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Erectile dysfunction and cardiovascular risk: a review of current findings

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Abstract

Introduction: A large body of evidence has clearly documented that erectile dysfunction (ED) represents not only a complication of cardiovascular (CV) diseases (CVD) but often an early sign of forthcoming CVD.

Areas covered: All the available data from meta-analyses evaluating the association between ED and CV risk were collected and discussed. Similarly, all available meta-analyses investigating the significance of ED as a possible early marker for major adverse cardiovascular events (MACE) were analyzed. In addition, data originally obtained in a Florence cohort, dealing with a large series of patients seeking medical care for sexual dysfunction, will be also reported.

Expert opinion: Available evidence indicates that ED represents a risk factor of CV mortality and morbidity. Not only conventional CV risk factors but also unconventional ones, derived from a perturbation of the relational and intrapsychic domains of ED, might play a possible role in CV risk stratification of ED subjects. Finally, penile doppler ultrasound can give important information on CV risk, especially in younger and low risk subjects. The presence of ED should become an opportunity – for the patient and for the physician – to screen for the presence of comorbidities improving not only sexual health but, more importantly, men's overall health.

Key words: erectile dysfunction, cardiovascular risk, MACE, penile doppler ultrasound, hypoactive sexual desire

Article highlights
• Erectile dysfunction should be considered an early marker of forthcoming cardiovascular [CV] diseases.
• ED is associated with an increased risk of CV mortality and morbidity. In addition, an association with an increased risk of all-cause mortality has also been reported.
• In ED patients, besides traditional CV risk factors, also unconventional determinants, derived from psychological [depressive symptoms] as well as relational [perception of reduced partner's love; reduced frequency of sexual intercourse; fatherhood] fitness, should be considered in the stratification of CV risk.
• Penile Doppler ultrasound can give important information on CV risk, especially in younger and low risk ED subjects.

1. Introduction

Cardiovascular (CV) diseases (CVD) are still the leading cause of mortality and morbidity in the western countries and a major barrier to sustainable human development [1]. In 2015, 422.7 million prevalent cases of CVD and 17.92 million of CVD deaths were reported worldwide [1]. Ischemic heart disease (IHD) represents the leading cause of all health loss globally [1]. Concerning CVD, a gender difference has been recognized for a long time, with males at a higher risk when compared to females. In 2011, the United Nations formally recognized non-communicable diseases, including CVD, as a major concern for global health and planned a series of actions to reduce the effect of these diseases in all regions [2]. Between 1990 and 2015, substantial declines in age-standardized CVD death rate have been reported in all high-income and in some middle-income countries [1,3]. Hence, identification of subjects at high CV risk represents a crucial step for an effective primary prevention program. For this specific purpose, several population-specific CV risk engines - essentially based upon multivariate risk prediction equations, derived from large prospective cohort studies -have been developed [4]. Although these instruments have demonstrated their utility in clinical practice, they also present some limitations related to a reduced reliability when applied to populations which present different characteristics to those in which they were developed [4]. Accordingly, the Framingham risk engine, the most commonly used risk prediction equation, developed in the United States, demonstrated to overestimate CV risk when used in European populations [5]. In addition, the concept of "residual risk" represents another confounding factor in CV risk stratification. Data from the general population have documented that the majority of CV events occur in subjects classified, by using conventional parameters, as at "lower-risk" [6-10]. Hence, identifying new parameters contributing to this "residual CV risk" represents a challenge for the near future.

Erectile dysfunction [ED] represents a multidimensional symptom which affects globally > 100 million people with a projection in 2025 of more than 300 million affected subjects. ED and CVD are frequent co-morbid conditions sharing the same CV risk factors, including smoking [12-13], obesity [14-17], diabetes [18-20], dyslipidemia [18,21] and arterial hypertension [22-23]. A large body of evidence has already documented that ED represents not only a complication of CVD but often an early sign of forthcoming CVD [11, 24-28]. Hence, ED patients should be considered paradoxically lucky since the appearance of the symptoms provides a valuable time window [2-5 years] for earlier modification of associated risk factors and potentially an improvement in outcomes [29]. Interestingly, not only traditional CV risk factors but also unconventional related factors including relational and intrapsychic determinants have been described as playing a possible role in the CV risk stratification of ED subjects [7-10]. The recognition and the early detection of these conditions can lead to decreasing the "residual CV risk" thus improving CV risk prevention.

The aim of the present review is to provide an overview of the available evidence related to the association between ED and forthcoming CV events. Both conventional and unconventional CV risk factors related to ED-associated risk will be extensively analyzed.

2. Research methods

A comprehensive Medline, Embase and Cochrane search was performed including the following words: ("erectile dysfunction"[MeSH Terms] OR ("erectile"[All Fields] AND "dysfunction"[All Fields]) OR "erectile dysfunction"(All Fields]) AND ("cardiovascular system"[MeSH Terms] OR ("cardiovascular"[All Fields] AND "system"[All Fields]) OR "cardiovascular system"[All Fields] OR "cardiovascular"[All Fields]) AND ("risk"[MeSH Terms] OR "risk"[All Fields]). Publications from January 1, 1969 up to November 31st, 2019 were included. When available, meta-analytic data were preferred. In addition, data originally obtained in our population dealing with a large series of patients seeking medical care for sexual dysfunction will also be reported.

