**Name of Journal:** *World Journal of Clinical Cases*

**Manuscript NO:** 56300

**Manuscript Type:** REVIEW

**Gender medicine: lessons from COVID-19 and other medical conditions for designing health policy**

Machluf Y *et al.* Gender medicine and adolescent health

Yossy Machluf, Yoram Chaiter, Orna Tal

**Yossy Machluf,** Shamir Research Institute, University of Haifa, Kazerin 1290000, Israel

**Yoram Chaiter, Orna Tal,** The Israeli Center for Emerging Technologies in Hospitals and Hospital-based Health Technology Assessment, Shamir (Assaf Harofeh) Medical Center, Zerifin 7030100, Israel

**Orna Tal,** Shamir (Assaf Harofeh) Medical Center, Affiliated to the Sackler Faculty of Medicine, Tel Aviv University, Zerifin 7030100, Israel

**Orna Tal,** Department of Management, Program of Public Health and Health System Administration, Bar Ilan University, Ramat Gan 5290002, Israel

**Author contributions:** All authors equally contributed to this paper with conception and design of the study, literature review and analysis, drafting and critical revision and editing, and final approval of the final version; Machluf Y conceived and prepared the figures.

**Corresponding author: Yoram Chaiter, MD, MSc, Academic Research, Senior Researcher,** The Israeli Center for Emerging Technologies in Hospitals and Hospital-based Health Technology Assessment, Shamir (Assaf Harofeh) Medical Center, Zerifin 7030100, Israel. [chaiter@bezeqint.net](mailto:chaiter@bezeqint.net)

**Received:** April 24, 2020

**Revised:** May 29, 2020

**Accepted:** August 12, 2020

**Published online:**

**Abstract**

Gender-specific differences in the prevalence, incidence, comorbidities, prognosis, severity, risk factors, drug-related aspects and outcomes of various medical conditions are well documented. We present a literature review on the extent to which research in this field has developed over the years, and reveal gaps in gender-sensitive awareness between the clinical portrayal and the translation into gender-specific treatment regimens, guidelines and into gender-oriented preventive strategies and health policies. Subsequently, through the lens of gender, we describe these domains in detail for four selected medical conditions: asthma, obesity and overweight, chronic kidney disease and coronavirus disease 2019. As some of the key gender differences become more apparent during adolescence, we focus on this developmental stage. Finally, we propose a model which is based on three influential issues: (1) investigating gender-specific medical profiles of related health conditions, rather than a single disease; (2) the dynamics of gender disparities across developmental stages; and (3) an integrative approach which takes into account additional risk factors (ethnicity, socio-demographic variables, minorities, lifestyle habits *etc.*). Increasing the awareness of gender-specific medicine in daily practice and in tailored guidelines, already among adolescents, may reduce inequities, facilitate the prediction of future trends and properly address the characteristics and needs of certain subpopulations within each gender.

**Key words:** Gender medicine; Adolescent health; Model; Risk factors; Guidelines and policy; Asthma; COVID-19; Obesity; Chronic kidney disease

Machluf Y, Chaiter Y, Tal O. Gender medicine: lessons from COVID-19 and other medical conditions for designing health policy. *World J Clin Cases* 2020; In press

**Core tip:** An accumulating body of evidence demonstrates gender-specific differences in medical conditions, in terms of prevalence, incidence, prognosis, severity and comorbidity. Yet, little has been translated into an approach to gender-specific treatments, guidelines and prevention strategies. The evidence and gaps are discussed by providing four examples: asthma, obesity, chronic kidney disease and coronavirus disease 2019. We propose a broader approach to gender medicine that integrates information regarding medical profiles of coexisting medical conditions, rather than focusing on a single disease, considers the dynamics of medical profiles across developmental stages, focuses on adolescence, paving the way for adulthood morbidity, and is adjusted to diverse risk factors, and hence tailored to diverse subpopulations.

