Risk Factors for Abdominal Aortic Aneurysm in population-based studies: a systematic review and meta-analysis

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Abstract: Abdominal aortic aneurysm (AAA) represents an important public health problem with a prevalence between 1.3% and 12.5%. Several population-based randomized trials have evaluated ultrasound screening for AAA providing evidence of a reduction in aneurysm-related mortality in the screened population. The aim of our study was to perform a systematic review and meta-analysis of the risk factors for AAA. We conducted a systematic review of observational studies and we performed a meta-analysis that evaluated the following risk factors: gender, smoking habits, hypertension, diabetes mellitus, Coronary Artery Disease and family history of AAA. Abdominal aortic aneurysm prevalence is higher in smokers and in males. It is important to underline that all countries, where AAA screening was set up, had high income level and the majority belong to Western Europe (United Kingdom, Sweden, Italy, Poland, Spain and Belgium). Abdominal aortic aneurysm

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screening is fundamental for public health. It would avoid deaths, ruptures, and emergency surgical interventions if abdominal aortic aneurysm was diagnosed early in the population target for screening.

Keywords: abdominal aortic aneurysm, risk factors, observational studies, meta-analysis

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1. Introduction

Abdominal aortic aneurysm (AAA) is defined as a permanent dilation of the abdominal aorta, with a diameter of 3 cm or more [1], that generally remains asymptomatic until its rupture. It is the result of a loss of elastic lamina and smooth muscle cells, which could be due to inflammatory agents and matrix metalloproteases [2].

Abdominal aortic aneurysm represents an important public health problem with a prevalence between 1.3% and 12.5% in males, and between 0.0% and 5.2% in females [3]. In women, it generally appears ten years later than in males [4]. Abdominal aortic aneurysm represents about 1% of deaths in males over the age of 65, causing more than 175,000 deaths worldwide [5]. The mortality rate associated with rupture is very high and varies between 60-80% [6], early diagnosis and treatment therefore is very important before its rupture. Rupture rates increase markedly with aneurysm diameter; for each 0.5 cm increase in AAA diameter, rates increase by 0.5 mm/year and rupture rates double. Average growth rates are higher in smokers (by 0.35 mm/year) and lower in patients with diabetes (by 0.51 mm/year) [7]. Other more frequent risk factors associated with AAA are: age, gender, hypertension, family history and coronary artery disease [8]. Although the role of

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the hypertension is still controversial [9-12], while, in some studies hypertension is a risk factor [13-15].

Diabetes Mellitus is considered as potential risk factor, but in most studies in which it is considered as an independent variable it is not associated with AAA [16-18]. Moreover, it is important to underline that the presence of AAA in a part of the population remains unexplained and other risk factors may be involved as well as interaction between genetic and epigenetic background [19,20]. Abdominal aorta aneurysm can be easily diagnosed using ultrasound, a simple highly reliable non-invasive reproductive method. Intervention at this stage could reduce the frequency of rupture, reduce mortality and the requirement for emergency hospital treatment.

Several population-based randomized trials, have evaluated ultrasound screening for AAA providing evidence of a reduction in aneurysm-related mortality in the screened population [21-24]. Thompson *et al.* showed the mortality benefit of screening men aged 65-74 for abdominal aortic aneurysm is maintained up to 10 years and cost effectiveness becomes more favorable over time [25].

Furthermore, from data of recent review it is shown that the implementation of a screening system reduces not only costs, but has many benefits in terms of life expectancy [26]. Based on this evidence, the World Health Organization has included AAA screening among the interventions that proved to be cost effective. Despite this, only a few developed countries in the world have set up screening programmes for AAA [27]. At present, US Preventive Service Task Force (USPSTF) guidelines [28], have strongly recommended a one-time AAA screening for men aged 65-75 who have smoked. The aim of our study was to perform a systematic review and meta-analysis of the literature of the observational studies that evaluated the presence of following determinants: gender, smoking habits, hypertension, diabetes mellitus, Coronary Artery Disease (CAD) and family history of AAA.

2. Material and Methods

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2.1 Search method for identification of studies

The papers to be included in this systematic review and meta-analysis were sought in the MEDLINE, EMBASE, Scopus, Clinicaltrials.gov, Web of Science, and Cochrane Library databases up to June 30, 2018. The search strategy was conducted using the following terms: Abdominal Aortic Aneurysms OR Aneurysms, Abdominal Aortic OR Aortic Aneurysms, Abdominal OR Abdominal Aortic Aneurysm OR Aneurysm, Abdominal Aortic AND Screening OR Mass Screenings OR Screening, Mass OR Screenings, Mass OR Screenings AND Factor, Risk OR Factors, Risk OR Risk Factor OR Population at Risk OR Risk, Population at OR Populations at Risk OR Risk, Populations at NOT surgical repair. The period considered was June 1st 1990-June 1st 2018. Only papers written in English language will considered.

The methodology used is described in Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) Flow-Chart (Figure 1) [29].

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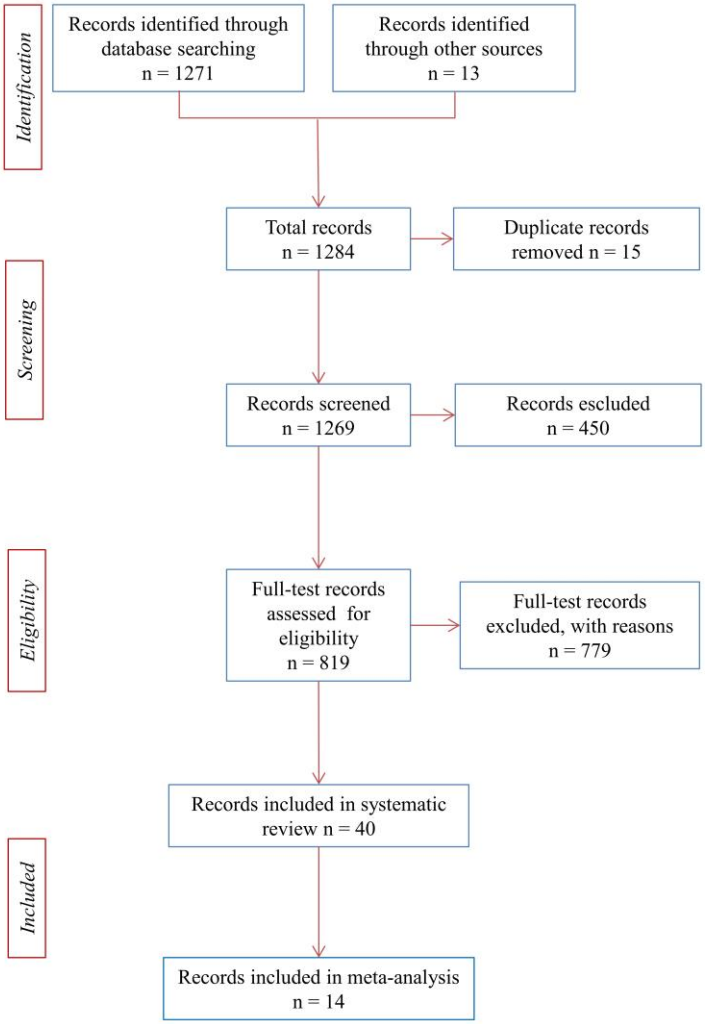
Figure 1. Flow chart of search strategy