3. Association between ED and CV risk factors

Nine meta-analyses, published so far, have investigated the relationship between conventional CV risk factors and ED risk (Tables 1 and 2). In particular, four studies [18,20,22,23] have evaluated the possible association between metabolic syndrome (MetS) or its specific determinants and ED (Table 1). In addition, five systematic meta-analyses [12-13, 15, 30-31] investigated the impact of modifiable CV risk factors, including smoking habit, alcohol consumption, cannabis use and the level of physical activity and the risk of ED (Table 2). The number of the studies included ranges from 4 to 89 and the number of subjects considered from 3,395 to 348,865 (Table 1-2). The relationship between ED and arterial hypertension or diabetes mellitus was investigated in three and two studies, respectively, whereas only one meta-analysis has evaluated the association between ED and the other MetS parameters or MetS itself (Table 1). Finally, the possible association between ED and smoking habit, alcohol consumption, cannabis use or physical activity was assessed in two studies respectively (Table 2). Past and current smoking behavior as well as cannabis use was associated with a higher risk of ED, whereas physical activity and moderate alcohol exerts a protective role (Figure 1, panel A). In addition, heavy alcohol consumption increased the risk of ED, although it did not reach statistical significance (Figure 1, panel A). Finally, as expected, associated morbidities including MetS, diabetes mellitus, arterial hypertension and elevated triglycerides were all associated with an increased risk of ED (Figure 1 Panel B). Reduced high density lipoprotein (HDL) cholesterol was associated with a higher risk of ED; however, this association did not reach statistical significance (Figure 1, Panel 2).

4. ED as a marker of forthcoming CVD

Up to now, six systematic meta-analyses evaluating the relationship between ED and CV mortality and morbidity have been published (Table 3). The number of the studies included ranges from 7 to 25 and the number of subjects considered from 36,744 to 111,440 (Table 3). Among the available studies, four were related to a mixed population [11, 24-25, 27], whereas one analysis was limited to diabetic subjects [26] or to the general population [28], respectively. The relationship between ED and overall CVD was analyzed in five studies whereas on only two and three meta-analyses, respectively, investigated the risk related to AMI and CHD (Table 3). The relationship between ED and stroke was analyzed in three studies. Finally, all-causes and CV mortality was investigated in five and two studies, respectively (Table 3). Independently of the meta-analysis considered, ED was associated with an increased risk of CV morbidity with a trend toward a higher risk when a diabetic population was investigated (Figure 2, Panel A). In addition, a higher risk of all-cause mortality was also observed, whereas only a trend toward an increased CV mortality was reported (Figure 2, panel B). Interestingly, the only meta-analysis which applied meta-regression analysis to investigate the contribution of several parameters to ED-related CV mortality and morbidities [27] showed that the risk was higher in younger and those with a lower number of associated morbidities.

5. Unconventional risk factors and ED-related CV risk

We previously developed and validated a 13-item structured interview on ED (SIEDY) dealing with the assessment of the components simultaneously underlying ED [32]. This instrument has demonstrated its utility in various cross-sectional studies [21, 33-35].

By extending longitudinal information on a consecutive series of 1,687 patients attending our unit for ED for the first time between 2000 and 2007, we collected the incidence of major adverse cardiovascular events (MACE) from the City of Florence Registry Office, which contains complete and updated records of all persons living within city boundaries. In this population, after up to eight-years of follow-up, we confirm that several well-known conventional CV risk factors, including smoking, arterial hypertension, obesity and MetS, were associated with a higher risk of MACE at follow up [36; Table 4]. Interestingly, however, in the same population we reported that other unexpected and non conventional CV concurred with an increase in the forthcoming risk of MACE at follow up. These factors included organic (reduced T levels< 8 nmoles/L [37] and reduced prolactin, PRL, levels <246 mu/L or 11.7 ng/ml [38]), psychological [depressive symptoms; 39] as well as relational [perception of reduced partner's love [36], reduced frequency of sexual intercourse [40] and fatherhood [10]] components.

These data suggest that physicians dealing with patients with sexual dysfunction should adequately investigate, and when possible treat, not only organic factors but also relational and psychological determinants.

6. Role of penile Doppler ultrasound in the stratification of ED-related CV risk

Lue et al. at the end of the 1980s introduced for first time penile color Doppler ultrasound (PCDU) for the evaluation of penile blood flow [41-42]. Studies performed in a limited number of subjects have shown that a cavernosal artery peak systolic velocity (PSV) <25 cm/s, detected in dynamic conditions after the injection of a vasodilating agent (dynamic PCDU) such as prostaglandin E1 (PGE1), can identify, with a sensitivity and specificity ≥95%, an impaired cavernosal blood flow at angiography [43-44]. However, these data were not confirmed by other authors and the role of PCDU in the management of ED patients is still conflicting. In fact, several limitations have been reported. In particular, PCDU is operator dependent, and an incorrect diagnosis can result as a consequence of anxiety and its related sympathetic stimulation [45] or due to the high prevalence of arterial anatomical variants [46]. Accordingly, available guidelines do not recommend its routine use in the screening of ED [47-50].