**INTRODUCTION**

***The fundamentals and background of gender medicine***

Buoncervello and colleagues[[1](#_ENREF_1)] claimed that "biology of sex differences deals with the study of the disparities between females and males and the related biological mechanisms" where "the term gender refers to a complex interrelation and integration of sex–as a biological and functional determinant and psychological and cultural behaviors (due to ethnical, social or religious background)" as well as aspects related to preferences, views and values. Gender differences may also develop and change over time, as they are age-related. Biological differences between males and females are apparent even from the early stage of pregnancy, and become more pronounced with development. Fundamental gender variation exists not only at the whole organism level, organ system level, organ level, and tissue level but most likely also at the cellular and molecular levels[[2](#_ENREF_2),[3](#_ENREF_3)]. Gender differences are manifested in a wide range of fields such as: genetics, anatomy, physiology, biochemistry and metabolism, psychology, nutrition, behavior and sociology, exposure, diet and lifestyle. Differences have also been acknowledged in medicine–health status in general, and from disease states (occurrence and severity[[4](#_ENREF_4)]) to drug-related aspects (such as toxicokinetics and toxicodynamics[[5](#_ENREF_5)], as well as pharmacological response[[6](#_ENREF_6)]) and their outcomes in particular. Gender medicine focuses on the impact of gender and sex on human physiology, pathophysiology, prognosis, and clinical features (management, treatment and outcome) of diseases that are common to women and men. Clinical examples with broad applicability that highlight sex and gender differences in key domains, such as epigenomic modifiers, hormonal milieu, immune function, neurocognitive aging processes, vascular health, response to therapeutics, and interaction with healthcare systems have been recently reviewed[[7](#_ENREF_7)]. Therefore, here we will try to highlight other aspects, while emphasizing those related to adolescents. There are three main reasons for us to focus on adolescents: (1) gender differences, including diverse medical differences (developmental/anatomical, physiological, hormonal, psychological, behavioral *etc*.), become more apparent at this developmental stage; (2) currently, we  believe there is a lack of attention to gender differences at early stages, although those might contribute to gender differences in morbidity at later stages and may allow the medical community to trace the origin of gender differences in old age; and (3) our vast experience in studying gender-specific medical profiles among adolescents.

***A call for a paradigm shift in the approach of gender medicine***

In this review, we attempt to look at the accumulating body of evidence about the already known gender-specific differences in medical conditions–in terms of prevalence, incidence, prognosis, comorbidities *etc*.–and how these are translated into approaches to gender-specific treatments, guidelines and prevention strategies. The opening section of this article will provide a literature review on these three main aspects of health-related gender differences–namely: occurrence of medical conditions, treatment, and health policy. We will provide an overview on the extent to which research in these domains has developed over the years. In the main section of this article we will document the most important findings of these aspects of gender medicine in four chosen fields: asthma, obesity, chronic kidney disease and Coronavirus disease 2019 (COVID-19). In each of these fields, we will present the accumulated body of evidence related to gender medicine, and the gaps between these three aspects of health-related gender differences. In the last section of this article, we will introduce a broader, integrative, and novel approach to facilitate the formulation of an evidence-based, gender-oriented health policy to bridge these gaps and realize the full potential of basic and applied research and maximize the impact of the field of gender medicine. We rely on a model of transforming evidence generation to support the design of health policy and programs, as well as improved decision making about health and healthcare, at all levels: individual, communal, organizational, and national[[8](#_ENREF_8)] and adapt it to a gender-specific and age/race/socioeconomic-related model, to illustrate and illuminate a possible bridge between these pivotal, yet usually not well-connected steps.