2.2 Criteria for selecting studies

2.2.1 Eligibility criteria and study design

Risk factors as gender, smoking habits, hypertension, diabetes mellitus, family history of AAA and CAD are considered in our Meta-Analysis. All publication years and only English language papers are included in a specific table (Table S1). Observational studies were included in meta-analysis.

2.2.2 Participants

Males and females are considered together. The age of the population target included in our Meta-Analysis vary according to each study. Therefore, a unique range cannot be defined.

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2.2.3 Outcome

Abdominal Aortic Aneurysm is a pathology diagnosed when abdominal aorta has a diameter of 3 cm or more. We included studies that evaluated the potential risk factors associated to AAA and described above in eligibility criteria and study design section.

2.2.4 Quality assessment

The papers were selected by two independent reviewers (V.F.P and L.R.); a methodologist (E.A.) resolved any disagreements.

2.3 Statistical analysis

Meta-Analysis were performed when there were at least four studies. Chronic Obstructive Pulmonary Disease (COPD) studies were not included in Meta-Analysis because they were less than four. Odds ratios (ORs) with 95% CI and p-value was used as a measure of effect size. A random effects model was applied as a conservative approach to account for different sources of variation among studies. Heterogeneity was assessed using Q statistics and I^2. Publication bias analysis was estimated using Egger's linear regression test [30], Begg's [31], Mazumdar's rank correlation test [31]. Finally, trim and fill procedure was used to check publication.

Prometa 3 was used all statistical analysis.

3. Results

3.1 Systematic review of the literature and meta-analysis

Records identified through database searching were 1271, in addition, records identified through other sources were 13. 470 records were excluded. The other 813 were analyzed. We excluded 82 records because they were case reports/case series, 12 were comments, 10 were editorials, 9 clinical guidelines, 80 were systematic reviews, 13 were meta-analysis, 573 were about other topics. 40 papers were considered for systematic review (Figure 1) [4,9-13,15-18,32-61].

The selected studies for systematic review are summarized in table 1. Author, year of publication, city or region, age-group, level of participation (%) or screened people (n) and AAA detection rate

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(%) were reported. Studies on AAA, according to the screening programme start, are reported in table 2.

Table 1. Characteristics of the studies included in the Systematic Review

Country[a] Reference, year	**Region**	**Age-group**	**Level of participation (%) or screened people**	**AAA detection rate (%)**
Population-Based				
Italy				
Gianfagna, 2018	Varese, Lombardia	M 50-75 F 60-75	M 65.3 F 61.3 T 63.8	M 1.3 F 0.3 T 0.9
Palombo, 2010	Genoa, Liguria	M, F 65-92	M 61.6 F 48.8 T 54.3	M 10.8 F 1.1 T 6.2
Simoni, 1995	Genoa, Liguria	M, F 65-75	M 58.5	M 8.8 F 0.6 T 4.4
Belgium				
Makrygiannis, 2016	Chaudfontaine, Liege, Wallonia	M 65-85 F 74-85	M 39.5 F 31.7 T 36.0	M 4.8 F 1.3 T 3.6
Vazquez, 1998	Liege, Wallonia	M 75-65	T 41.0	T 4.5
China				
Kun Li, 2018	Zhengzhou City, Middle China	M, F < 55 M, F 55-75 M,F >75	M 2,555 F 2,847 T 5,402	M 0.55 F 0.14 T 0.33
Denmark				
Dahl, 2018	Viborg, Central Denmark	F (Born 1936, 1941, 1946, 1951)	F 107,491	NR
Kvist, 2016	Northen part of Funen and City of Odense	T 65-74	M 64.9 F 63.0	M 12.4 F 1.1
Poland				
Dereńzíski, 2017	Gniewkowo, Central Poland	M>60 F>65	M 61.0	M 6.3 F 0.82 T 4.12
Janwien, 2014	Kuyavia-Pomeranian	M >60	M 1,556	M 6.0
Spain				
Sisó-Almirall, 2017	Barcelona, Catalonia	M 60-65	M 74.9	M 1.5
Salcedo Jódar, 2014	Ciudad Real, Castilla La Mancia	M 65-80	M 93.5	M 3.3
Salvador-González, 2016	Barcelona, Catalonia	M 65-74	M 66.9	M 2.3
Barba, 2013	Asturias	M (born in 1943)	M 70.8	M 4.7
Sweden				