We originally demonstrated that PSV < 13 cm/sec, performed in flaccid conditions (before PGE1 stimulation), was able to identify silent coronary heart disease in a small number (n=20) of subjects with uncomplicated type 2 diabetes [51]. Interestingly, the same parameter predicted the incidence of MACE in the aforementioned population of 1,687 patients with ED [36]. In the latter population we also confirmed that dynamic PSV < 25 cm/sec was associated with a two-fold increased risk of forthcoming CVD [36]. Similar results were more recently reported by other authors [52]. In a further analysis, we documented that reduced flaccid penile acceleration (FPA< 1.17 m/s^2) represented the best parameter in predicting MACE incidence when compared to PSV evaluated either in flaccid or dynamic conditions [8]. This is not surprising since FPA is probably the best PCDU parameter reflecting vascular stiffness [8]. Interestingly, in the latter study, we also reported that the role of FPA in predicting MACE was confirmed when younger and not complicated patients were considered. This finding supports the idea that FPA could represent a new parameter capable of identifying “residual CV risk” in ED populations (see above).

7. Role of hypogonadism in stratification of ED-related CV risk

ED patients represent a population also enriched in hypogonadism, in fact, reduced testosterone (T) levels are frequently observed in subjects seeking medical care for sexual dysfunction [53-54]. T plays a major role in the control of sexual function, acting both centrally and peripherally [55]. Endothelial and smooth-muscle cells are the main targets for androgen effects in penile and CV systems. Both experimental and clinical evidence demonstrated a permissive role of T in supporting endothelial integrity and reducing atherosclerosis [56]. In particular, systemic inflammation has been considered a possible confounding bias in the evaluation of “residual CV risk”. Much evidence, mainly derived from animal models, has documented that low T could be involved in the regulation of the inflammation in several tissues [56]. Accordingly, a recent meta-analysis has documented that low T is associated with an increased CV mortality and morbidity risk [57]. Hence low T can further support, at least partially, the link between ED and CV risk.

8. ED in diabetes

The role of ED in predicting CVD in diabetic populations deserves particular attention. Diabetic population represents a group of people at an increased risk for CVD, which is often asymptomatic. The CV screening in asymptomatic diabetic patients remains yet to be elucidated. Accordingly, either myocardial scintigraphy or coronary CT scan have been demonstrated as useful in reducing the incidence of IHD in this population [58]. Hence, current recommendations suggest identifying patients at high CV risk based on their history and clinical findings to be tested for asymptomatic IHD [58]. Considering the data published so far, the presence of ED identifies a high risk population which deserves a better CV evaluation and periodical screening to rule out an asymptomatic IHD or the presence of other subclinical CVD. In addition, diabetic population is tightly associated with secondary hypogonadism which can further increase the CV risk [57]. Accordingly, the use of T in this population has been demonstrated to improve body composition and metabolic profile [59], although the number of the patients considered is too limited to draw final conclusions [60]. Interestingly, the use of phosphodiesterase type 5 inhibitors [PDE5i], the widespread recognized first line therapy in the management of ED patients, has demonstrated to reduce CV risk in diabetic patients [61]. Similar results have been reported also the general population [62]. The analysis of the specific mechanisms supporting this effect is beyond the aim to the present manuscript and revised elsewhere [62].

9. Conclusions

For a long time, ED has been considered a direct complication of CVD since the two conditions often overlap in risk factor prevalence and manifestations. Available evidence from longitudinal studies suggests that ED represents an early marker of CVD risk, independently from the type of population analyzed. Accordingly, similar rates have been described in studies involving the general population, diabetic subjects or several other cohorts, including mixed populations. Several hypotheses have been drawn to support the latter links. The artery-size hypothesis [63] proposes that the time window between the manifestation of ED and CVD might be related to the difference in size among smaller vessels [1-2 mm penile arteries] and larger ones [3-4 mm, coronary arteries or 5-7 mm carotid arteries] with regard to the ability to tolerate the invasion of the lumen by atherosclerotic plaque. Another hypothesis includes the impairment of the arterial stiffness of the large vessels. As a consequence, pulse pressure [PP, difference between systolic and diastolic blood pressure] increases, forcing pressure waves of cardiac pulsation farther into the smaller arteries than is normally the case. This repetitive mechanism accelerates penile arteries aging and endothelial dysfunction, thus favoring the development of ED [56]. Accordingly, we previously reported that higher PP is associated with arteriogenic ED and higher risk of MACE [64].

Interestingly, available data have documented that ED is not associated only with an increased CV risk but also with an increased risk for all-cause mortality. The latter point deserves further explanations. When the

impact of known CVD on ED-related mortality risk was assessed, ED resulted as being a stronger predictor of all-cause mortality in patients with known CVD when compared to those without CVD [27]. The latter suggests that common pathogenetic mechanisms such as aging, inflammation and oxidative stress might explain, at least partially, this association. In addition, ED is closely associated with obesity, diabetes mellitus and dyslipidemia, all of which might increase the risk of mortality [59].

