              | 372   | 290   | 82    | 3.54             |
| J02.0 Pleural plaques                      | 280   | 198   | 82    | 2.41             |

Table 2 Malignant mesothelioma deaths according to anatomical sites and sociodemographic characteristics in men 30 years of age or more, Brazil, 1996–2017

| Variables | Malignant mesothelioma (ICD-10) | Total n (%) |
|-----------|----------------------------------|-------------|
|           | Pleura n (%)                     | 626 (44.6)  |
|           | Peritoneum n (%)                 | 186 (13.2)  |
|           | Pericardium n (%)                | 29 (2.1)    |
|           | Others n (%)                     | 87 (6.2)    |
|           | Unspecified n (%)                | 476 (33.9)  |
| Total     |                                  | 1,404 (100.0)|

| Age range (years) | Pleura n (%) | Peritoneum n (%) | Pericardium n (%) | Others n (%) | Unspecified n (%) |
|-------------------|--------------|------------------|-------------------|--------------|------------------|
| 30–50             | 106 (16.9)   | 43 (23.1)        | 7 (24.1)          | 16 (18.4)    | 93 (19.5)        |
| 51–64             | 220 (35.1)   | 64 (34.4)        | 12 (41.4)         | 28 (32.2)    | 165 (34.7)       |
| >64               | 300 (47.9)   | 79 (42.5)        | 10 (34.5)         | 43 (49.4)    | 218 (45.8)       |

| Skin color/ethnicity | Pleura n (%) | Peritoneum n (%) | Pericardium n (%) | Others n (%) | Unspecified n (%) |
|----------------------|--------------|------------------|-------------------|--------------|------------------|
| White                | 392 (70.9)   | 101 (65.2)       | 7 (24.1)          | 55 (75.3)    | 284 (71.5)       |
| Black                | 28 (5.1)     | 5 (3.2)          | 1 (7.1)           | 5 (5.5)      | 28 (7.1)         |
| Brown                | 73 (13.2)    | 29 (18.7)        | 3 (21.4)          | 6 (8.2)      | 75 (18.9)        |
| Asian                | 19 (3.4)     | 6 (3.9)          | 2 (14.3)          | 5 (6.8)      | 9 (2.3)          |
| Indigenous           | 41 (7.4)     | 14 (9.0)         | 1 (7.1)           | 3 (4.1)      | 1 (0.2)          |

| Schooling**         | Pleura n (%) | Peritoneum n (%) | Pericardium n (%) | Others n (%) | Unspecified n (%) |
|---------------------|--------------|------------------|-------------------|--------------|------------------|
| Primary incomplete  | 9 (2.8)      | 7 (7.9)          | 0 (0.0)           | 2 (4.8)      | 5 (2.0)          |
| Primary complete    | 46 (14.6)    | 7 (7.9)          | 1 (14.2)          | 4 (9.5)      | 25 (10.2)        |
| Secondary           | 78 (24.7)    | 24 (27.0)        | 2 (28.6)          | 11 (26.2)    | 79 (32.1)        |
| Higher incomplete   | 99 (31.3)    | 32 (35.9)        | 2 (28.6)          | 12 (28.5)    | 58 (23.6)        |
| Higher complete     | 84 (26.6)    | 19 (21.3)        | 2 (28.6)          | 13 (31.0)    | 79 (32.1)        |

Sources: SIM, SIH-SUS, SINAN, CIHA, INCA, outpatient clinics specialized in respiratory worker health.

* Skin color/Ethnicity- 212 missing data.
** Schooling - 704 missing data.
plagues, the repository from the three specialized clinics was the second [19].

Underdiagnosis and underreporting lead to underestimation of health outcomes [23]. The use of multiple data sources is one of the tools to reduce underestimation. Linkage computer-based resources are easily available have a good performance and can be the seed to set up national ARD-T registers. Recently, Gerwen et al. (2019) [8] presented a review of national mesothelioma registries from several countries. These systems are usually based on real-time case capture and have already been implemented in several European countries, such as Italy, Belgium, France, Germany, England, and Scandinavian countries, in addition to South Africa, Turkey, and Australia. The main challenges to these national mesothelioma information systems are the need to ensure accurate standardized diagnosis procedures, in addition to detailed occupational history which will enable to establish the causal work-relatedness, required to legal indemnities and compensation benefits.

Worldwide, an estimate of 232,000 deaths from typical and other asbestos-related diseases was reported for the year 2017 [24], being 27,000 MM and 3,000 asbestos deaths. In a more recent GBD analysis on occupational carcinogens, asbestos had the greatest population impact, causing 62.3% of all work-related cancer deaths [7]. Lung cancer showed the greatest number of asbestos-related cancer deaths, revealing its importance even though mesothelioma is the most studied because of its largest asbestos attributable fraction [7].