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Johansson, 2018	Uppsala, Dalarna, Södermanland, Västra Götaland	M > 65	M 25,265	NR
Stackelberg, 2017	Vastmanland, Orebro	M 65-75	M 49.0	M 1.2
Wanhainen, 2016	All Nation except Halland Country	M 65-75	M 84.0	M 1.5
Hager, 2013	Östergötland	M >70	M 84.0	M 3.0
Svensjö, 2013	Uppsala and Darlana	F >70	M 74.2	F 0.4
Svensjö, 2011	Uppsala, Darlana, Sörmland, Gävleborg	M >65	M 85.0	M 1.7
United Kingdom				
Oliver-Williams, 2018	Gloucestershire, England	M 65	M 80.7	M 1.9
Kanagasabay, 1996	London, England	M, F 65-80	NR	M 7.6 F 1.3
Smith, 1993	Birmingham, England	M 65-75	M 76.3	T 8.4
Grismhaw, 1994	Birmingham, England	M, F 60-75	M 76.1	M 7.2
Norway				
Singh, 2001	Tromsø	M,F 25-84	25-44 62.0 45-54 81.0 55-64 83.0 65-74 79.0 75-84 58.0	M 9.7 F 2.2 T 4.7
Japan				
Takei, 1995*	Ueno, Central Japan	M, F 60-79	M 69.0	M 3.9 F 5.0 T 4.6
United States				
Alcorn, 1996	Pittsburgh cohort	M, F >65	T 656	T 2.9
Not Population-Based				
Australia				
Nicholls, 1992	Perth	M, F 60-80	T 1,225	M 4.7 F 0.35 T 2.64
Italy				
Corrado, 2016	Como, Lombardia	M, F 60-85	T 1,555	M 2.5 F 0.4 T 1.4
France				
Laroche, 2015	All Nation *(metropolitan and overseas departement "Operation Vésale"*	M 50-75 F 60-75	T 6,691	M 3.1 F 0.3 T 1.7
Greece				
Makrygiannis, 2018	Larissa, Central Greece	NR	NR	NR
Spain				
Belloch García, 2018	La Ribera, Spain	T > 50	T 241	T 2.9
Ortega-Martín, 2007	León	M 65-75	M 66.0	M 4.2
Norway				
Krohn, 1992*	Oslo	M, F 60-89	T 500**	NR

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Switzerland				
Engelberger, 2017	Lugano, Ticino	M 65-80	M 68.2	M 4.1
Saudi Arabia				
Al-Zahrani, 1996	Jeddah, Western Saudi Arabia	M, F 60-80	NR	T 2.0
Turkey				
Kilic, 2018	Turkey	T ≥ 65	T 1,948	T 3.7
United States				
Chun, 2016	North Carolina *(Veterans Affair Health care system*)	M 65-75	T 9,571	T 7.1
Kent, 2010	All Nation	M, F <85	T 3,056,455	M 1.7 F 0.2 T 0.7
Lederle, 2000	15 Department of veterans affair	M, F 50-79	NR	T 1.4

NR: Not Reported; E: Echography; **M: Male; F: Female; T: Total Sample Size.**

[a]All countries have high income level.

***Aorta diameter >2.5cm.**

****** The study reports only the results of the first 500 patients

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Table 2. Characteristics of the studies included in the Systematic Review: programme start

Country[a] **Reference, year**	**Program start**																												
	1900											2000																	
	89	90	91	92	93	94	95	96	97	98	99	00	01	02	03	04	05	06	07	08	09	10	11	12	13	14	15	16	17
Population-Based (PB)																													
Italy																													
Gianfagna, 2018																													
Palombo, 2010																													
Simoni, 1995																													
Belgium																													
Makrygiannis, 2016																													
Vazquez, 1998																													
China																													
Li, 2018																													
Denmark																													
Dahl, 2018																													
Kvist, 2016																													
Japan																													
Takei, 1995																													
Norway																													
Singh, 2001																													
Poland																													
Derezinski, 2017																													
Janwien, 2014																													
Spain																													
Sisó-Almirall, 2017																													
Salcedo Jodar, 2014																													
Salvador-Gonzales, 2016																													
Barba, 2013																													

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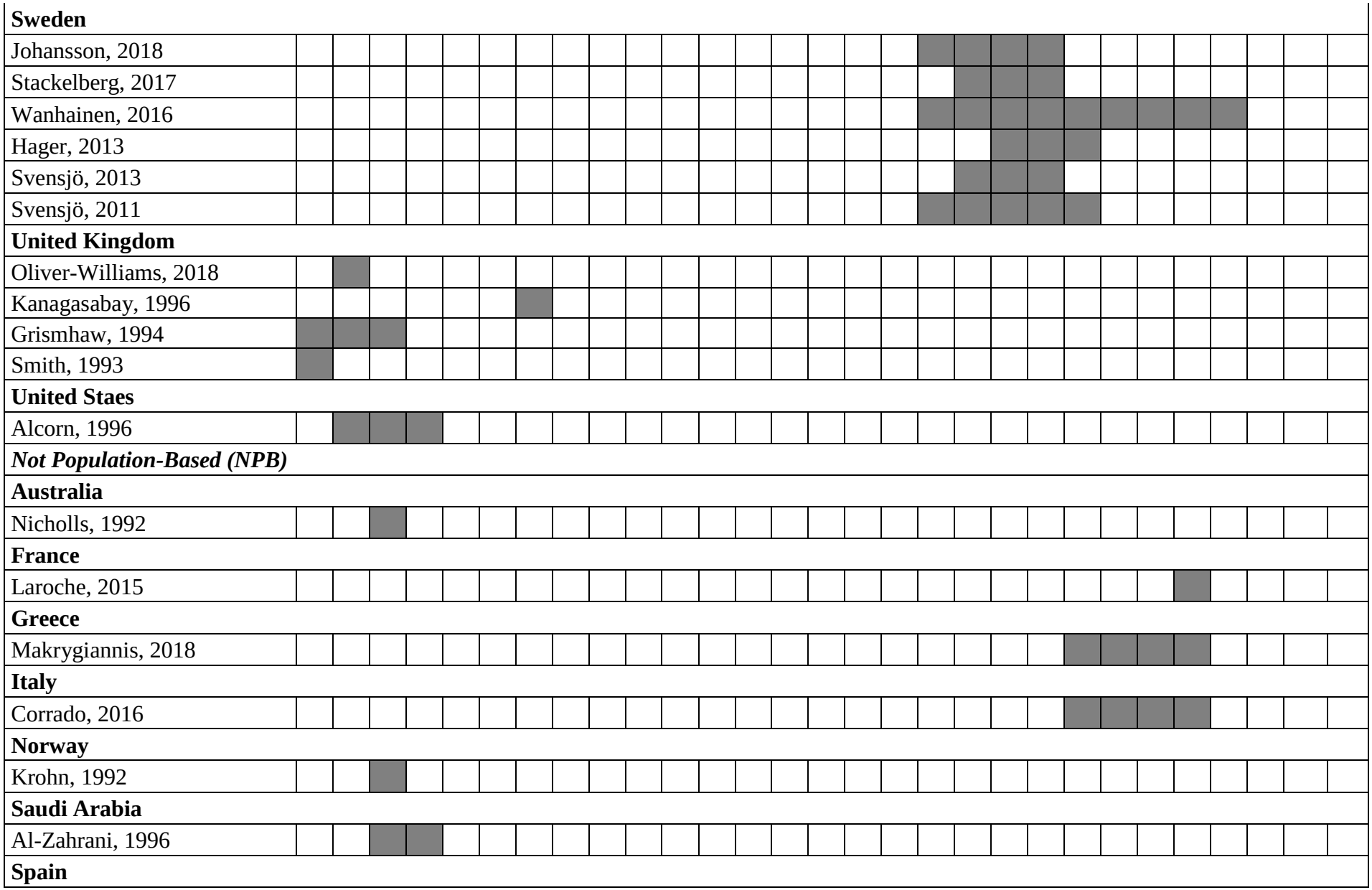

