SM = SM: The Interface of Systems Medicine and Sexual Medicine for Facing Non-Communicable Diseases in a Gender-Dependent Manner

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ABSTRACT

Introduction: Complex non-communicable diseases (NCDs), including cancer, cardiovascular disease, obesity, diabetes, and chronic respiratory disorders, are major causes of morbidity and mortality globally. The complexity of NCDs requires innovative, integrated, and interdisciplinary approaches for diagnosis, treatment, and prevention by adopting the new paradigm called *systems medicine*. A growing body of evidence suggests that sexual dysfunction in general and erectile and lubrication dysfunctions in particular are, in a sex-dependent manner, efficient predictors of overall systemic well-being. However, the relation between systems medicine and sexual medicine is not well defined.

Aim: To demonstrate that in combating the major NCDs, sexual health can be used as a surrogate marker of systemic health and can facilitate the diagnosis, treatment, and prevention of NCDs.

Methods: A comprehensive review of peer-reviewed publications on the topic was performed through a PubMed search.

Main Outcome Measures: Because there is a strong biological basis for the developmental origins of health and disease not only in the early phases of development but also later in life, the identification of appropriate biomarkers is essential for monitoring these timelines and trajectories for better understanding NCD processes, risk stratification for NCD intervention, and prevention.

Results: In this review, I propose a novel approach in which sexual medicine can be used as a new tool to understand and manage NCDs and as a marker of systemic health. Moreover, the multipronged application of systems medicine to pathophysiologic changes leading to sexual dysfunction might sustain the growth of a young science such as sexual medicine.

Conclusion: This multilevel approach has the potential to suggest novel avenues for the comprehensive management of NCDs and sexual dysfunction in a sex-dependent manner. **Jannini EA. SM = SM: The Interface of Systems Medicine and Sexual Medicine for Facing Non-Communicable Diseases in a Gender-Dependent Manner. Sex Med Rev 2017;5:349–364.**

Key Words: Systems Medicine; Sexual Medicine; Non-Communicable Diseases; Developmental Origins of Health and Diseases; Erectile Dysfunction; Cardiovascular Diseases

INTRODUCTION

Systems medicine looks at the systems of the human body as part of an integrated whole, incorporating genomic, biochemical, physiologic, behavioral, and sociocultural -environment interactions.[1] Although used for the first time approximately 25 years ago,[2] the term *systems medicine* is currently receiving renewed scientific attention. This is due to the fact that systems medicine is a new, integrated approach to one of the major challenges of the current era, the complex non-communicable diseases (NCDs) that include cardiovascular disease (CVD), diabetes mellitus (DM), cancer, and chronic respiratory diseases (chronic obstructed pulmonary disease [COPD] and asthma).[3] NCDs are the leading causes of morbidity and mortality globally, accounting for 38 million deaths per year. Approximately 82% of NCD deaths have occurred in low- and middle-income countries, where half these deaths were premature (<70 years of age) compared with high-income countries.[4]

The prominent NCDs are multifactorial in origin,[5] arising from any combination of underlying, modifiable, non-modifiable, and intermediate risk factors. Most NCDs are

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strongly associated with modifiable health behaviors such as illegal drug, tobacco, and alcohol use and abuse, unhealthy diet, and physical inactivity, which in turn might lead to increased levels of blood pressure, blood glucose, and cholesterol and excess body weight. The risks of NCDs are worsened by environmental factors such as urbanization, migration, and air pollution and factors associated with greater economic prosperity, including nutritional changes, which together form a "mismatch" between human evolved biology and current habitat.[6]

Although NCDs are most prominent during adulthood, development in early life influences the predisposition to NCDs, starting as early as pregnancy when the maternal body composition and diet influence the infant's risk of NCDs later in life. Therefore, NCDs should be studied using a life course approach, with overall risk depending on the sequential effects of the developmental timeline with different metabolic trajectories, age-dependent decrease in plasticity, and differential responses to subsequent risk factors. Thus, identification of appropriate biomarkers is essential for monitoring these timelines and trajectories for better understanding NCD processes, risk stratification for NCD intervention, and prevention.[7]

Sexual health, an important feature of overall health, is a complex interplay of cultural, social, relational, intrapsychic, and medical aspects.[8] Sexual medicine is a very young but rapidly growing science that needs a multidisciplinary approach to study male and female sexual dysfunctions (MSD and FSD, respectively) from not only the traditional, psychosocial perspective but also from a novel molecular and biomedical approach. SD in turn can be considered a systemic disease with several comorbidities whose prevalence is increasing globally.[9] SD is reported to have a major effect on quality of life (QoL) and psychological and emotional well-being and therefore has to be managed by a multidisciplinary approach.[10,11]

The Global Study of Sexual Attitudes and Behaviors, an international survey of sexual health in in 13,882 women and 13,618 men 40 to 80 years old from 29 countries, showed that sexual difficulties are relatively common throughout the world and strongly associated with physical health.[12] Furthermore, recent literature supports the link between NCDs, including obesity, metabolic syndrome, DM, and CVD, and MSD and FSD, possibly because of common pathogenetic mechanisms, such as inflammation, and common risk factors, such as "diabesity" (DM caused by obesity), hypertension, and sedentary lifestyle.[13,14] In addition, evidence suggests considering MSD, particularly erectile dysfunction (ED), a potential marker for underlying silent cardiac or vascular disease processes.[15] The complex association between ED and NCDs requires a systemic approach in terms of innovative, integrated, and interdisciplinary approaches for diagnosis, treatment, and prevention.

There is increasing evidence that maternally mediated environmental modulation of gene-environment interactions is an important determinant of later disease risk. The in utero environment, a key determinant of fetal health and development, can have long-term effects on the physiology of the fetus and the risk of NCDs in adult life.[16] This belief that adaptive responses to a range of stimuli are important contributors to the risk of NCDs forms the crux of a multidisciplinary field known as the Developmental Origins of Health and Disease (DOHaD) paradigm, which examines how "environmental factors acting during the phase of developmental plasticity interact with genotypic variation to change the capacity of the organism to cope with environment in later life."[16] There is a strong biological basis for the DOHaD model of disease pathogenesis usually described for the first 1,000 days of life.[17]

Although the relation between systems medicine and NCDs is well established, the multilevel approach in combating NCDs using sexual health as a marker combined with systems medicine is not currently defined. Therefore, in this review, I propose a novel approach in which systems medicine can be used as a tool to understand and manage NCDs, with sexual medicine being used as a marker of systemic health. In addition, I present the extended use of the DOHaD concept to further understand the very close relation between NCDs and SD. With these aims, a comprehensive review of peer-reviewed publications on the topic was performed through a PubMed search using the search terms *sexual medicine, systems medicine, sexual dysfunction, non-communicable diseases, erectile dysfunction, cardiovascular disease, diabetes mellitus, chronic respiratory diseases, cancer,* and *developmental origins of health and disease.* The search was limited to articles in English and was completed up to August 2016.