Here, we call for a shift in the approach of gender medicine to three main issues: medical profile, age of subjects, and stratified populations. While the current approach examines each medical condition separately, the broader approach of a gender-specific medical profile or signature which takes into account diverse comorbidities and health conditions should be adopted. In addition, special attention should be given to health conditions among adolescents, as some of the key gender differences become more apparent at this developmental stage. Moreover, research at younger ages may provide evidence and insights on gender differences, at early stages of life, and may allow the medical community to trace the origin of gender differences which are known at older ages, and follow their course of development. This approach may indicate the need for gender-specific interventions, such as screening, diagnosis, continuous monitoring, treatment, guidelines, preventive strategies and health policies for both acute and chronic care. Such actions may achieve a better health status and impactful medical outcome, both during adolescence and later in life, not only for gender-specific medical conditions, but most importantly, for medical conditions that are not gender-specific. Lastly, to increase precision and generate tailored, high-resolution practical guidelines and health policy, we recommend analyzing additional independent key risk factors, such as race/ethnicity, diverse socio-demographic variables (socio-economic status (SES), parental education etc.), lifestyle habits etc. Hence, the characteristics and needs of certain subpopulations within each gender will be properly addressed.

**GENDER-SPECIFIC MEDICINE-WHAT HAS BEEN DONE TO DATE AND WHAT IS LACKING?**

Interest in gender differences related to medical conditions and health status has developed over the years. A search in the PubMed database (<https://pubmed.ncbi.nlm.nih.gov/>) revealed a total of 20944 publications, the first of them as early as 1966 (Figure 1). While until the mid-1980s no more than 10 articles were published each year, dozens of articles were published each year during the late 1980s, and the annual numbers steadily grew to over a hundred during the early 1990s, a few hundred during the 2000s, and over one thousand during the early 2010s, reaching approximately 2000 and more articles per year in recent years (Figure 1).

While most of the literature revolves around gender differences in the prevalence or incidence of medical conditions, only few studies–5007 publications to be precise–acknowledge gender-specific guidelines (596) or approaches to treatment (3575) or intervention (1372) of the same medical conditions among males and females. Furthermore, even fewer studies–3418 articles–deal with policy (621) or prevention strategies (2955) related to these gender-specific differences. A similar upward trend has also been observed in the numbers of such studies, yet the first articles were only published during the late 1970s and early 1980s, respectively, and the highest annual publication rates were approximately 600 and 400, respectively. Of note, a significant proportion of these articles only call for action, namely to convert the evidence for gender differences in health status and comorbidities into actual guidelines and treatments, as well as preventive strategies and health policy which is adapted to each gender, rather than proposing or studying those gender-oriented guidelines, strategies and policies.

Altogether, these trends suggest an increasing interest in studying differences in the occurrence and severity of health conditions among males and females. Following the slow initial accumulation of evidence, and more rapid accumulation in recent years, gender-specific guidelines for treatment or intervention programs have begun to emerge, as well as prevention strategies and health policies that consider each gender-disease pair specifically. There appears to be a fundamental understanding and recognition of the importance of formulating guidelines for treatments and medical policies based on the cumulative information, but in practice this has only been partially realized.

**FROM EVIDENCE FOR GENDER DIFFERENCES IN HEALTH CONDITIONS TO TREATMENT GUIDELINES AND HEALTH POLICY**

A sex-and gender-informed approach promotes discovery and expands the relevance of biomedical research. Issues of motivation, subject selection, sample size, data collection, analysis, and interpretation, considering implications for basic, clinical, and population research have been recently addressed and discussed[[9](#_ENREF_9)], as well as the consideration of sex disparities in preclinical studies including *in vitro* and *in vivo* approaches[[1](#_ENREF_1)]. Furthermore, the pursuit of gender differences in biomedical research has gained momentum, based on thoughtful study designs and deliberate methodologies to address gender disparities[[9](#_ENREF_9)].