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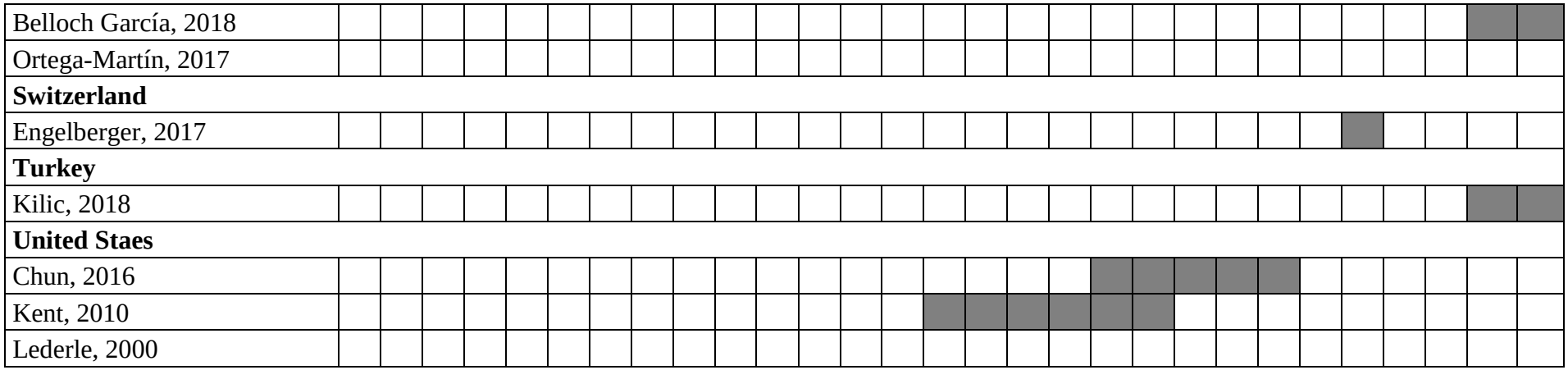

[a]**All countries have high income level.**

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14 papers were considered in Meta-Analysis: 13 prevalence studies and 1 case-control hospital-based study [4,11-13,15,18,34,35,44,47,50,52,54,56].

The diagnostic test used for screening was ultrasound, except for Denmark where TC scan was used [32].

3.2 Meta-Analysis

3.2.1 Gender

Thirteen studies, between those selected, report information on male gender [4,11-13,15,18,34,35, 44,47,50,54,56]. The overall effect size was OR=5.93 (4.26-8.25), p<0.0001, with Q=132.89, I^2=90.97, p<0.0001 (Figure 2A and Table 3). Sensitivity analysis shows an equal trend among studies (Figure 2B). Cumulative analysis indicated that all the studies agreed except for Nicholl's [50] and Simoni's [35] (Figure 2C). Although publication bias analysis, by the trim and fill method trimmed two studies (Figure 2D), the results of Egger's linear regression test and Begg's and Mazumdar's rank correlation tests were not statistically significant (p=0.339 and p=0.542, respectively) (Table 3).

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Table 3. Meta-analysis with studies included males and females

Risk factors	Pooled analysis				Heterogeneity			Publication bias		NNT pooled
	k=n. of studies	ES (OR)	95% CI	p-value	Q	p-value	I^2	Egger p-value	Begg and Mazumdar p-value	
Gender	13	5.93	4.26-8.25	<0.0001	132.89	<0.0001	90.97	0.339	0.542	64
Smoking habits	6	2.97	1.20-7.30	0.018	390.71	<0.0001	98.72	0.229	0.573	85
Hypertension	8	1.55	1.02-2.34	0.039	112.34	<0.0001	93.77	0.127	0.322	184
Diabetes mellitus	6	1.18	0.99-1.41	0.067	8.45	0.133	40.85	0.008	0.851	298
Coronary Artery Disease (CAD)	5	2.29	1.75-3.01	<0.0001	5.98	0.200	33.15	0.032	0.624	25
Family history of AAA	4	9.64	1.72-53.98	0.01	30.77	<0.0001	90.25	0.467	0.174	59