SYSTEMS AND SEXUAL MEDICINE APPROACH FOR MANAGEMENT OF NCDs

NCDs encompass a common group of diseases with intertwined gene-environment and socioeconomic interactions and comorbidities that lead to complex phenotypes that are specific to the individual, thus requiring stringent management moving toward holistic multimodal integrated care and multiscale, multilevel systems approaches. Systemic diseases lead to hypoactive sexual desire disorder[18,19] and arousal disorders.[20–26] Because it has been proposed that NCDs should be considered a single expression of disease with different risk factors,[27] they can be considered a major risk factor of SD. Furthermore, the "systems medicine" approach to tackle all components of NCD complexity involves the multilevel integration of heterogeneous patient information generated by different data sources, which include environmental, clinical, and biological data.[27] It is not surprising that sexual medicine also requires a multifaceted approach. Thus, the systems medicine approach to NCDs enables the simultaneous scrutiny of multilevel data from actual experimental and computational in silico sources for better understanding of the complex molecular interactions that influence the course of medical conditions and for identification of clinically important molecular targets for diagnostic and therapeutic interventions.[27]

RISK FACTORS OF NCDS

Many acute and chronic systemic diseases affect male and female gonadal function mainly by disrupting the hypothalamic-pituitary-gonadal axis.[28–30] In women, systemic diseases lead to several derangements, which directly inhibit the reproductive hormone-producing organs, thereby causing chronic anovulation[28] and SD. Although SD manifests in women in different ways, the complexity of FSD makes the diagnosis difficult.[31,32] However, in men, erection is considered a very efficient marker of phenotypic conditions, including vascular, endocrine, neurologic, immunologic, oncologic, systemic, toxicologic, psychiatric, but also environmental, intrapsychic, and rational, health.[33,34] A disruption in erection leads to ED, a form of MSD, which is associated with risk factors common to NCDs.[35] For these reasons, the relative lack of comparable studies on FSD, and several objective and sociocultural aspects, ED can be considered an excellent paradigm of the link between NCDs and SD.

Vascular health is due to correct cross-talk between the endothelium and smooth muscle cells.[36] It has been stated that "Erection is a vascular event. Penis is a vascular organ. To have an erection integrated endothelium is needed."[37] Thus, endothelial dysfunction is the key mechanism in the pathogenesis of ED[38] according to a famous acronym (ED = ED).[39] The combined search strategy yielded more than 1,300 entries in Medline, underlying the importance of the link between the two dysfunctions. The causes of (sexual) ED can be classified into psychogenic (anxiety related to performance, depression, and fear of intimacy), neurogenic (multiple sclerosis, spinal cord injury, surgical injury to pelvic nerves, and peripheral neuropathy), endocrine (hypogonadism and DM), vasculogenic (hypertension, hyperlipidemia, and atherosclerosis), cellular (oxidative stress, smooth muscle dysfunction, and decreased nitric oxide availability), and iatrogenic (drugs causing sexual impairment, recreational drugs, surgery, and radiotherapy) causes.[40]

These risk factors lead to atherosclerosis and endothelial dysfunction. Atherosclerosis decreases arterial inflow by stenosis, leading to relative hypoxia and smooth muscle loss, dysfunction, and cavernosal fibrosis. When smooth muscles malfunction, arterial dilatation is incomplete, cavernosal relaxation fails to occur, and the veno-occlusive mechanism fails, leading to ED. Chronic hyperglycemia induces free radicals (reactive oxygen species) through advanced glycation end products, leading to microstructural changes at a molecular level. Advanced glycation end products are increased in cavernosal tissues in men with DM, impairing smooth muscle relaxation.[41] Endothelins are powerful constrictors released in large quantity by the diabetic vascular endothelium, inducing atherosclerotic change. Endothelin-induced vasoconstriction is associated with Rho-kinase activation, further decreasing nitric oxide production in the cavernosal muscle.[42] This combination of vascular factors increases the severity of ED. The other causes of ED include aging,[43] decreasing androgen levels,[44] and corpora cavernosa injury.[45]

ASSOCIATION BETWEEN SD AND CVD

ED is an independent risk factor and an important predictor for the development of major CVDs. A growing body of evidence links CVD and ED, with the two conditions having similar risk factors.[46] Several studies have reported an association between ED and CVD, mainly because of the interaction among CV risk factors, androgens, and chronic inflammation that determines endothelial dysfunction and atherosclerosis, resulting in disorders of penile and coronary circulation. Moreover, it has been demonstrated that ED precedes CVD and, hence, can be used as an early marker to identify men at a higher risk of CV events.[23] This has been proposed as the artery size hypothesis, a possible mechanism to explain the relation between ED and CVD. This interesting theory relies on evidence that atherosclerosis is a systemic disorder in which all major vascular beds should be affected to the same extent. However, symptoms at different districts in the system rarely become evident at the same time. In fact, smaller vessels (ie, the penile arterial supply) obviously have lesser capacity to tolerate the same amount of atherosclerosis compared with larger ones (ie, the coronary arteries). Hence, ED will develop before CVD.[47]

Several experimental findings are in line with the artery size hypothesis. A large, prospective, 25-year follow-up trial evaluating the impact of CV risk factors on ED showed that age, body mass index, cholesterol, and triglycerides were significantly associated with ED.[48] ED is common in patients with overt and silent coronary artery disease (CAD). The bidirectional association between ED and CAD was first described by Montorsi et al[49] for approximately 50% of patients with acute chest pain and angiographically documented CAD who developed ED. In this study, SD preceded CAD in most cases (70%), becoming clinically evident more than 3 years before coronary symptoms, implying a temporal association between ED and CAD. These data highlighted the possible common pathologic link between the two conditions, suggesting ED as a biomarker for subsequent symptomatic CAD. In addition, ED has been confirmed as a predictor of CAD in men at a higher risk of CVD.[50–53] In a subanalysis of the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) and the Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease (TRASCENDED) trials, the investigators evaluated whether ED was predictive of CV events in a population at a high risk for CVD. Interestingly, men complaining of ED were at a higher risk of CV death (hazard ratio = 1.93, $P = .016$), myocardial infarction (hazard ratio = 2.02, $P = .017$), and overall mortality (hazard ratio = 1.84, $P = .005$) compared with men without ED.[54] A large nationwide population-based cohort study showed that the incidence of ED was significantly higher in men with atrial fibrillation than in those without atrial fibrillation (20.6 vs 12.5 per 10,000 person-years; $P < .001$).[55]