Yet, almost simultaneously the premise of personalized medicine[[10](#_ENREF_10)] or precision medicine[[11](#_ENREF_11),[12](#_ENREF_12)] has emerged and became more popular, driven by novel and low-cost genetic technologies, rapid advances in computational power, massive, linked databases, and new targeted therapies, in concordance with the rising perception of individualism and patient autonomy. The gender approach in medicine has not been neglected in basic research and applied medicine, but rather it has been (or may be) incorporated into precision medicine approaches[[13-16](#_ENREF_13)] and translational medicine[[17](#_ENREF_17)], or into epidemiological and pathophysiological data as well as into information on treatment options and clinical outcomes[[18](#_ENREF_18)]. All these, in turn, may not only shed light on the basis and origin of clinical conditions, but may also shape and dictate actionable guidelines for diagnosis and detection, monitoring, treatment and intervention programs, drug development and administration, and facilitate the design of preventive strategies and health policy, which are all specific to subpopulations with regard to gender (and other factors such as age, risk factors etc.), and even individuals.

Gender-specific differences in health status have been acknowledged in the occurrence of diverse conditions such as cardiovascular diseases (CVD)[[19-22](#_ENREF_19)], diabetes[[23-26](#_ENREF_23)], renal diseases[[27](#_ENREF_27)], asthma[[28-30](#_ENREF_28)], autoimmune diseases[[31](#_ENREF_31)], migraine[[32](#_ENREF_32)], cancer[[33-36](#_ENREF_33)], spondyloarthritis[[37](#_ENREF_37)], multiple sclerosis[[38](#_ENREF_38),[39](#_ENREF_39)], Alzheimer’s disease[[40-42](#_ENREF_40)], sleep apnea and sleep disordered breathing[[43](#_ENREF_43)], epilepsy[[44](#_ENREF_44)], stroke[[45](#_ENREF_45)], autism[[46](#_ENREF_46)], depression[[47](#_ENREF_47)], anxiety[[48](#_ENREF_48)], addiction and substance use[[49](#_ENREF_49),[50](#_ENREF_50)], and others. Calls or recommendations for further studies to establish guidelines for gender-specific treatment and health policy have been recorded in many of these and other fields. Nevertheless, they have only been partially realized–in terms of both the medical conditions (in only certain types and to a limited degree) and the target population (mainly among adults and the elderly).

Hereafter, four medical conditions have been chosen and the diverse aspects of gender differences among children and adolescents–from occurrence to treatment and policy–will be described. The criteria and incentives for choosing the medical conditions–asthma, obesity, chronic kidney disease and COVID-19 were: (1) conditions which are relatively frequent among adolescents; (2) conditions that are of great interest to the medical and scientific communities worldwide; (3) the impact of the condition–both in term of medical aspects, individuals' level of functioning and life quality as well as economic burden on healthcare systems, their preparedness and quality of service–at present on adolescents and in the future, as individuals mature and age, thus providing the opportunity to investigate how gender differences evolve with time, and accordingly to establish gender-sensitive guidelines and policies; (4) availability of data on gender differences among adolescents; and (5) our own experience and expertise in studying these conditions with regard to gender-specific medical profiles. Of note, not all of the selected conditions answer all of these criteria. We do not aim to provide a comprehensive review on each condition, but to depict key evidence for gender disparities and the existing gap in converting it into gender-specific or gender-adjusted treatment and health policy.

***Asthma***

Asthma is a multifaceted, complex and common chronic respiratory disease that affects over 330 million people worldwide. Its prevalence, clinical impact upon quality of life and healthcare expenditure, as well as mortality and morbidity statistics, provide a complete and relevant indication of its significance and global burden[[51-53](#_ENREF_51)]. Its pathophysiology includes abnormalities of the immune regulation of allergic, inflammatory and neuroendocrine responses[[54](#_ENREF_54),[55](#_ENREF_55)]. It is characterized by intermittent bronchial hyper-responsiveness and reversible airway obstruction, yet presents with multiple clinical forms and levels of severity.

A notable sex disparity has been observed in asthma prevalence, incidence, severity, hospitalization rate and duration, being more common and severe in boys during early childhood, equalizing during adolescence, and having female predominance in adulthood[[56-59](#_ENREF_56)]. The role of sex hormones, genetic predisposition and comorbidities in airway inflammation, smooth muscle contraction, mucus production and airway mechanics has been demonstrated[[28](#_ENREF_28),[60](#_ENREF_60)]. Delineating the relevant pathways in animal models as well as human subjects with various phenotypes of asthma will help determine whether women with asthma should take (or avoid) hormonal contraceptives as well as predict changes in asthma symptoms during life phases, including pregnancy and menopause, when sex hormone levels change dramatically [[29](#_ENREF_29),[30](#_ENREF_30)].