Gender difference in CV mortality and morbidity still represents a challenge for preventive care programs. It has been reported that men usually look for help with specific, acute problems rather than for more general, preventive health concerns [65]. This behavior can, in turn, results in a delay and worsening of health problems increasing the likelihood of hospital admissionand death. ED represents a condition which can negatively affect general well-being and quality of life of the affected subjects. Hence, ED subjects should be considered 'lucky', since this symptom can favor getting a medical consultation, allowing for the identification of all underlying CV risk factors. Physicians dealing with ED patients should stress the importance of unmasking metabolic and CV derangements, promoting a virtual journey based on life-interventions and pharmacological optimization of the associated morbidities. Encouraging changes in lifestyle, thought, diet and/or physical exercise can improve not only sexual health but also overall men's health reducing associated CV risk. Accordingly, present data indicate that smoking and cannabis use as well as heavy alcohol intake represent risk factors for ED whereas physical exercise and moderate alcohol intake play a protective role. In line with these findings, it has reported that a Mediterranean diet enriched in fish, fresh fruit and vegetables protects from ED [66] and overall CV risk [67].

However, it is important to recognize that ED and CVD share the same CV risk factors so that a bidirectional relationship better describes their association. In fact, Vlachopoulos et al, [68] previously documented that a considerable proportion of patients with ED of vascular origin had angiographically documented silent CHD.

10. Expert opinion

CVD represents the most important non-transmittable chronic disease to be prevented, because it accounts for nearly one-third of all deaths and leads to significant morbidity. Several risk stratifying methods determining risk profile, using multiple physiological and comorbidity data, were developed and applied to favor CVD prevention and treatment. However, all the available algorithms cover only a small fraction of the entire CV risk spectrum and therefore identification of "residual risk" factors is urgently needed. We strongly believe that considering ED, in its multifaceted expression, as a useful "residual risk" factor for CVD will help to minimize CV morbidity and mortalityin males. There are several reasons justifying this believe. Meta-analyses, summarized in the Forest plot of Figure 1 indicate that ED shares several major risk factors [smoking, lack of physical activity, arterial hypertension, diabetes mellitus, MetS, central obesity, hypertriglyceridemia] with CVD. In addition, meta-analyses summarized in the Forest plot of Figure 2, all

show that ED is a risk factor for overall CVD, CHD, AMI, stroke and all-cause mortality. Hence, understanding ED will help in understanding possible "residual risk" factors for CVD.

ED represents a condition enriched wtih conventional and unconventional CV risk factors. In fact, ED is a multidimensional disorder deriving from a continuous spectrum of clinical elements, including not only organic problems [organic component] but also reactions to stress [intrapsychic component of ED] and unhappy marital relationships [relational component of ED]. Our studies in an ED population unexpectedly documented that several unconventional risk factors can play a significant role in the stratification of ED-related CV risk. First of all, we documented that men's perception of reduced women's sexual interest represented an independent predictor of forthcoming MACE [36]. The reasons of such association are not easy to explain. Some epidemiological data have suggested that social relations might play a protective role on health in patients with CVD [69-70]. Accordingly, a meta-analysis of the available evidence indicates that poor social relationships were associated with a 29% increase in risk of incident CHD and a 32% increase in risk of stroke [71]. Similarly, social isolation was associated with a 55% greater risk of hospital readmission in patients with heart failure [72]. In particular, much data published over the last decades indicates that dyadic functioning is consequential for health, whereas negative dimensions of marital functioning have harmful influences on health outcomes [73-74]. The best-known example of the effect of marital relations on health is the"widowhood effect": an increased risk of death in the months following the loss of a spouse [74]. This condition is particularly evident for CVD [75-76] and is relatively gender-specific, beingmore apparent in widowed males than females [77]. A satisfying marriage is associated with reduced stress and stress-related illness [78] possibly acting in reducing the effects of stress on CV hyperreactivity and on exaggerated sympathetic nervous system activity [79]. In addition, eros [so-called perceived women's sexual interest] represents avital ingredient for many individuals in fostering and maintaining strong and satisfying interpersonaland sexual intimacy and, most probably, CVhealth. In line with these hypotheses, in a cross-sectional study on the same ED population, we previously reported that perceiving a reduced partner's desire was associated with some risky behaviors, such as smoking and drinking, with delayed medical consultation and with a stepwise increase of free-floating anxiety and depressive symptoms [80]. Depression, in turn, represents another confounding factor for the evaluation of "residual CV risk", since depressed people often show unhealthy behaviors and attitudes that can increase CV risk of MACE, such as physical inactivity, eating disorders, poor self-care, active smoking, low motivation, or non-treatment adherence [39].

The importance of good social interactions and a stratifying couple relationship is also documented by the finding, in an ED population, of a protective role of a higher frequency of sexual intercourseon MACE incidence [40]. In line with what has been reported above, frequent sexual activity with a regular partner might create a better supportive intimate relationship, leading to stress reduction and social support, which might improve CV outcome [40].

We originally reported that another organic unconventional factor might be associated with an increased CV risk in ED population. In particular, in the above aforementioned population we found that relatively low PRL, but within the physiological range [< 246 mu/L or 11.7 ng/ml] was related to an increased risk of MACE independent of traditional CV risk factors. Underlying mechanisms supporting this association are unclear. Animal data have supported the role of PRL in regulating glucose and lipid metabolism [81]. In humans both hyperprolactinaemia and [82-83] a blunted PRL response to a serotoninergic challenge [84-85] are associated with obesity and MetS and worse metabolic profile. Hence, low PRL levels might be considereda mirror of a blunted central serotonergic function which has been associated withpreclinical vascular disease also in other populations [86].