Male deaths predominated, particularly in the non-malignant disease group. Global studies of MM revealed an M:F ratio of 3.6 [11]. Nevertheless, our findings demonstrated an M:F ratio of 1.40 for MM and 2.98 for non-malignant ARD-T. Commonly, occupational asbestos exposure prevails among men because asbestos mining and manufacturing industries are mainly male jobs, while women predominate in the textile industry. In Brazil, D’Acri et al. (2003) [25] reported a higher number of asbestos cases in females working in a textile factory located in the state of Rio de Janeiro in the early 2000s. In contrast, our national database showed the largest M:F for asbestos: 3.54. Women MM deaths are likely to be associated with environmental exposure compared to men [26]. Environmental asbestos exposure may occur when washing

### Table 3

| Variables | Malignant mesothelioma (ICD-10) | Total n (%) |
|-----------|---------------------------------|-------------|
|           | Pleural n (%) | Peritoneum n (%) | Pericardium n (%) | Others n (%) | Unspecified n (%) |
| Total     | 380 (37.9) | 229 (22.9) | 13 (1.3) | 63 (6.3) | 316 (31.6) | 1,001 (100.0) |
| Age range (years) | | | | | | |
| 30–50     | 70 (18.4) | 28 (12.2) | 5 (38.5) | 14 (22.2) | 52 (16.2) | 160 (16.9) |
| 51–64     | 128 (33.7) | 58 (25.3) | 5 (38.5) | 17 (27.0) | 96 (30.4) | 304 (30.4) |
| >64       | 182 (47.9) | 143 (62.4) | 3 (23.1) | 32 (50.8) | 168 (53.2) | 528 (52.7) |

### Table 4

| Variables | Asbestos deaths n (%) | Pleurales deaths n (%) | Total n (%) |
|-----------|-----------------------|------------------------|-------------|
| Total     | 290 (59.4) | 198 (40.6) | 488 (100.0) |
| Age range (years) | | | |
| 30–50     | 16 (5.5) | 24 (12.1) | 40 (8.2) |
| 51–64     | 77 (26.6) | 71 (35.9) | 148 (30.3) |
| >64       | 197 (67.9) | 103 (52.0) | 300 (61.5) |
| Skin color/ethnicity | | | |
| White     | 10 (12.2) | 13 (15.9) | 23 (14.0) |
| Black     | 19 (23.2) | 8 (9.8) | 27 (16.5) |
| Asian     | 53 (64.6) | 61 (74.4) | 114 (69.5) |
| Indigenous| 26 (8.5) | 11 (9.5) | 0 (–) |
| Schooling** | 173 (100.0) | 114 (100.0) | 1 (100.0) |

Sources: SIM, SIH-SUS, SINAN, CIHA, INCA, specialized outpatient clinics in respiratory worker health.

| Skin color/ethnicity - 196 missing data. ** Schooling- 532 missing data.

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**Table 3**

Malignant mesothelioma deaths according to anatomical sites and sociodemographic characteristics in women 30 years of age or more, Brazil, 1996–2017

| Variables | Asbestos n (%) | Pleural n (%) | Total n (%) |
|-----------|---------------|--------------|-------------|
|            |               |              |             |
| Total      | 290 (59.4) | 198 (40.6) | 488 (100.0) |
| Age range (years) | | | |
| 30–50     | 16 (5.5) | 24 (12.1) | 40 (8.2) |
| 51–64     | 77 (26.6) | 71 (35.9) | 148 (30.3) |
| >64       | 197 (67.9) | 103 (52.0) | 300 (61.5) |
| Skin color/ethnicity | | | |
| White     | 10 (12.2) | 13 (15.9) | 23 (14.0) |
| Black     | 19 (23.2) | 8 (9.8) | 27 (16.5) |
| Asian     | 53 (64.6) | 61 (74.4) | 114 (69.5) |
| Indigenous| 26 (8.5) | 11 (9.5) | 0 (–) |
| Schooling** | 173 (100.0) | 114 (100.0) | 1 (100.0) |

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**Table 4**

Asbestos and pleural plaques death records, 30 years of age and more, according to sociodemographic characteristics, Brazil, 1996–2017

| Variables | Men | Women | All |
|-----------|-----|-------|-----|
|            | Asbestos n (%) | Pleural n (%) | Total n (%) | Asbestos n (%) | Pleural n (%) | Total n (%) | Asbestos n (%) | Pleural n (%) | Total n (%) |
| Total      | 290 (59.4) | 198 (40.6) | 488 (100.0) | 82 (50.0) | 82 (50.0) | 164 (100.0) | 372 (50.0) | 280 (53.0) | 652 (100.0) |
| Age range (years) | | | | | | | | | |
| 30–50     | 16 (5.5) | 24 (12.1) | 40 (8.2) | 10 (12.2) | 13 (15.9) | 23 (14.0) | 26 (7.0) | 37 (13.2) | 63 (9.7) |
| 51–64     | 77 (26.6) | 71 (35.9) | 148 (30.3) | 19 (23.2) | 8 (9.8) | 27 (16.5) | 96 (25.8) | 79 (28.2) | 175 (26.8) |
| >64       | 197 (67.9) | 103 (52.0) | 300 (61.5) | 53 (64.6) | 61 (74.4) | 114 (69.5) | 250 (67.2) | 164 (58.6) | 414 (63.5) |
| Skin color/ethnicity | | | | | | | | | |
| White     | 60 (48.7) | 63 (51.3) | 123 (100.0) | 32 (53.3) | 42 (66.7) | 74 (82.2) | 160 (60.2) | 100 (62.9) | 260 (61.2) |
| Black     | 3 (5.0) | 7 (9.8) | 10 (8.0) | 2 (3.3) | 8 (12.5) | 10 (10.0) | 10 (3.3) | 12 (7.2) | 22 (4.5) |
| Asian     | 22 (36.7) | 15 (23.8) | 37 (30.1) | 5 (8.1) | 6 (10.0) | 11 (11.0) | 7 (2.3) | 9 (5.2) | 16 (3.3) |
| Indigenous| 3 (5.0) | 1 (1.6) | 4 (3.3) | 8 (3.0) | 1 (0.6) | 9 (2.1) | 14 (4.5) | 13 (7.8) | 27 (5.4) |
| Schooling** | 143 (72.9) | 53 (27.1) | 196 (100.0) | 41 (64.0) | 34 (36.0) | 75 (100.0) | 184 (67.8) | 87 (32.2) | 271 (100.0) |