Alongside asthma symptoms and severity, asthma comorbidity also places a significant burden on individuals and the healthcare system with higher rates of hospitalization, emergency department visits and ambulatory care claims among individuals with asthma compared to those without asthma[[61-63](#_ENREF_61)]. Cross-sectional surveys and small cohorts support the relationship of asthma[[64-68](#_ENREF_64)], particularly the severe asthma phenotype[[69](#_ENREF_69),[70](#_ENREF_70)], with diverse comorbidities such as upper airway diseases, neurologic disorders including migraine[[71](#_ENREF_71)] and psychological dysfunction, diverse gastrointestinal diseases, laryngeal dysfunction, pulmonary and bronchial diseases, atherosclerotic cardiac disease and circulatory disorders, dermatologic conditions, connective tissue/rheumatic diseases, metabolic disorders and hormonal imbalance, immunologic and hematologic disease, obesity and overweight[[72](#_ENREF_72),[73](#_ENREF_73)], sleep apnea and chronic pain conditions. Cluster analyses of asthma-related comorbidities have identified diverse profiles and clinical asthma phenotypes in children and adults[[74-76](#_ENREF_74)]. These comorbidities have been shown to be more prevalent among asthmatic subjects and some may be related to a more severe form of asthma or refractoriness to treatment, and may influence its clinical manifestation and treatment response, impair health-related quality of life and increase demand on resources. The associations of specific asthma phenotypes with specific comorbidities and their impact on asthma control and management have been investigated[[70](#_ENREF_70),[77](#_ENREF_77),[78](#_ENREF_78)], as such comorbidities may be coincidental findings or they may contribute directly to asthma severity[[79](#_ENREF_79)] and to the difficult-to-treat phenotype[[70](#_ENREF_70)]. However, in most studies the gender approach was not applied.

Recently, we employed a comparative approach to characterize mild asthma and moderate-to-severe asthma in comparison to subjects without asthma among Israeli adolescent males and females separately, while examining secular trends and relationships with sociodemographic variables and anthropometric indices[[80](#_ENREF_80)], as well as coexisting medical conditions[[81](#_ENREF_81)]. These studies not only strengthened the growing body of evidence supporting the notion that perhaps different mechanisms and probably etiological bases are involved in the pathogenesis of mild compared to moderate-to-severe asthma, but they also highlighted the differences between young males and females with regard to sociodemographic risk factors associated with asthma development and the medical signature or profile (of either mild or moderate-to-severe asthma).

A diagnostic and management algorithm for assessing comorbid conditions in patients with severe asthma has been outlined[[70](#_ENREF_70" \o "Bardin, 2018 #832)]. Additionally, identifying gender-specific risk factors for asthma among both young and adult populations[[80-84](#_ENREF_80)] may have potential gender-specific diagnostic, therapeutic, prognostic and preventive implications for reducing the burden of asthma itself and its associated comorbidities. These are even more critical considering the 'gender shift' in disease occurrence from childhood to adolescence and maturity.

Nevertheless, despite the vast and diverse body of data on gender-specific differences in asthma development that have accumulated in recent years, data on studies or programs aimed at differentially dealing with asthma among (young or elderly) males and females–from diagnosis, to monitoring the disease and its progression, through investigating possible different treatment managements and responses to drugs, and to preventive strategies and health plans–have not been described.