Another important topic to be discussed is the role of PCDU in the management of ED patients. We support the concept that the identification of a pathological arteriogenic ED, with PCDU evaluated only in the flaccid condition can represent an early marker of forthcoming MACE, particularly in a low-risk population, according to conventional parameters [8, 36]. In particular, we found that FPA is an early marker of an impaired arterial stiffness closely associated with MACE incidence [8]. Hence, this parameter allows for the identification of individuals at residual risk of incident vascular events, opening new possibilities for lifestyle or pharmaco-therapeutic intervention. If the latter data will be confirmed in other populations, it is our opinion that the use of PCDU, performed in flaccid conditions should be part of the routine practice in the work up of ED patients

In conclusion, ED should be considered an opportunity – for the patient and for the physician – to open a window on possible CV risk and to screen for the presence of comorbidities. In ED patients, besides classic conventional CV risk factors, several other unconventional conditions can contribute to the CV burden of the patient. Physicians should be aware of the importance of the context in which the sexual symptom develops and should be strongly invited to analyze the quality of the patient's relationship andthe partner's behavior and diseases. Improving or even resolving the couple relational fitness and the sexual framework might help not only in improving ED treatment outcomes but also in ameliorating the ED-associated partner HSD, which, in turn, is important for the patient's general and CV health.

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Papers of special note have been highlighted as:

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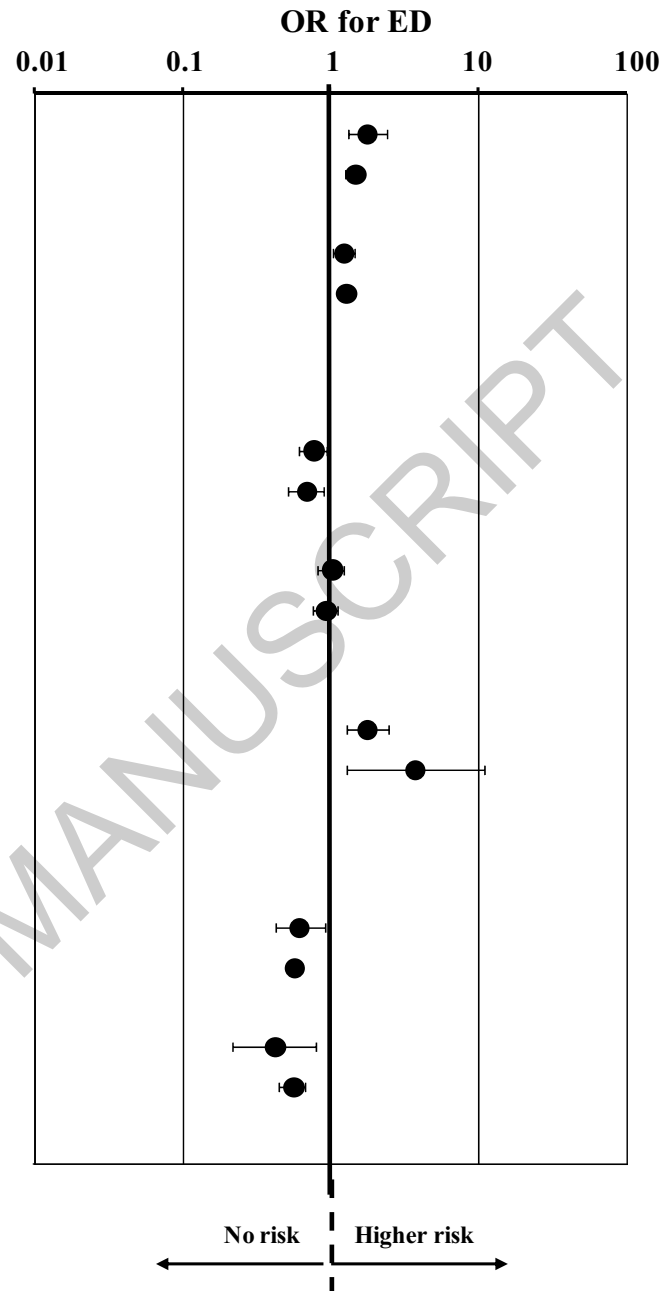
Source	# trials	OR
Smoking		
Current smoker		
Cao et al., 2013	8	1,8
Allen et al., 2018	28	1,4
Past smoker		
Cao et al., 2013	4	1,2
Allen et al., 2018	17	1,2
Alcohol intake		
Moderate vs no-/occasional		
Allen et al., 2018	10	0,7
Wang et al., 2018	7	0,7
Heavy vs no-/occasional		
Allen et al., 2018	10	1,0
Wang et al., 2018	4	0,9
Cannabis		
Allen et al., 2018	3	1,8
Pizzol et al., 2019	5	3,8
Physical activity		
Moderate		
Cheng et al., 2007	4	0,6
Allen et al., 2018	8	0,5
High		
Cheng et al., 2007	4	0,4
Allen et al., 2018	8	0,5