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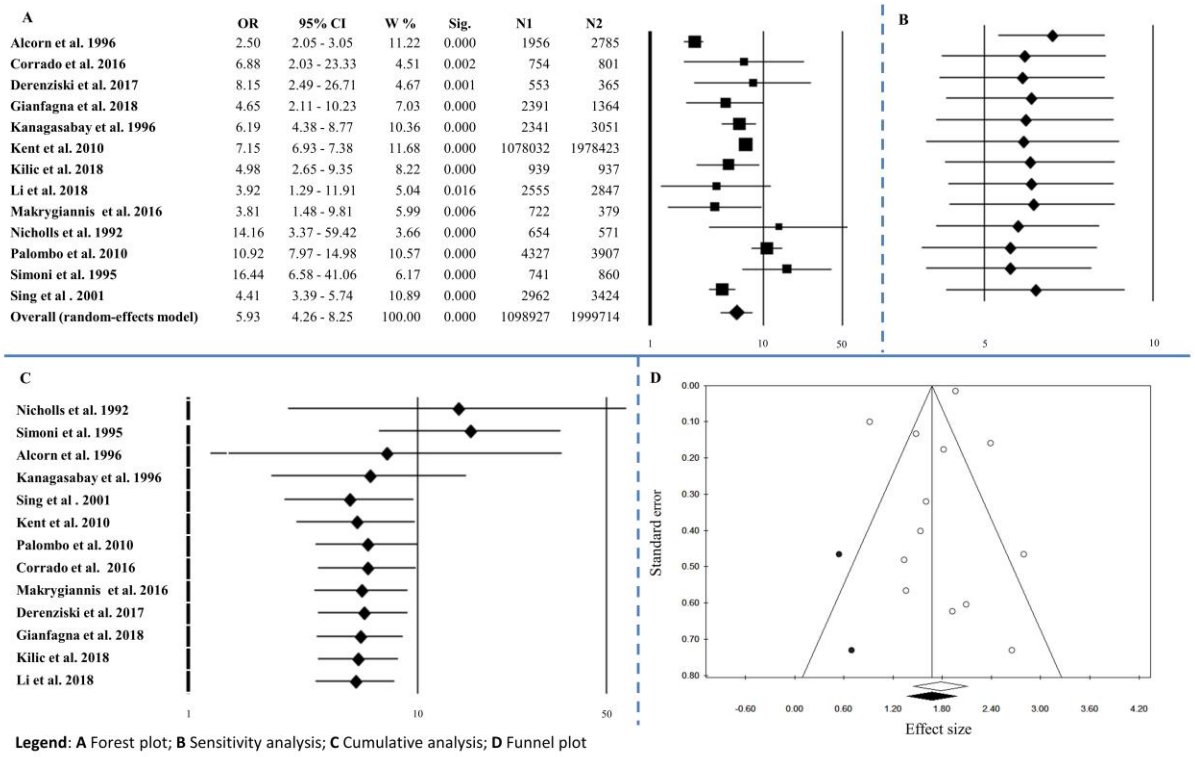
Figure 2. Gender



Legend: **A** Forest plot; **B** Sensitivity analysis; **C** Cumulative analysis; **D** Funnel plot

3.2.2 Smoking habits

Six papers report information about smoking habits [12,18,34,35,54,56]. The overall effect size was OR=2.97 (1.20-7.30), p=0.018, with Q=390.71, I^2=98.72, p<0.0001 (Figure 3A and Table 3). Sensitivity analysis shows an unequal trend among studies (Figure 3B). Cumulative analysis indicated that all the studies agreed except for Simoni's [35] (Figure 3C). Publication bias analysis by the trim and fill method did not involve the exclusion of any paper (0 trimmed studies) (Figure 3D) and the absence of publication bias is underlined by the results of Egger's linear regression test and Begg's and Mazumdar's rank correlation tests that were not statistically significant (p=0.229 and p=0.573, respectively) (Table 3).

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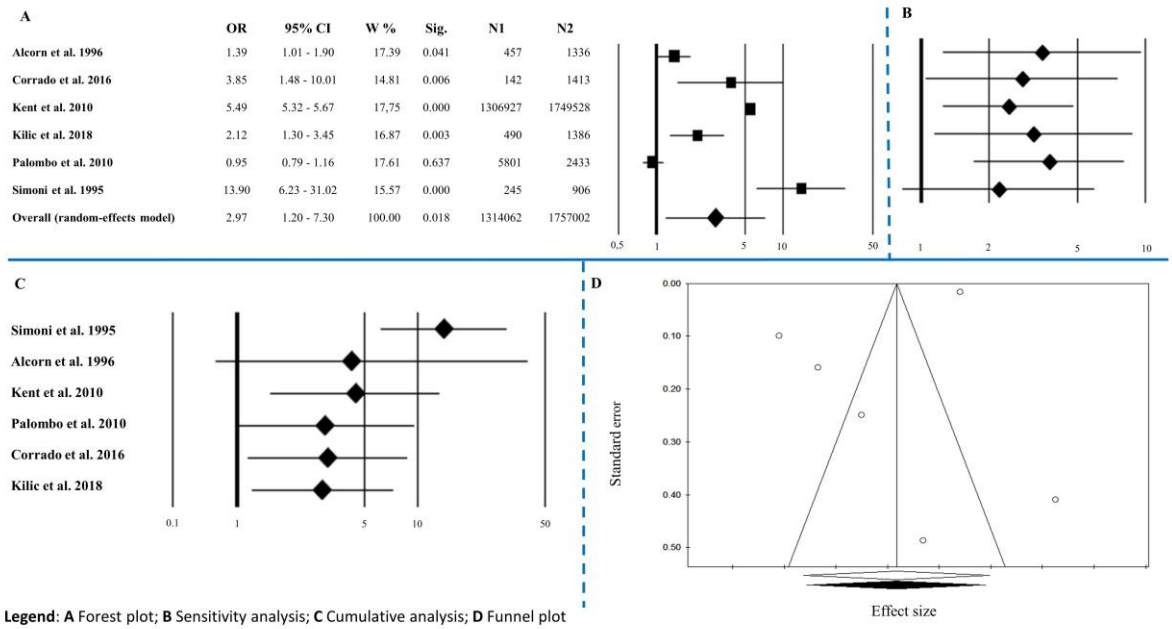
Figure 3. Smoker



Legend: **A** Forest plot; **B** Sensitivity analysis; **C** Cumulative analysis; **D** Funnel plot

3.2.3 Hypertension

Eight papers contain frequencies on hypertension [12,15,18,34,35,52,54, 56]. The overall effect size was OR=1.55 (1.02-2.34), p=0.039, with Q=112.34, I^2=93.77, p<0.0001 (Figure 4A and Table 3). Sensitivity analysis shows an equal trend among studies except for Kent's [54] (Figure 4B). Cumulative analysis indicated that all the studies agreed except for Alcorn's [56] (Figure 4C). Publication bias analysis by the trim and fill method did not exclude papers (0 trimmed studies) (Figure 4D). The absence of publication bias is highlighted from results of Egger's linear regression test and Begg's and Mazumdar's rank correlation tests that were not statistically significant (p=0.127 and p=0.322, respectively) (Table 3).