In contrast, some studies failed to demonstrate an independent association between ED and CVD.[56,57] However, a meta-analysis

by Vlachopoulos et al[58] of 92,757 patients demonstrated a significant association between ED and the risk of CV events. The study showed that patients with ED had significantly increased risks of 44% for CV events, 62% for myocardial infarction, and 25% for overall mortality compared with those without ED. The study further showed that the relative risk for future adverse events was higher at younger ages and in the intermediate CVD risk population. A meta-analysis of 12 prospective cohort studies showed that ED was significantly and independently associated with an increased risk of CVD, coronary heart disease, stroke, and all-cause mortality.[59] Details of studies showing the association between CVD and ED are presented in Table 1.[46–48,55,56,58–67]

The third Princeton Consensus Conference updated recommendations and assessed, for the first time, the association between FSD and the presence of systemic vascular endothelial dysfunction and its consequences in women.[68] In general, women treated for hypertension have greater FSD than normotensive women. Women with hyperlipidemia but without CVD have greater FSD than women without hyperlipidemia. Women with metabolic syndrome and obesity have greater FSD than those without. Cardiometabolic risk factors, diabetes, and coronary heart disease are associated with greater FSD. Data support the association between treatment of metabolic syndrome and obesity and less FSD. The lack of data to support that FSD is a predictor of future CV events, as in men, is probably because of the dearth of well-designed studies[69] and the evidence that female sexual health is more complex and multifaceted than male sexual health. Furthermore, in women, there is a relative independence between subjective and objective aspects of arousal and desire, with numerous contributing factors (hormonal, psychological, interpersonal, and social factors). In conclusion, the simple evaluation of sexual health is an excellent marker of CV health in men. In future, this might hold true for women.

ASSOCIATION BETWEEN SD AND DM

The pathogenesis of ED in DM is multifactorial, depending on psychological and organic factors.[70] The proposed mechanisms of ED in patients with DM are represented by vasculopathy, neuropathy, visceral adiposity, insulin resistance, and hypogonadism. ED from endothelial dysfunction has long been recognized as a common complication of DM in men.[71] Hyperglycemia and increased oxidative stress on the penile endothelial cells lead to apoptosis of endothelial cells and vasodilation processes dependent on endothelial nitric oxide synthase, thereby disrupting erectile tissue homeostasis. In this context, it has been shown that ED, probably also in its subclinical, initial form, could ultimately emerge as the presenting symptom of DM, at least in some men; that is, the predicted probability of having undiagnosed DM was found to be 1 in 10 men in the presence of ED.[72] The Massachusetts Male Aging Study (MMAS), the earliest study on ED and DM, showed that the prevalence of ED was almost three times higher in men with DM compared with the general population.[73] A prospective study investigating the prevalence of undiagnosed DM in a cohort of 129 men showed a higher prevalence of undiagnosed DM in men with ED compared with that of the general population.[74] Similar results were obtained in a recent cross-sectional study with ED showing a strong association in patients with undiagnosed DM compared with those with undiagnosed hypertension and hypercholesterolemia.[75] Hypertension and DM were likely to increase the risk of ED. Compared with men without DM and without hypertension, the odds ratios were 1.4 (95% CI = 0.7–3.2) for men with hypertension without DM, 4.6 (95% CI = 1.6–13.7) for men with DM without hypertension, and 8.1 (95% CI = 1.2–55.0) for men with DM and hypertension.[76] The sub-analysis of the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified-Release Controlled Evaluation (ADVANCE) trial prospectively investigating CVD outcomes during a 5-year follow-up period reported an increased risk for CV death, myocardial infarction, and overall mortality in men with DM complaining of ED compared with men without ED.[54] These studies highlight the importance of ED as an early marker for undiagnosed DM and could be useful in initiating DM screening. However, future longitudinal studies with uniform patient characteristics are required to evaluate the potential clinical use of serum biomarkers in men with DM for the development and progression of ED. Thus, DM is a well-known risk factor for ED and a significant correlation between the two conditions has been widely reported, the details of which are presented in Table 2.[54,72–77]

Studies assessing SD in women with type 2 DM are scanty. However, the overall prevalence of FSD in women with DM was 53.4% and significantly higher in menopausal women (63.9%) compared with non-menopausal women (41.0%; $P < .001$). There was no association between hemoglobin A_{1c}, duration of DM, hypertension, or cigarette smoking status and FSD; on the contrary, age, metabolic syndrome, and atherogenic dyslipidemia were significantly associated with FSD.[78,79] Depression and marital status were independent predictors of FSD, whereas physical activity was protective.[80] Hence, as for other complications of DM, evaluation of female sexuality should become a routine assessment in women with type 2 DM. In conclusion, male and female arousal symptoms and hypoactive sexual desire disorder are considered excellent markers of obesity, metabolic syndrome, diabesity, and overt type 2 DM.

ASSOCIATION BETWEEN SD AND CHRONIC RESPIRATORY DISEASES

Decreased levels of testosterone and ED have been reported in men with respiratory diseases, such as COPD, asthma, and obstructive sleep apnea.[81] A nationwide, population-based database study was conducted in two different cohorts from 2000 to 2007; the first cohort consisted of 18- to 55-year-old men with newly diagnosed asthma and the other was an age-, sex-, and comorbidity-matched control group without asthma.