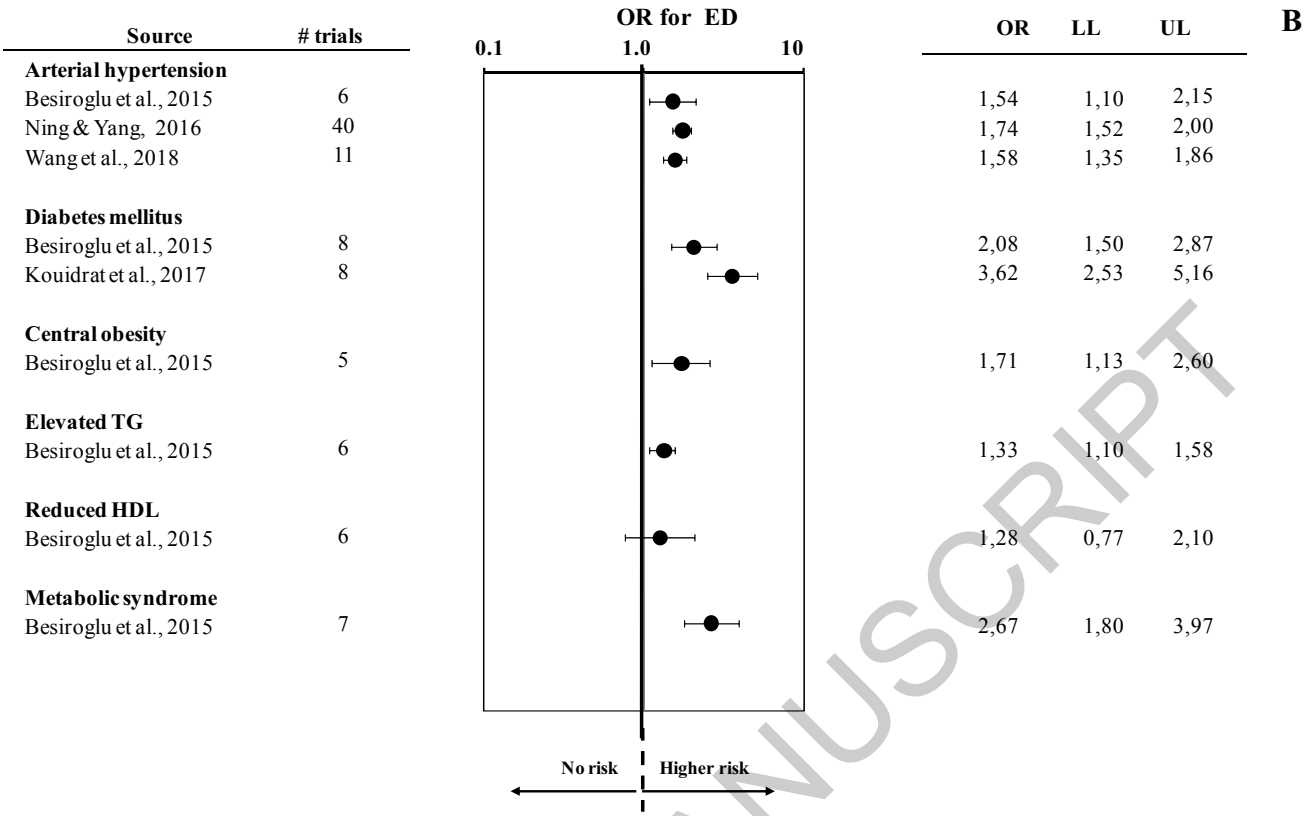
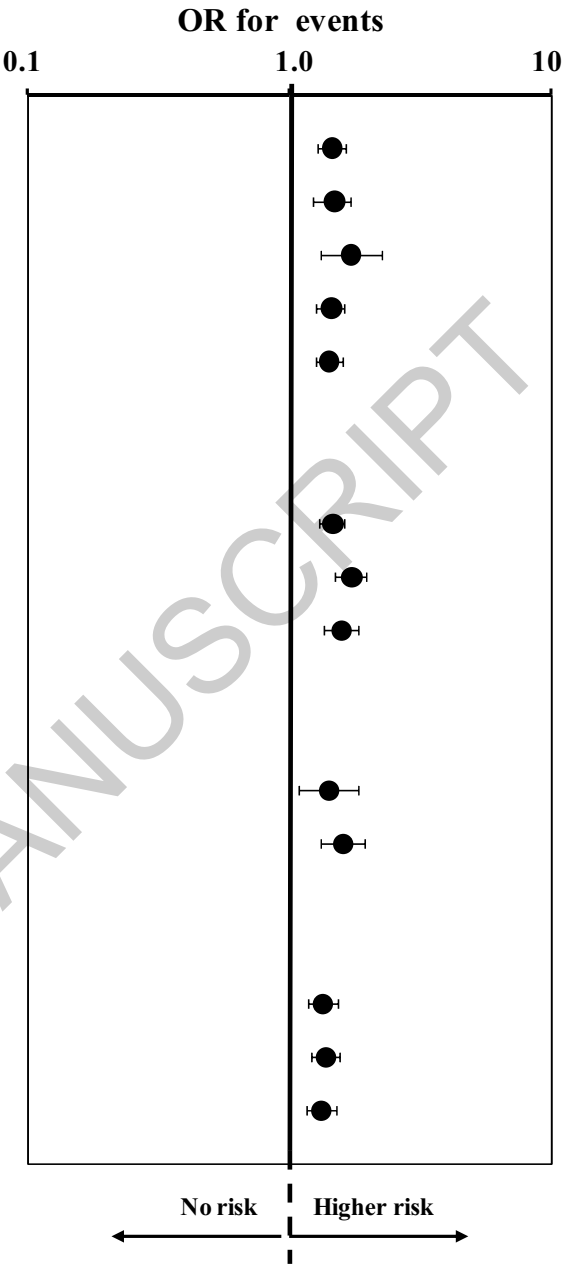