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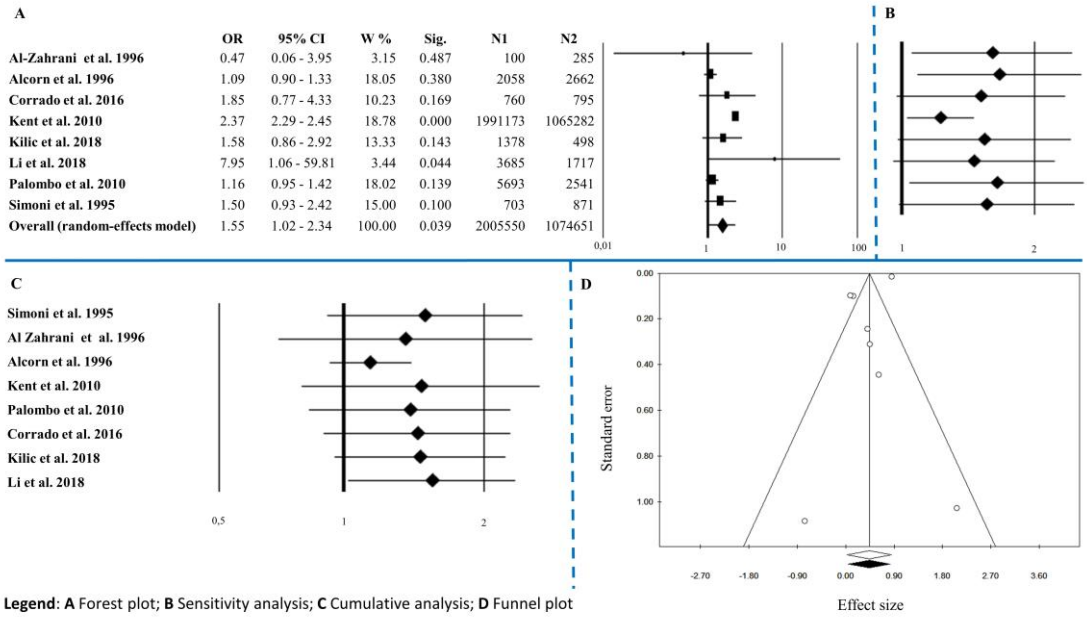
Figure 4. Hypertension



Legend: **A** Forest plot; **B** Sensitivity analysis; **C** Cumulative analysis; **D** Funnel plot

3.2.4 Diabetes Mellitus

Six papers report information on diabetes mellitus [12,15,18,34,35,54]. The overall effect size was OR=1.18 (0.99-1.41), p=0.067, with Q=8.45, I^2=40.85, p=0.133 (Figure 5A and Table 3). Sensitivity analysis shows an unequal trend among studies (Figure 5B). Cumulative analysis indicated that all the studies agreed except for Simoni's [35] (Figure 5C). Publication bias analysis by the trim and fill method did not involve the exclusion of any paper (0 trimmed studies) (Figure 5D). According to Egger's linear regression test (p=0.008) there is bias, but Begg's and Mazumdar's rank correlation tests (p=0.851) not show presence of publication bias (Table 3).

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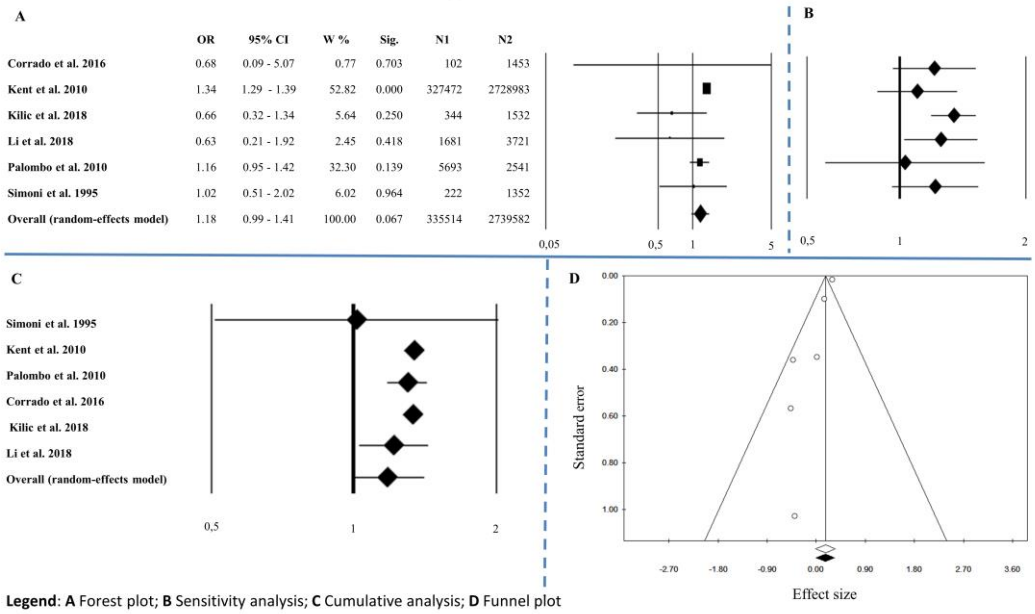
Figure 5. Diabetes



Legend: **A** Forest plot; **B** Sensitivity analysis; **C** Cumulative analysis; **D** Funnel plot

3.2.5 Coronary Artery Disease

Information on Coronary Artery Disease were reported in 5 studies [12,15,18,35,56]. The overall effect size was OR=2.29 (1.75-3.01), p<0.0001, with Q=5.98, I^2=33.15, p=0.200 (Figure 6A and Table 3). Sensitivity analysis shows an equal trend among studies except for Alcorn's and Kilic's [56,12] (Figure 6B). Cumulative analysis indicated that all the studies agreed except for Simoni's [35] (Figure 6C). Publication bias analysis, by the trim and fill method, trimmed two studies (Figure 6D). The results of Egger's linear regression test are statistically significant (p=0.032) but, Begg's and Mazumdar's rank correlation tests was not statistically significant (p=0.624) (Table 3).