Table 1. Association between CVD and ED

Study	Study type	Study population (mean age)	Outcome measurements	Outcome results
Banks et al, 2013[46]	Prospective	95,038 men ≥45 y old; 65,495 with no previous CVD; 29,323 with previous ED (45 and Up Australian Study; 62 y)	CVD events and all-cause mortality	Patients with ED without prior CVD had significantly increased risks of ischemic heart disease (adjusted RR = 1.60, 95% CI = 1.31–1.95), heart failure (RR = 8.00, 95% CI = 2.64–24.4), peripheral vascular disease (RR = 1.92, 95% CI = 1.12–3.29), all-cause mortality (RR = 1.93, 95% CI = 1.52–2.44), and acute MI (RR = 1.66, 95% CI = 1.22–2.26) compared with patients without ED
Montorsi et al, 2005[47]	Prospective	300 patients with acute chest pain and CAD (62.5 ± 8 y)	ED prevalence and time of onset	ED prevalence in 49% of patients; patients with type 1 DM and ED had SD before CAD onset ($P < .001$); mean interval from ED onset to CAD = 38.8 mo
Fung et al, 2004[48]	Prospective	community-dwelling men	Common CHD risk factors	Age, BMI, current smoking, high BP, and high cholesterol and TG levels were associated with ED 25 y later
Hotaling et al, 2012[56]	Prospective	31,296 community-based men in Washington (VITAL cohort study; 50–76 y)	CV death occurred in 7,762 men with ED and death occurred in 486 men with ED	Patients with ED had 23% increased risk of CV death after adjusting for age, marital status, and education (HR = 1.23, 95% CI 1.01–1.49); further adjustment of CVD risk factors such as DM, treatment for hypertension or hyperlipidemia, family history of MI or stroke, BMI, exercise, and ED not independently associated with CV death (HR = 0.93, 95% CI = 0.76–1.15)
Ho et al, 2016[60]	Prospective	395 men with hypogonadism (56.1 ± 6.7 y)	Framingham Risk Score; 10-y risk of CVD	ED severity was a predictor of high 10-y CVD risk for mild-to-moderate ED (OR = 2.37, 95% CI = 1.24–4.51), moderate ED (OR = 4.39, 95% CI = 1.78–8.43), and severe ED (OR = 12.81, 95% CI = 4.65–26.11)
Fang et al, 2015[61]	Prospective	965 men without CVD (44.3 y)	Framingham CVD risk and change in Framingham CVD risk	Transient and persistent ED significantly associated with increased Framingham risk; Framingham risk was 1.58 percentage points higher in younger men with ED (95% CI = 0.11–3.06) and 2.54 percentage points higher in older men with ED (95% CI = 1.5–6.59) than in those without ED
Lahoz et al, 2016[62]	Prospective	614 subjects; 373 volunteers and subjects with ED and 241 subjects without ED (61 y)	Mean c-IMT, prevalence of carotid plaques, mean ABI, prevalence of ABI	Men with ED had significantly higher mean c-IMT (0.762 ± 0.151 vs 0.718 ± 0.114 mm; $P < .001$) and higher prevalence of carotid plaques (63.8% vs 44.8%; $P = .039$) after adjusting for age, CV risk factors, and ongoing treatment ($P = .039$)

(continued)

Table 1. Continued

Study	Study type	Study population (mean age)	Outcome measurements	Outcome results
Feldman et al, 2016[63]	Prospective	1,862 men free from known CVD and 839 patients with ED not taking ED medications (59.5 ± 9 y)	Subclinical vascular disease (CAC), ABI, atherosclerosis, or vascular stiffness or dysfunction, flow-mediated dilation	ED was significantly associated with CAC score > 100 (OR = 1.43, 95% CI = 1.09–1.88) and carotid plaque score ≥ 2 (OR = 1.33, 95% CI = 1.02–1.73)
Vlachopoulos et al, 2014[64]	Prospective	344 patients with ED without established CVD (56 y)	Prediction of maces using aortic PWV	Patients with ED with highest PWV tertile (>8.8 ms^{-1}) had 4-fold higher MACE risk compared with those in lowest PWV tertile (<7.6 ms^{-1}; adjusted HR = 3.97, 95% CI = 1.23–12.54, P = .004)
Corona et al, 2010[65]	Prospective	1,687 men with ED (52.9 ± 12.8 y)	Prediction of maces using PBF	Lower PBF associated with increased risk of MACEs for flaccid (HR = 2.67, 95% CI = 1.42–5.04) and dynamic (HR = 1.57, 95% CI = 1.01–2.47) conditions
Liu et al, 2016[66]	Retrospective	patients with ED in Taiwan (n = 3,516) with average age of 40.0 ± 17.1 y from National Health Insurance Research Database	New incidence of AF	ED was not independently associated with incident AF compared with control group (HR = 1.031, 95% CI = 0.674–1.578, P = .888)
Puchalski et al, 2013[67]	Retrospective	62 men with MI and CVD risk factors (40–75 y)	ED before MI and serum CRP levels	ED was present in more than half the men before MI and could be the first symptom of CAD; patients with ED before MI had significantly higher plasma CRP level in peri-MI period compared with patients without ED (P = .01)
Lin et al, 2015[55]	Prospective population-based cohort	3,853 men with AF (68.4 ± 13.2 y) and 15,405 men without AF (67.6 ± 13.4 y)	Occurrence of ED	Incidence of ED was higher in AF group than in non-AF group (20.6 vs 12.5 per 10,000 person-years; P < .001); independent risk factors of ED were AF (HR = 1.53, 95% CI = 1.05–2.24) and hyperlipidemia (HR = 1.96, 95% CI = 1.36–2.81)
Vlachopoulos et al, 2013[58]	Meta-analysis	92,757 participants from 14 longitudinal studies (40–65 y)	CV events, CV mortality, MI, cerebrovascular events, and all-cause mortality	ED increases risk for future CV events (RR = 1.44, 95% CI = 1.27–1.63), MI (RR = 1.62, 95% CI = 1.34–1.96), cerebrovascular events (RR = 1.39, 95% CI = 1.23–1.57), and all-cause mortality (RR = 1.25, 95% CI = 1.12–1.39) and shows a trend to increase risk for CV mortality (RR = 1.19, 95% CI = 0.97–1.46) compared with men without ED
Dong et al, 2011[59]	Meta-analysis	36,744 participants from 12 prospective cohort studies (40–80 y)	Major CVD and all-cause mortality	ED significantly associated with increased risk of CVD (RR = 1.48, 95% CI = 1.25–1.74), CHD (RR = 1.46, 95% CI = 1.31–1.63), stroke (RR = 1.35, 95% CI = 1.19–1.54), and all-cause mortality (RR = 1.19, 95% CI = 1.05–1.34) independent of conventional risk factors

ABI = ankle-brachial index; AF = atrial fibrillation; BMI = body mass index; BP = blood pressure; CAC = coronary artery calcium; CAD = coronary artery disease; CHD = coronary heart disease; c-IMT = carotid-intima media thickness; CRP = C-reactive protein; CV = cardiovascular; CVD = cardiovascular disease; DM = diabetes mellitus; ED = erectile dysfunction; HR = hazard ratio; MACEs = major cardiovascular events; MI = myocardial infarction; OR = odds ratio; PBF = penile blood flow; PWV = pulse wave velocity; RR = relative risk; SD = sexual dysfunction; TG = triglycerides; VITAL = Vitamins and Lifestyle.