Figure 1. Forest plot of estimated odds ratio (95% confidence intervals) for ED according to several (smoking, alcohol intake, cannabis use and physical activity; panel A), (arterial hypertension, diabetes mellitus, central obesity, elevated TG, reduced HDL and metabolic syndrome; Panel B) cardiovascular risk factors. TG= triglycerides HDL=high density lipoprotein. LL=lower limits; UP= upper limits.

Source	# trials
Overall CVD	
Guo et al., 2010	7
Dong et al., 2011	8
Yamada et al., 2012*	3
Vlachopoulos et al., 2013	13
Zhao et al., 2019	19
CHD	
Dong et al., 2011	5
Yamada et al., 2012*	3
Zhao et al., 2019	6
AMI	
Guo et al., 2010	2
Vlachopoulos et al., 2013	4
Stroke	
Dong et al., 2011	3
Vlachopoulos et al., 2013	6
Zhao et al., 2019	4



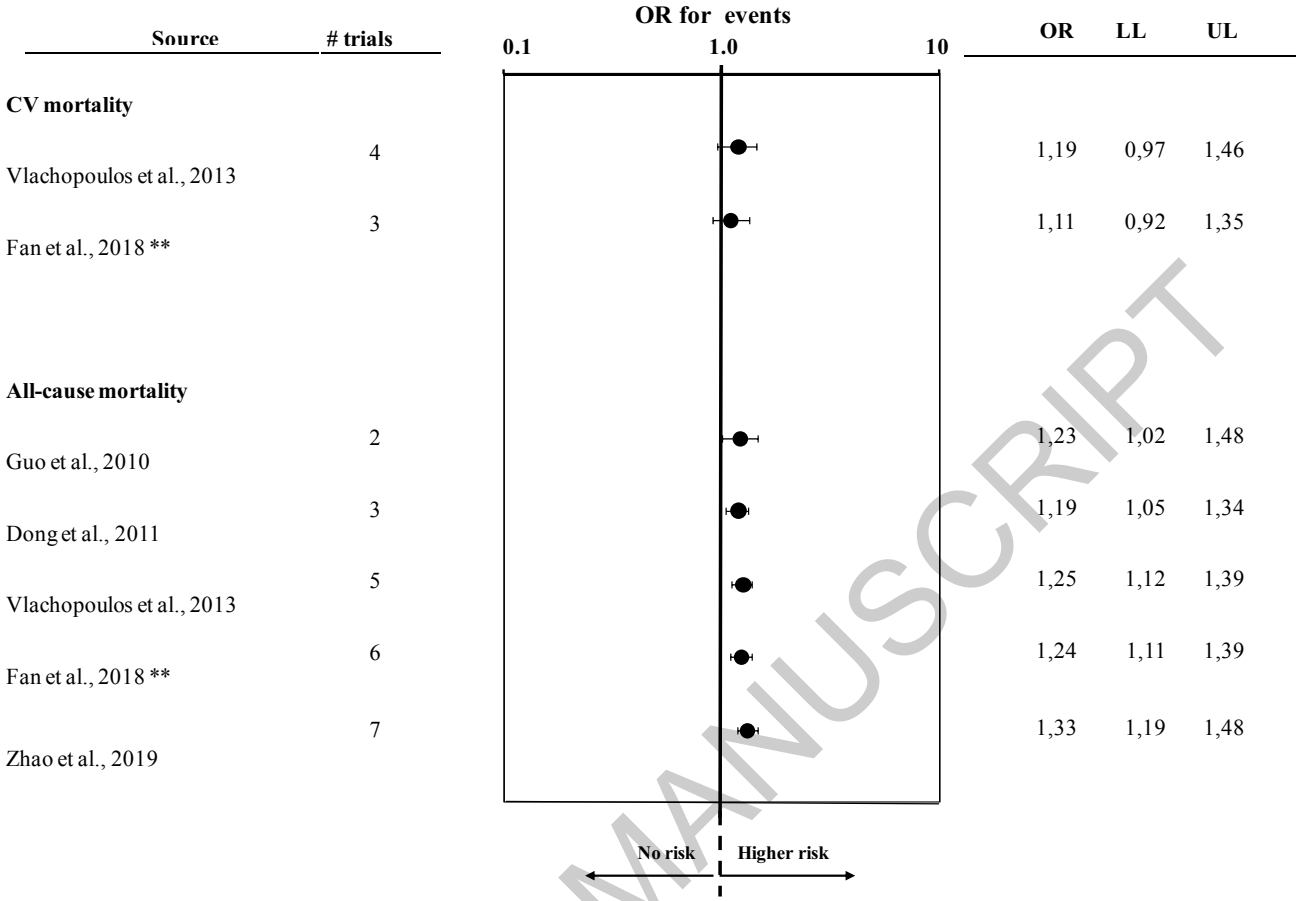


Figure 2. Forest plot of estimated odds ratio (95% confidence intervals) for forthcoming cardiovascular (CV) morbidity (A) and mortality (B) in subjects with erectile dysfunction. AMI= acute myocardial infarction; CHD=coronary artery diseases. CVD= cardiovascular diseases. LL=lower limits; UP= upper limits.

	Besiroglu et al., 2015 (18)		**Ning & Yang, 2016 (22)**		**Kouidrat et al., 2017 (20)**		**Wang et al., 2018 (23)**	
Number of trials included	8		4		8		18	
Number of patients analyzed	12,067		28,586		6,248		41,943	
Outcomes evaluated								
	yes	**no**	**yes**	**no**	**yes**	**no**	**yes**	**no**
Arterial hypertension	x		**X**			**X**	**X**	x
Diabetes mellitus	X			X	**X**			X
Obesity	X			X		**X**		x
Elevated triglycerides	X			x		**X**		x
Reduced HDL cholesterol	X			X		**X**		X
Metabolic syndrome	X			x		**X**		X

Table 1. Comparisons of the available meta-analyses evaluating the relationship between several morbidities and erectile dysfunction. HDL= high density lipoprotein.

	Cheng et al., 2007 (15)		**Cao et al., 2013 (12)**		**Allen et al., 2018 (13)**		**Wang et al., 2018 (30)**		**Pizzol et al., 2019 (31)**	
Number of trials included	7		9		89		24		5	
Number of patients analyzed	11,844		50,360		348,865		154,295		3,395	
Outcomes evaluated										
	yes	**no**	**yes**	**no**	**yes**	**no**	**yes**	**no**	**yes**	**no**
Smoking habit		X	X		X			X		X
Alcohol intake		X		X	X		X			X
Cannabis use		X		X	X			X	X	
Physical activity	X			X	X			X		X