Sources: SIM, SIH-SUS, SINAN, CIHA, INCA, specialized outpatient clinics in respiratory worker health.

| Skin color/ethnicity - 227 missing data. ** Schooling- 381 missing data. |
Diagnosis between these two conditions may be challenging [28]. Misdiagnosed cases of ovarian cancer, which is a more frequent the highest percentage of peritoneal MM in women resulted from asbestos consumption in the last 50 years and the long latency period of the ARD, the number of ARD deaths or ARD-T specifically was expected to grow over the last two decades and, further, similarly to other countries with earlier asbestos ban [4,16,29]. In spite of a global increment in MM death numbers, from 15,206 in 1990 to 27,612 in 2016, a modest 4% increase was estimated in global MM deaths per 100,000 persons — from 1.0 (95% uncertainty interval (UI): 0.9–1.2) in 1990 to 1.1 (95% UI: 1.0–1.1) in 2016 [7]. In contrast, our results show a consistent growth in both the absolute number of deaths and the annual mortality estimates.

In our study, 652 non-malignant ARD-T death records were retrieved. The proportional contribution of asbestosis was 57% and non-malignant ARD-T comprised 21.3% of all the analyzed cases. The ICD-10 coding does not provide a distinction of pleural thickening, deaths due to ARD-T were more likely to occur among the elderly, with 46.3% of MM records referring to males aged 64 years or more and 52.7% referring to females in the same age group. MM of the pericardium prevailed in younger ages among males and females, but the small numbers limited interpretation. Females with non-malignant ARD-T tended to die at older ages compared to males (Table 4). Likewise, in Italy, women who died of asbestosis were older than men [30]. Most individuals whose deaths were MM deaths were reported as having white skin color and higher educational level in comparison with those with non-malignant ARD-T. However, there were too many missing data and conclusions could not be checked. This study used mostly secondary data from several sources. Apart from the repository, where clinical data were available, diagnoses were based only on the HIS records and their accuracy could not be checked. A recent study that checked asbestos-related malignancies recorded in hospital admission forms compared to a hospital-based cancer registry showed that rare diagnoses in the SIH-SUS database, such as MM or cancer of the pleura, had low accuracy [31]. As it was a collection of secondary data without previous planning, there were many missing data related to sociodemographic variables, precluding firm conclusions.

Despite the advances, like the use of computational interoperability to increase the number of identified cases and the improvement in the quality of the data records, it is implausible that the total number of ARD-T was recovered because it represents only the cases whose diagnosis was recognized and registered. Based on time trends observed after the asbestos ban in other countries, the number of ARD-T deaths is expected to grow in the next decades. Future research on the diagnoses reporting quality and accuracy, as well as other data required for computational interoperability between various systems, should contribute to a better estimate of the burden of ARD-T.

**Authors’ contributions**

**Eduardo Algranti** - conception, design, analysis, literature review, and writing. He gave a final approval and agreed to be accountable to all aspects of the manuscript.

**Vilma Sousa Santana** – conception, design, analysis, literature review, and writing. She gave a final approval and agreed to be accountable to all aspects of the manuscript.

**Felipe Campos** – database management, analysis, interpretation of data, findings, and writing. She gave a final approval and agreed to be accountable to all aspects of the manuscript.

**Leonardo Salvi** - database management, analysis, and interpretation of data. He gave a final approval and agreed to be accountable to all aspects of the manuscript.

**Cézar Akiyoshi Saito** - database management, analysis, and interpretation of data. He gave a final approval and agreed to be accountable to all aspects of the manuscript.

**Franciana Cavalcante** - database management, analysis, interpretation of data, and literature review. She gave a final approval and agreed to be accountable to all aspects of the manuscript.

**Heleno Correa-Filho** – review and results checking, developed interpretations well-grounded in the theoretical framework, and published findings from the literature review. He gave a final approval and agreed to be accountable to the manuscript all aspects of the manuscript.

**Disclaimer**

The views and conclusions in this article are solely those of the authors.
Conflicts of interest

The authors have no conflicts of interest to declare.

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