***Obesity***

During recent decades, mean body mass index (BMI) and above normal BMI–i.e. overweight and obesity–in children and adolescents–have increased in most countries and regions of the world, among both males and females[[85](#_ENREF_85),[86](#_ENREF_86)]. Overweight and obesity are the result of complex relationships between genetic and sociodemographic factors and cultural influences. Reduced physical activity, dietary habits and food marketing practices are the most commonly suggested postulated causes of the obesity epidemic, although evidence supporting other putative contributors has also been found[[87](#_ENREF_87)]. Of note, agreement was sought among six indicators (BMI, triceps and subscapular skinfolds, the sum of four skinfolds, waist circumference and percentage body fat determined by bioelectric impedance analysis) used to classify youth as obese, yet it changes considerably with age and between genders[[88](#_ENREF_88)]. It seems that regardless of the threshold or definition, the estimates of severe obesity are higher among boys than among girls[[89-91](#_ENREF_89)], although the evidence is not conclusive[[92](#_ENREF_92)].

Being overweight or obese in childhood and adolescence is associated with greater risk and earlier onset of chronic disorders such as type 2 diabetes, metabolic syndrome, CVD and a variety of other comorbidities[[86](#_ENREF_86),[93-95](#_ENREF_93)], including hyperlipidemia, hypertension, and abnormal glucose tolerance[[96](#_ENREF_96)]. Moreover, childhood and adolescent obesity, mainly among girls, is associated with adverse psychosocial consequences[[86](#_ENREF_86)], social exclusion and depression[[96](#_ENREF_96),[97](#_ENREF_97)], as well as lower educational attainment[[98](#_ENREF_98),[99](#_ENREF_99)], lower income and increased rates of household poverty[[99](#_ENREF_99)]. Not only is overweight in adolescent subjects associated with increased risks of adverse health effects–only some of which are common to both males and females, and not to the same extent (see below)–it may also be associated with an increased risk of mortality among men, but not among women[[100](#_ENREF_100)]. Furthermore, the number of years living with obesity is directly associated with the risk of mortality[[101](#_ENREF_101)]. Recently, an algorithm that uses combinations of extractable electronic health record indicators and determines provider attention to high BMI and associated medical risk has been developed and validated[[102](#_ENREF_102)].

The associations between obesity and a wide range of comorbidities differ between genders, for example: migraine[[103](#_ENREF_103)], depression, eating disorders, anxiety and other mental disorders[[104](#_ENREF_104),[105](#_ENREF_105)], sleep apnea[[106](#_ENREF_106)], hypertension[[107](#_ENREF_107),[108](#_ENREF_108)], atrial fibrillation[[109](#_ENREF_109)], certain cancers etc. While most gender-specific differences in obesity-related comorbidities have been investigated and documented in adults, one cannot exclude the possibility that these, at least partially, reflect differences in health problems among obese children and adolescents. Profound differences between the medical profiles, or health condition signatures, of obese males and females were recently obtained (alongside common risk factors) for Israeli adolescents: obesity was associated with higher risk for hyperlipidemia, diabetes and mental disorders and lower risk for pre-hypertension only in males, whereas it was associated with a higher risk for micro-hematuria only in females, and differences in the magnitude of associations were also demonstrated[[4](#_ENREF_4)]. This study not only uncovered novel associations between BMI categories and medical conditions, but also enabled a portrayal of the medical signature of each gender–BMI group, and revealed the gender differences within each BMI category, while providing a broader view on health-status-compromising medical conditions, representing approximately 90% of all medical conditions among Israeli adolescents[[110](#_ENREF_110)]. Recently, the gender-specific associations between obese adolescents with cardiovascular and non-cardiovascular mortality in midlife were investigated[[111](#_ENREF_111)]. Furthermore, gender-biased access to deceased donor kidney transplantation was observed among obese patients, as obesity reduces the likelihood of being listed for deceased kidney donor transplantation, especially among women[[112](#_ENREF_112)].

Altogether, the rising prevalence of elevated BMI and its burden [[113](#_ENREF_113)]–in terms of health, social and economic consequences[[99](#_ENREF_99),[114-117](#_ENREF_114)]–highlight the local and international need for a continued focus on the surveillance of BMI and the identification, implementation, and evaluation of evidence-based interventions to address this problem generally, and specifically for each gender.