Table 2. Association between DM and ED

Study	Study type	Study population (mean age)	Outcome measurements	Outcome results
Batty et al, 2010[54]	Prospective	6,304 men from ADVANCE trial (55–88 y)	Fatal and non-fatal CVD outcomes, cognitive decline, and dementia	Baseline ED associated with increased risk of all CVD events (HR = 1.19, 95% CI = 1.08–1.32), coronary heart disease (HR = 1.35, 95% CI = 1.16–1.56), and cerebrovascular disease (HR = 1.36, 95% CI = 1.11–1.67)
Skeldon et al, 2015[72]	Cross-sectional	4,519 men from NHANES; undiagnosed hypertension in 2,224 men; undiagnosed hypercholesterolemia in 2287 men; undiagnosed DM in 1,417 men (≥20 y)	Undiagnosed DM, hypertension, and hypercholesterolemia	ED strongly associated with undiagnosed DM (OR = 2.20, 95% CI 1.10–4.37) but not with undiagnosed hypertension and hypercholesterolemia; there was a significant interaction between ED and age in fasting glucose sample ($P < .001$)
Parazzini et al, 2000[75]	Cross-sectional	2,010 men from Italy (>18 y)	Assessment of risk factors for ED	ED risk increased in men with DM without hypertension (OR = 4.6, 95% CI = 1.6–13.7) and in men with DM with hypertension (OR = 8.1, 95% CI = 1.2–55.0) compared with men without DM and without hypertension
Giuliano et al, 2004[76]	Prospective	5,391 patients with ED; 2,377 patients with DM and ED (58.9 y)	ED prevalence	Prevalence of ED in patients with DM was 67% (1,603 of 2,377)
Corona et al, 2014[77]	Prospective	499 patients with T2DM (58.8 ± 8.8 y)	ED prevalence	High prevalence of ED detected in men with recently diagnosed T2DM, with mild ED present in 19.4%, mild-to-moderate ED in 15.4%, moderate ED in 10.4%, and severe ED in 21.6%

ADVANCE = Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified-Release Controlled Evaluation; CVD = cardiovascular disease; DM = diabetes mellitus; ED = erectile dysfunction; HR = hazard ratio; NHANES = National Health and Nutrition Examination Survey; OR = odds ratio; T2DM = type 2 diabetes mellitus.

The two cohorts were followed for 7 years to evaluate the rate of ED development over time. The risk of developing a sexual dysfunction is significantly higher in the asthmatic group than in the control group.[82]

The symptoms of COPD, including dyspnea, cough, muscle weakness, and diminished physical activity, are the major causes of decreased physical activity in these patients.[83] Although some studies have investigated the relation between ED and COPD, the topic remains neglected. In a case-control study, various degrees of ED were reported in 78.6% of patients with COPD and 55.8% of control subjects.[84] In another case-control study, varying degrees of ED were reported to be similar between patients with COPD and subjects without COPD, although moderate and severe ED was higher in patients with COPD than in control subjects (57% vs 20%). The study further showed that the concentration of the systemic inflammatory marker tumor necrosis factor-α was higher in patients with moderate-to-severe ED than in those with mild-to-moderate ED. A study by Shen et al[85] demonstrated a higher ED prevalence in patients with COPD. Details of studies describing the association between ED and COPD are presented in Table 3.[82,84–86]

In premenopausal obese women, FSD was correlated with obstructive sleep apnea only when nocturnal hypoxia was present.[87] This means that respiratory insufficiency seems more related to MSD than to FSD.

ASSOCIATION BETWEEN SD AND CANCER

There is no direct evidence showing that SD is a symptom of malignant neoplasia. However, several cancers could have systemic symptoms, such as weight loss and malaise, before the appearance of the tumor. Hence, hypoactive sexual desire disorder, ED, and FSD can be considered, bona fide, as possible symptoms of malignancy. In fact, it has been reported that sexual functioning and intimacy are affected by cancer and its treatment.[88,89] Cancer-related MSD includes ED, structural changes within the penis, ejaculatory dysfunction, and hypogonadism.[90] SD after cancer can develop at any phase during the disease course, which includes diagnosis, treatment stage, and after active treatment during post-treatment follow-up.[91]

In patients with prostate cancer, ED can develop as a consequence of radical prostatectomy treatment, from tumor progression, or from induced hypogonadism.[92] Similarly, the risk of ED appears to be greater in men with bladder cancer after treatment with radical cystectomy.[93] However, a study by Ong et al[94] showed that severe ED was common in patients with prostate cancer before any curative treatment; details are presented in Table 4.[92,94]

Although the incidence of penile cancer is low (0.58 of 100,000) in developed countries, the rates are five times higher in African, South American, and Asian countries.[95] Moreover, treatment of penile cancer negatively affected QoL in up to

Table 3. Association between COPD and ED

Study	Study type	Study population (mean age)	Outcome measurements	Outcome results
Chou et al, 2011[82]	Population-based cohort	17,302 patients; 13,836 in control group, 3,466 in asthma group (34.44 y)	ED occurrence	ED occurrence in asthma vs control group = 0.98% vs 0.58% ($P = .009$); incidence of ED in asthma group increased by 1.909-fold (95% CI = 1.276–2.856, $P = .002$) independent of age, number of clinical visits, and other comorbidities; risk of ED increased with frequency of clinical visits by patients with asthma
Kahraman et al, 2013[84]	Case-control	138 men; 70 in COPD group, 68 in control group (45–80 y)	ED occurrence and blood tests	Various degrees of ED prevalence in COPD (n = 55, 78%) and control (n = 38, 55.8%) groups ($P = .000$)
Shen et al, 2015[85]	Retrospective	57,928 men from Taiwan; 29,042 in COPD group, 28,886 in non-COPD group (61 y)	ED occurrence	ED prevalence higher in COPD group (HR = 1.52, 95% CI = 1.30–1.79) than in non-COPD group; cumulative ED incidence in COPD group was 1.29% higher than in non-COPD group ($P < .001$)
Chung et al, 2015[86]	Prospective	1,436 patients with ED from Osteoporotic Fractures in Men study (74.5–76.5 y)	Cardiovascular and respiratory mortality by ICD-10	Patients with ED had significantly increased risk of respiratory mortality (HR = 3.16, 95% CI = 1.46–6.81) and cardiovascular mortality (HR = 3.94, 95% CI = 1.77–8.76) compared with patients without ED after adjusting for chronic conditions, sociodemographics, and lifestyle factors

COPD = chronic obstructive pulmonary disorder; ED = erectile dysfunction; HR = hazard ratio; ICD-10 = *International Statistical Classification of Diseases, Tenth Revision*; OR = odds ratio.