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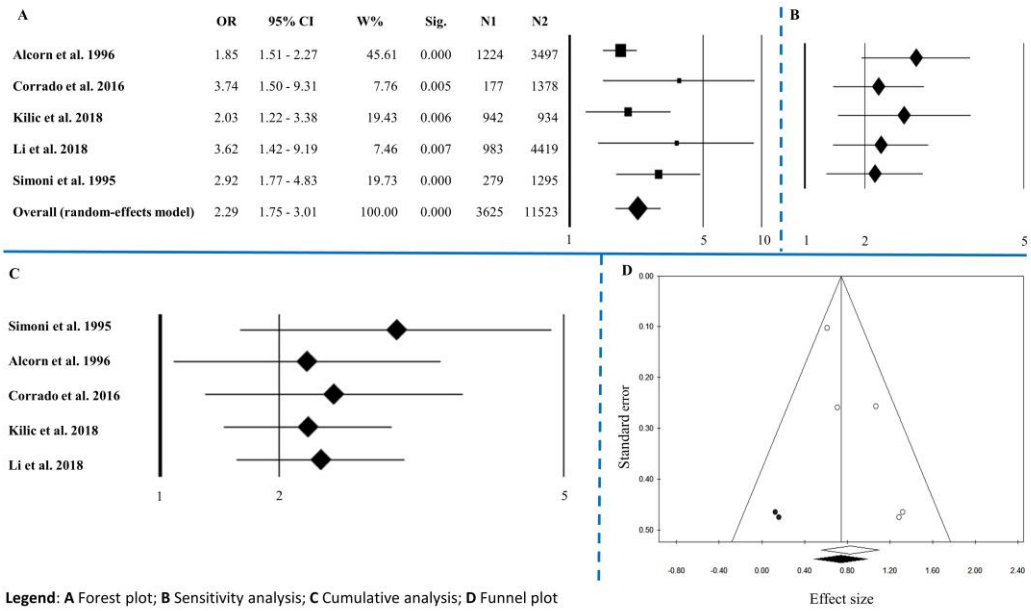
Figure 6. Coronary Artery Disease (CAD)



Legend: **A** Forest plot; **B** Sensitivity analysis; **C** Cumulative analysis; **D** Funnel plot

3.2.6 Family History of Abdominal Aortic Aneurysm

Four studies report information on family history of AAA [12,15,18,54]. The overall effect size was OR=9.64 (1.72-53.98), p=0.01, with Q=30.77, I^2=90.25, p<0.0001 (Figure 7A and Table 3). Sensitivity analysis shows an equal trend between studies except for Li's [15] (Figure 7B). Cumulative analysis indicated that all the studies agreed except for Li's [15] (Figure 7C). Publication bias analysis by the trim and fill method did not exclude papers (0 trimmed studies) (Figure 7D). The absence of publication bias is highlighted from Egger's linear regression test and Begg's and Mazumdar's rank correlation tests that were not statistically significant (p=0.467 and p=0.174, respectively) (Table 3).

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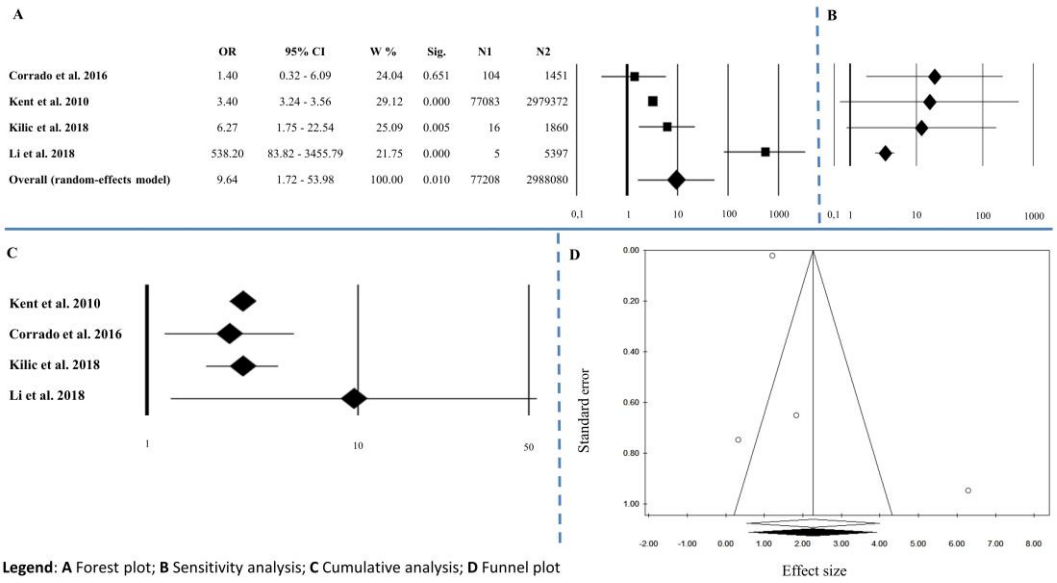
Figure 7. Family History of AAA



Legend: **A** Forest plot; **B** Sensitivity analysis; **C** Cumulative analysis; **D** Funnel plot

4. Discussion

In this study we show the results of a systematic review and a meta-analysis of observational studies.

4.1 Systematic review

Italian, European, Asian and Oceania screening studies shown similar results [4,9-13,15-18,32-61]. Indeed, in all studies gender and smoking habits are highly associated with AAA [4,9-13,15-18,32-61]. Other studies have shown an association among AAA and the following diseases: hypertension, peripheral vascular disease, ischemic heart disease, previous myocardial infarction, chronic obstructive respiratory disease, symptoms of occlusive arterial and coronary artery [43,45,52]. Some Italian studies included in our systematic review have showed AAA prevalence between 1.4% and 6.2% [13,18,34,35]. Other studies showed a range of prevalence AAA from 0.3% to

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12.4% or between 0.5% and 9.3% [4,9-11,13,17,18,32,50-58]. These differences could be due to the different age ranges of the enrolled patients in the studies.

Regarding to risk factors (gender and smoking) for the development of AAA, smoking is the main risk factor correlated to AAA [4,9-13,15-18,32,61-68]. In countries where the consumption of cigarettes has been reduced it showed a lower AAA prevalence [13,17,18,41,54,57,64].

According to Laroche *et al.* [17] the reduction AAA prevalence is parallel to the reduction in tobacco consumption, but anti-smoking information campaigns are insufficient.

Smoking is closely correlated with the diameter of the aorta; it, indeed, is bigger in smokers compared to non-smokers and also according to Al-Zahrani *et al.* [38,52] AAA was eight times more in smokers than non-smokers. Therefore, large aneurysm is considered high-risk for rupture and its reduction is essential for reducing aneurysm-related death [53].

Current smoking is associated with occurrence of AAA at younger ages [60]. Moreover, risk of AAA is higher for current smokers than past smokers and it increases with duration of smoking [54].

In the Multicentre Aneurysm Screening Study (MASS) the benefit of quitting smoking has been shown and this benefit leads to decrease of aortic rupture [64].