Table 2. Comparisons of the available meta-analyses evaluating the relationship between several modifiable cardiovascular risk factors and erectile dysfunction.

	Guo et al., 2010 (24)		**Dong et al., 2011 (25)**		**Yamada et a., 2012 (26)***		**Vlachopoulos et al., 2013 (27)**		**Fan et al., 2018 (28)****		**Zhao et al., 2019 (11)**	
Number of trials included	8		12		12		14		7		25	
Number of patients analyzed	45,558[1,248-25,650]		36,744 [291-9,006]		22,586[154-9,752]		92,757[291-31,296]		111,440[1,436-65,495]		154,794	
Outcomes evaluated												
	yes	No	**yes**	no	**yes**	**no**	**yes**	No	yes	No	yes	No
Overall CVD	X		**X**		**X**		**X**			X	X	
Coronary artery diseases		X	**X**		**X**			X		X	x	
AMI	X			x		**x**	**X**			X	X	
Stroke		X	**X**			**X**	**X**			X	x	
Peripheral vascular diseases		X		X	**X**			X		X		X
CV mortality		X		X		**X**	**X**		x			X
Overall mortality	x		**X**			**X**	**X**		x		x	

Table 3. Comparisons of the available meta-analyses evaluating the relationship between erectile dysfunction and forthcoming cardiovascular (CV) diseases (CVD) mortality and morbidity. AMI= acute myocardial infarction. * performed only in diabetic subjects. ** performed in the general population.

Risk factor	**OR for MACE**	**Ref#**
Higher education	0.59[0.37;0.95]	36
Past smoking	1.61[1.02;2.53]	36
Current smoking	1.72[1.06;2.80]	36
History for CVD	3.63[2.47;5.32]	36
SBP (20 mmHg)	1.21[1.01;1.45]	36
BMI > 30 Kg/m^2	1.55[1.01;2.38]	36
# MetS factor (#1-5)	1.76[1.01;3.16]	36
Reduced T levels (< 8 nM)	7.1 [1.8–28.6]	37
Reduced PRL levels (<249 mU/L)	1.70[1.07;1.90]	38
Severe depressive symptoms	1.42[1.02;5.79]	39
Partener's HSD	2.02[1.35;3.02]	36
Fatherhood (each child)	1.02[1.01;1.03]	10
Reduced sexual intercourse (<7/months)	4.44[1.82;13.89]	40

Table 4. Risk of incident major adverse cardiovascular events (MACE) and several conventional and unconventional cardiovascular risk factors. The data were derived from a consecutive series of 1,687 patients attending our unit for seeking medical care for erectile dysfunction between 2000 and 2007. CVD= cardiovascular diseases, SBP= systolic blood pressure; BMI= body mass index; MetS= metabolic syndrome; T= testosterone; PRL= prolactin; HSD= hypoactive sexual desire.