Table 4. Association between cancer and ED

Study	Study design (follow-up)	Study population (mean age)	Outcome measurements	Outcome results
Johansson et al, 2011[92]	Population-based study (12.2 y)	400 patients with prostate cancer from SPCG-4 (77 y)	Physical symptoms, quality of life	Prevalence of ED was 84% (146 of 173) in radical prostatectomy group, 80% (122 of 153) in watchful-waiting group, and 46% (95 of 208) in control group
Ong et al, 2015[94]	Prospective cohort	699 patients with prostate cancer (63 y)	Baseline erectile function with localized prostate cancer	Before permanent seed brachytherapy, 335 patients (48%) reported no ED, 129 reported (17%) mild ED, 42 reported (6%) mild-to-moderate ED, 37 (5%) reported moderate ED, and 165 (24%) reported severe ED

ED = erectile dysfunction; SPCG-4 = Scandinavian Prostate Cancer Group-4.

40% of patients with decreased SD.[96] The prevalence of ED has been reported in 12% to 40% of men treated for testicular cancer, irrespective of the cancer treatment method.[97] In a study by Puhse et al,[98] SD was assessed in a group of 539 testicular cancer survivors, 32% of whom had ED. Hence, assessment of baseline ED is important before curative treatment of cancer to offer appropriate advice on the likelihood of preserving erectile function after treatment and to avoid patient dissatisfaction.[93]

Studies that have addressed SD in women with cancer have shown that cancer can impair sexual function in women. Although most studies (56%) had low to moderate quality, the mean score of the Female Sexual Function Index (FSFI) was lower than 20 at all cancer sites: 16.25 (pooled random effect, 95% CI = 14.91−17.58; I^2 = 14.5%) for colorectal cancer, 18.11 (95% CI = 14.45−21.77; I^2 = 97.8%) for gynecologic cancer, and 19.58 (95% CI = 17.64−21.53; I^2 = 90.9%) for breast cancer. The prevalence of FSD was higher than 60% at all cancer sites, with the highest value for gynecologic cancer (78.44%; 95% CI = 68.36−88.52; I^2 = 94.1%). Women with cancer had low FSFI scores, indicating a high prevalence of FSD. This demonstrated that FSD is a symptom of several female cancers.[99]

Pelvic exenteration surgery for the treatment of primary and recurrent pelvic malignancies, including rectal, gynecologic, and urologic malignancies, improves the overall survival rate but profoundly affects health-related QoL, such as sexual function. Studies have reported normal sexual function in women (50%−100%) preoperatively that was significantly disrupted post-operatively. Therefore, the profiling and understanding of health-related QoL, including baseline sexual function assessment, is integral to the long-term management of this patient cohort.[100] Future evidence will more robustly demonstrate that addressing and managing sexual and relational aspects in patients with malignant neoplasia will improve not only their QoL but also their reaction to treatments and overall survival.

OTHER DISEASES AND RISK FACTORS ASSOCIATED WITH SD

Several other diseases not discussed in this review have been linked to MSD and FSD (Table 5). Although acute or infectious diseases can directly affect sexual health, most illnesses listed in Table 5 are considered chronic NCDs. Very interestingly, their relation with SD is continuously increasing and new association data are continuously produced. These associative studies are robustly grounded on the described evidence that they share the same risk factors, mostly related to the same modifiable (the majority) or non-modifiable (genetic and age) factors. Risk factors associated with SD include genetics and age (non-modifiable) and many factors related to lifestyle, such as smoking, alcohol and drug consumption, lack of physical activity, and the wrong diet. SD in general and ED in particular are related to age as shown by the analysis of published works on the prevalence of SD by the International Consultation Committee for Sexual Medicine. Prevalences of ED were 1% to 10% in men younger than 40 years, 2% to 9% in men 40 to 49 years of age, and 20% to 40% in men 60 to 69 years of age, reaching the highest rate in men older than 70 years (50%−100%).[101]

Cross-sectional and prospective epidemiologic studies have shown an association between ED and obesity or overweight. In the MMAS, it was observed that obesity doubles the risk of having ED.[102] Subsequently, in the largest population study from the Health Professionals Follow-up Study in the United States, which included 31,724 men free of ED at baseline, obesity was associated with an increased risk of ED (relative risk = 1.3, CI = 1.2−1.4).[103]

Table 5. Taxonomy of 10 major causes of erectile dysfunction*[33]

Etiology	Illnesses
Systemic	Cancers and blood, chronic cardiac, pulmonary, liver, renal failure, infective, and parasitic diseases
Vascular	Atherosclerotic disease and related cvds
Endocrine	Hypogonadism, hyperprolactinemia, hypo- and hyperthyroidism, acromegaly, adrenal hypo- and hyperactivity
Metabolic	Obesity, metabolic syndrome, diabetes mellitus, hyperlipidemia, gout, and zinc deficiency
Immunologic	Aids, systemic sclerosis, and rheumatoid arthritis
Neurologic	Stroke, temporal lobe epilepsy, parkinson and alzheimer diseases, multiple sclerosis, Arnold-chiari and Guillain-barré syndromes, spinal cord injuries, arthritis, and peripheral neuropathies
Urologic	Peyronie's disease, priapism, pelvic, and penile trauma
Psychiatric	Depression and schizophrenia
Psychological	Environmental stress, anxiety, and widower's syndrome
Pharmacologic	Alcohol, illegal drug abuse, nicotine, antihypertensives, antidepressants, antipsychotics, anxiolytics, h_2 antagonists, antiandrogens, digoxin, clofibrate, etc

CVD = cardiovascular disease.
*The large majority of the listed illnesses also can provoke hypoactive sexual desire disorder in men and women and female sexual dysfunction. Furthermore, the large majority of these illnesses are non-communicable diseases.