As regards to the systematic review, the first important aspect that has emerged is that the organized screening is nationwide only in the UK and Sweden [57,39-43], while in other countries it is mainly local (regional or provincial), as in Italy. In particular, Italy is one of the countries with a substantial number of screening programmes, but most of these are organized mainly in the North (Genoa, Como, Varese) [13,18,34,35].

The second important consideration is only high-income level countries have activated AAA screening programmes as highlighted in cancer screening [69,70]. Therefore, this aspect should be considered in order to avoid social inequalities and greater flexibility for access to treatment and to

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prevention of AAA. Altobelli *et al*. [69-73] showed that in many European countries there are no primary prevention campaigns against the main risk factors related to non-communicable diseases and therefore in these nations there is scarce attention to prevention. Sildoff *et al.* [63]compared the mortality due to AAA in some countries where population-based screening is active, like UK, Sweden, Australia, compared to those where there is no population-based screening, like Austria, Hungary and Romania. In those countries where screening campaigns are active, the mortality rate is in constant decline. The introduction of AAA screening saves lives, prevents the rupture risk, coincides with a falling prevalence of the disease, reduces the incidence of aneurysm rupture, decreases the mortality [1,9,18,34,36,40,57,66,67].

Some studies that include females show that AAA prevalence is always higher compared to males [4,11,17,18,34,35,39,42,44,47,50,51,54,55]. It is important to underline that association between males and AAA could be attributed to a greater predisposition of males than to females to cardiovascular disease, known as “male disadvantage” [62].

According Forsdahl *et al.* [68] male gender, advancing age, low HDL cholesterol and smoking are risk factors associated with AAA and therefore they are factors to be investigated. Takei *et al.* [51] considered risk factors in population target, atherosclerosis, hypertension, obesity, abnormal serum lipid levels and history of smoking. Kim *et al.* [66] demonstrated that the group invited to be screened had approximately half the risk. The risk reduction was even greater in patients who attended the screening.

4.2 Meta-analysis

A previous meta-analysis on studies about the role of risk factors such as gender, smoking habits, hypertension, diabetes mellitus, myocardial infarction and peripheral vascular disease in development of AAA was conducted in 2004 [74]. We performed a new meta-analysis considering the same risk factors and adding CAD and family history of AAA with more update studies. Respect to Cornuz *et al.* [74], in our meta-analysis we added the following: the funnel plot to examine the ef-

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fect sizes estimated from individual studies against a measure of their precision; sensitivity analysis to check the stability of study findings and estimate how the overall effect size would be modified by removal of one study; cumulative analysis to evaluate the trend between studies in relation to publication year. We performed a meta-analysis using the random effect according to Der Simonian and Laird for calculate the overall effect-size [75].

The data of our meta-analysis showed presence of heterogeneity for gender, smoking habits, hypertension and family history of AAA. The absence of homogeneity could be due to different sample size among studies included in our meta-analysis. Egger linear regression test and mostly Begg's and Mazumdar's rank correlation tests show absence of publication bias. The homogeneity among studies included was supported by Cochrane's and Higgins's tests. For such risk factors there is no publication bias. Our results are similar to those reported in previous meta-analysis [74]. The results of our Meta-Analysis, relatively to male gender and smoking habits, are in line with those of previous researches [4,11-13,15,18,34,35,44,47,50,54,56]. In our analysis males smokers have major risk of AAA. In agreement to some authors [11-13,15,18,34,35,47,50,54,56], our results confirm male gender and smoking habits as risk factors for AAA (OR=5.93 and 2.97, respectively). Also hypertension, CAD and family history of AAA are risk factors for AAA, but, it is important to underline family history should be considered with caution because the confidence interval is wide enough, therefore effect size pooled could be influenced. As regard to the role of hypertension as potential risk factor for AAA same authors [8,36,43,59,68] are in disagreement. Alcorn *et al.* [56] suggest that individuals with hypertension are more likely to be evaluated clinically for the identification of AAA and this leads to a greater number of AAA diagnoses. In our meta-analysis hypertension presents an effect size of 1.55 and p=0.039. In agreement with previous studies diabetes mellitus is not statistically significant [4,11,12,15,16,18]. De Rango and collegues [76] suppose that high blood glucose forms advanced glycation-end products due to the non-enzymatic oxidation of vascular matrix protein, which over times, becomes less incline to dilatation and leads to a different sphygmic

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wave propagation. Abdominal Aortic Aneurysm is correlated to risk factors associated to an incorrect lifestyle, such as smoking, a wrong diet, absence of regular exercise and gender. In fact, males respect to females have higher risk of cardiovascular disease. Kent *et al.* [54] found that consumption of fruit, vegetables, nuts and regular exercise reduces the risk of AAA. The importance of a correct diet is highlighted also in other diseases correlated to nutrition [79]. Male gender, diabetes mellitus and family history of AAA are "non-modifiable" factors; while smoking habits, hypertension, CAD can be avoided and, therefore, are "modifiable". In fact, it is important to underline that quitting smoking, following a correct diet and practising sports could reduce risk of AAA and consequently the mortality due to rupture of the aorta.

5. Conclusion

Our systematic review showed that all countries where AAA screening was set up, were at high income level and the majority belong to Western Europe (United Kingdom, Sweden, Italy, Poland, Spain, Belgium). The purpose of this meta-analysis was to provide a contribution to future research on the role of common risk factors, such as gender, smoking habits, hypertension, diabetes mellitus, CAD, family history of AAA and to address AAA screening to target population at high risk.

The best method of AAA screening is ultrasonography, which is cheap, accurate, safe, rapid, noninvasive, good reproducible and cost-effective.

In conclusion, these findings, together with continuous lengthening of average life, foreshadow a real "vascular emergency". Prevention is a fundamental aspect of modern medicine that should be promoted and incentivized in a healthcare system that takes care not only of the illness itself but of the person, even when one is apparently in good health.

Supplementary Materials: Table S1: Included studies in Meta-analysis

Author Contributions

Emma Altobelli contributed to this paper with conception and design of the study, literature review, developed statistical analysis, drafting and critical revision and editing. Leonardo Rapacchietta participated to literature search, participated to build database. Roberto Fagnano and Valerio F. Profeta participated to acquire the data. All authors have approved the final version of manuscript.

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Conflict Of Interest

The authors declare that they have no conflict of interest.

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