Smoking causes oxidative stress and is considered a risk factor for ED.[104] Smokers were 1.5 times more likely to have ED than non-smokers.[105] Compared with never smokers, the odds ratios of ED for current smokers and previous smokers were 1.7 (95% CI = 1.2−2.4) and 1.6 (95% CI = 1.1−2.3), respectively, and increased with duration of the habit.[75] A meta-analysis of four prospective cohort studies and four case-control studies involving 28,586 participants showed that the overall odds ratios of ED were 1.51 (95% CI = 1.34−1.71) for current smokers and 1.29 (95% CI = 1.07−1.47) for former smokers compared with non-smokers.[106] Adherence to a Mediterranean diet was assessed and compared with FSFI scores in women with DM.[107] Women with DM and the highest adherence to the diet had a lower body mass index, showed a better metabolic profile, and had a lower prevalence of depression and metabolic syndrome.

Women with the highest score of adherence also had a lower prevalence of SD compared with women with lower tertiles (higher tertile = 47.6%; middle tertile = 53.9%; lower tertile = 57.8%; $P = .01$).[107] Hence, as largely demonstrated in men, in women with type 2 DM, evidence suggests that greater adherence to a fundamental environmental factor that dramatically influences NCS, such as the Mediterranean diet, is associated with a lower prevalence of MSD and FSD.

Projections for 2025 show a prevalence of approximately 322 million for ED and other SDs in men and women.[108] The largest projected increases are in the developing world (ie, Africa, Asia, and South America), mirroring the projections of NCDs owing to changes in pollutants and lifestyles[109,110] and further suggesting the link connecting modifiable risk factors, SDs, and NCDs.[111]

IMPLICATIONS OF DOHaD in relation to NCD and SD

The scope of the DOHaD concerns understanding the mechanism by which the early life environment can alter the epigenome, leading to long-term changes in disease, which is crucial in the development of interventional strategies to combat the rapid increase in NCDs.[112] The main focus of the DOHaD has been that environmental exposures during critical periods of developmental plasticity can cause subtle changes in certain biological functions that are not necessarily identifiable as pathologic but can increase the risk of disease and dysfunction later in life.[113] In such a case, functional changes can be considered markers of an increased risk of NCDs.

From the systems medicine perspective, NCDs are exquisitely multifactorial and risk factors leading to NCDs include measurable phenotypes such as hypertension, hypercholesterolemia, and obesity coupled with lifestyle factors such as smoking, poor diet, and insufficient physical activity. As reviewed here, a noticeably growing body of evidence links NCDs with SD, particularly ED, with the two conditions having similar risk factors.

From the DOHaD perspective, the onset of NCDs is influenced at different stages of the life course by a combination of genetic, epigenetic, and environmental factors. Although it has been proposed that the associations between fetal or infant growth and later adult disease occur as result of the pleiotropic effect of genes (non-modifiable stressors) transmitted from the mother to the child, maternally mediated environmental modulation of gene expression in offspring and gene-environment interactions (modifiable stressors) appear to be even more important than purely heritable genetic risk. There is growing evidence that epigenetic mechanisms (DNA methylation, histone modification, and non-coding RNAs) are responsible for tissue-specific gene expression during growth and development and that these mechanisms underlie the processes of developmental plasticity.[114] It is postulated that the adverse effect of maternal nutrition, particularly undernutrition exposure in utero, can cause increased risk of developing multiple causalities such as metabolic, neurodegenerative, and systemic diseases and very

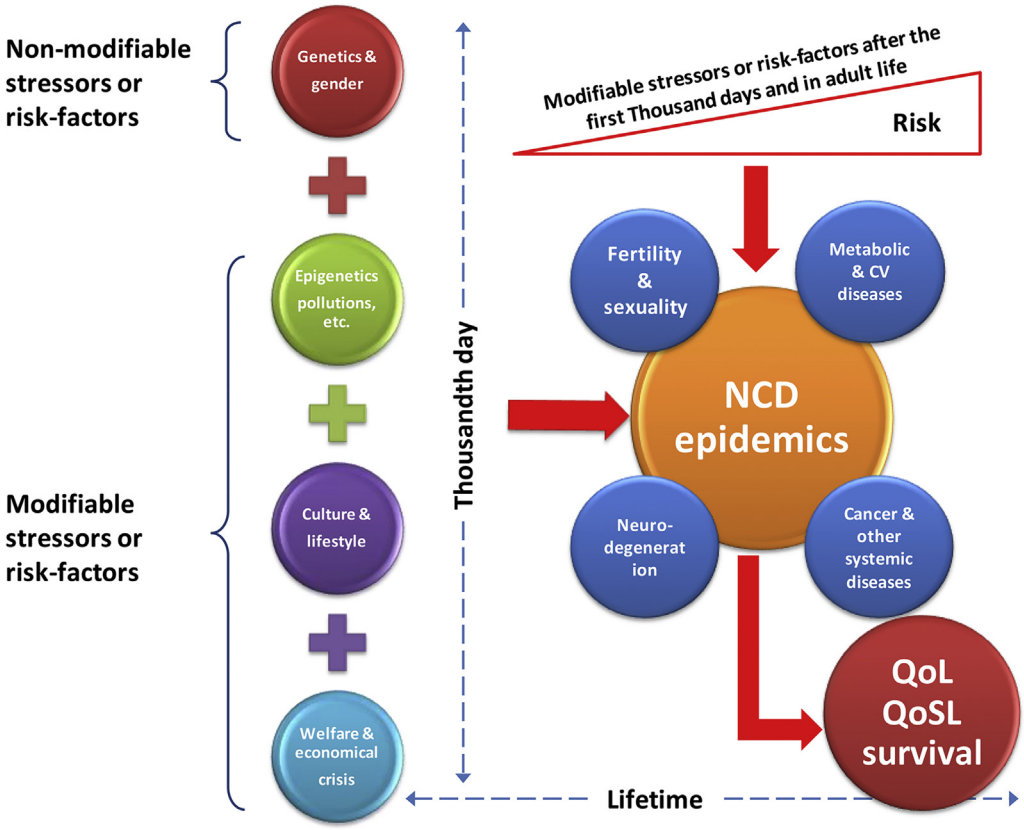

Figure 1. The Developmental Origins of Health and Disease theory: the timeframe of the association between NCDs and their risk factors. From the perspective of the Developmental Origins of Health and Disease theory, the risk of NCDs increases across the lifespan as result of decreasing plasticity and accumulative effects of inadequate responses to modifiable and non-modifiable stressors. The greatest increase occurs in adulthood because of modifiable lifestyle and cultural factors, in addition to overall welfare and economic crisis. However, the trajectory is set much earlier, being influenced by factors such as the mother's diet and body composition before and during pregnancy and fetal, infant, and childhood nutrition. NCD = non-communicable disease; QoL = quality of life; QoSL = quality of sexual life. Figure 1 is available in color online at www.smr.sexmed.org.

likely other aspects such as sexuality and fertility through induced epigenetic and phenotypic changes. A trans-generationally altered sperm genome will influence the epigenome and transcriptome of derived somatic cells, generating altered phenotypes that manifest as adult-onset disease states.[115,116] If the risk factors predisposing an individual to NCDs in formative years are the same as those in adulthood, then it could be hypothesized that the non-modifiable and modifiable stressors in the first 3 years of life also might affect the development of SD. Exposure to environmental toxicants during the first 1,000 days of life (and later on) also can lead to different epigenetic modifications, which have a strong correlation to predisposition to reproductive pathologies and might be transmitted to future generations. In fact, the motto of the Lorenzini Foundation (a US-Italy scientific community aiming to translate and link the latest international expertise in prevention and translational medicine) is "Beyond the First One Thousand Days and Healthy Aging," which means that the continued development of the human being after the first 3 years of life, with lifestyle conditions and factors, continue to play significant roles in reinforcing the risks for NCDs or act as important preventive measures to decrease risk factors.[117] Considering the identity of risk factors, the same can be inferred for sexual health.

The risk of NCDs increases across the lifespan as a result of decreasing plasticity and accumulative effects of inadequate responses to new challenges (modifiable stressors), as shown in Figure 1. The greatest increase occurs in adulthood from modifiable lifestyle and cultural factors, in addition to overall welfare and economic crisis, but the trajectory is set much earlier, being influenced by factors such as the mother's diet and body composition before and during pregnancy and fetal, infant, and childhood nutrition.

Therefore, a systems biology approach can be applied to understand the mechanism of MSD and FSD and thereby identify potential biomarkers for NCDs. In this approach, phenotypes of NCDs analyzed in an integrative manner using mathematical and statistical modeling can be correlated with biomarkers of SD by combining datasets from genomics, epigenetics, proteomics, transcriptomics, metabolomics, and metagenomics. The combination of high-throughput technologies, computational tools, and integrated knowledge bases for understanding the

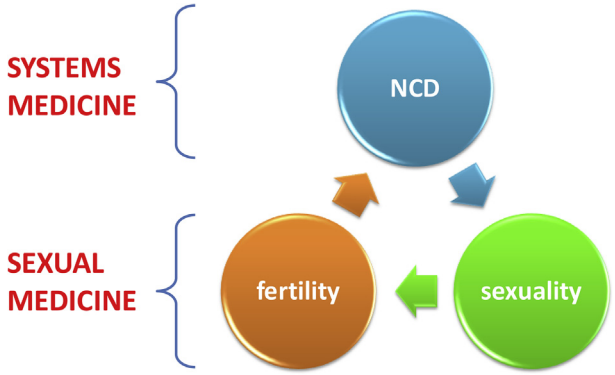

Figure 2. Proposed holistic link between systems and sexual medicine. The pathogenesis of NCD is studied by systems medicine, but NCD shares the same risk factors of sexual and reproductive dysfunctions studied by sexual medicine. NCD = non-communicable disease. Figure 2 is available in color online at www.smr.sexmed.org.

pathogenetic mechanisms, disease progression and remission, disease spread and cure, treatment responses and adverse events, and disease prevention at the epidemiologic and individual patient levels is the challenge of systems medicine.[118] Hence, application of systems medicine to sexual medicine is vital in combating the growing global burden of NCDs (Figure 2). This novel approach should give renewed emphasis to changing lifestyle habits to counteract SD and thus NCDs and vice-versa. For example, the risks of an impaired sexual life should be always highlighted in campaigns on smoking cessation or prevention in young and adult populations.[119,120]

SYSTEMS MEDICINE APPROACH FOR MANAGEMENT OF SD

Systems medicine in turn can work as a new instrument to increase science and knowledge in the relatively young field of sexual medicine. It is, in fact, characteristic of the systems medicine approach to use continuous and reciprocal feedback between clinical investigations and practice using statistical analysis and bio-mathematical models of pathogenetic mechanisms and the spread, progression, and cure of NCDs at the epidemiologic and individual patient levels.[121] The same approach should be used for sexual medicine, which has to evolve from systems medicine, which aims at a measurable improvement of patient health through systems-based approaches and practice.

There is another important likeness between systems and sexual medicines: the two forms face the same challenge because different cultures, societies and communities use different approaches and languages for the same pathogenetic mechanisms and (sexual) diseases. Therefore, systems medicine and sexual medicine need to develop so-called personalized medicine, or 4P medicine (ie, medicine that is predictive, preventive, personalized, and participatory),[122] especially with regard to approaches to disease prevention and personalized therapies. This concept has been recently claimed by the Coordinating Action Systems Medicine Consortium, which aims to function as a strategic managing and coordinating platform to develop a clear road map for the implementation of systems medicine across Europe[123] under the umbrella of the European Commission. The future will further demonstrate that sexual medicine needs the systems medicine approach to increase this scientific power and ability to improve QoL of the population and will further demonstrate how much systems medicine needs SD as a novel instrument to understand and prevent NCDs.

CONCLUSION

NCD management is essential to prevent premature deaths and disability and involves timely detection, screening, and treatment. Ample evidence has demonstrated that a holistic approach has to be adopted to combat NCDs. The management of NCDs has evolved and the paradigm of systems medicine is currently being explored. Through the literature reviewed in this article, the following items are the key drivers:

- A correlation between NCDs and SD has been derived. Hence, the application of systems medicine could be applied to the management of SD.
- A general awareness needs to be created in the masses by introducing the notion that SD shares not only the same risk factors and several pathogenetic mechanisms as NCDs but also all the prevention strategies in youth, adulthood, and old age.
- Moreover, if it can be demonstrated that the first 1,000 days are crucial not only for the development of NCD but also for SD by the identification of risk factors and pathogenesis common to these diseases and communicating, then this new powerful concept of DOHaD would demonstrate that early intervention and prevention are possible and effective in changing the destiny of general and sexual health.

A multidirectional approach that links systems medicine, DOHaD, NCDs, and sexual medicine might be used to develop some important medical innovations that use MSD, and probably FSD, as new, powerful, and virtually universal markers of systemic health and facilitate the prevention, diagnosis, and treatment of NCDs. This multilevel approach not only might have the potential to suggest novel avenues for the comprehensive management of NCDs in a sex-dependent manner but also might help the scientific community to better understand the relation between the systems biology approach and sexual medicine. Thus, the proof that systems medicine equals sexual medicine is demonstrated.

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