It is widely accepted and recommended that conservative approaches such as intensive, family-based lifestyle modification/behavioral therapy for weight management should be a prerequisite for all obesity-aggressive interventions (including medications and invasive procedures such as bariatric surgeries, gastric bypass, and gastric banding), for the general population, and particularly for children and adolescents[[118](#_ENREF_118)]. Obesity control and prevention programs in children and adolescents mainly involve diet/nutrition and physical activity, education, multi-component lifestyle interventions, and community or family involvement or friends' support for eating and exercise[[119-125](#_ENREF_119)]. There is more evidence that obesity prevention programs produce larger effects for females than males[[126](#_ENREF_126)], although this difference is usually non-significant[[122](#_ENREF_122)]. Moreover, gender differences have also been observed in obese people’s preferences, perceived value and willingness to pay for weight loss, lifestyle changes and reduction of long-term risks to health[[127](#_ENREF_127)]. For example, female participants providing open-ended responses included wanting to have a baby, not wanting to embarrass their children, physical pain, quality-of-life improvements, and stigma, while males’ responses were associated with health insurance coverage and better employment opportunities[[127](#_ENREF_127)]. Policy makers should assess compliance and prioritize treatment opportunities by analyzing these aspects, and differentially refer young males and females to relevant programs that are adjusted to population characteristics and needs, including gender-related issues. Yet, none of this is implemented in practice.

Specific criteria for integrating overweight into routine preventive screening of adolescents have been determined[[128](#_ENREF_128)], and recommendations that provide practical guidance to pediatric clinicians who evaluate, treat and prevent overweight and obesity in children and adolescents have been developed[[129](#_ENREF_129),[130](#_ENREF_130)]. Certain medical associations also provided physicians with a comprehensive and multidisciplinary protocol for guiding and personalizing innovative obesity care for safe and effective weight management[[118](#_ENREF_118),[131](#_ENREF_131)]. Yet, none of these guidelines or recommendations consider gender differences.

Specific national calculations for adolescent obesity plans and policy have been conducted in a number of countries, such as Germany[[132](#_ENREF_132)] and Australia[[133](#_ENREF_133)]. Policy directives concerning childhood obesity combine medical effectiveness at the individual level with cumulative investment requirements at the population level that are expected to cause growth in healthcare expenditure[[134](#_ENREF_134)]. Gender differences in the economic impact of obesity have been estimated by quality of life, years of life lost[[135](#_ENREF_135)] and hospitalization costs[[136](#_ENREF_136)] which are essential for population decision making (in comparison to guidelines to treat the individual patient) and policy. This would provide a platform for priority setting of interventions to prevent and treat obesity, based on value gained for investment, aiming to increase health and reduce costs of secondary implications. Social determinants, such as the burden to minorities[[137](#_ENREF_137)], low income countries[[138](#_ENREF_138)] or deprived populations, have already been inspected through the gender lens.

***Chronic kidney disease***

Chronic kidney disease (CKD) is currently defined by abnormalities of kidney structure or function. It is characterized by persistent renal damage and loss of nephron mass and glomerular function that may lead to progressive decline and even loss of renal function over time. The condition may progress from early disease to advanced stages that require kidney replacement therapy (KRT)[[139](#_ENREF_139)]. This common disorder is a major risk factor for end-stage renal disease (ESRD), which is the endpoint of chronic renal disease, as well as CVD. Through these effects it contributes markedly to the global burden of morbidity and mortality[[140](#_ENREF_140" \o "Lv, 2019 #1134)]. Additionally, CKD, especially in later stages, may cause chronic anemia[[141](#_ENREF_141)], mostly due to a lack of erythropoietin, osteoporosis[[142](#_ENREF_142)] and cognitive impairment[[143](#_ENREF_143)]. It has been recognized as a leading public health problem worldwide. The age-standardized global prevalence of CKD stages 1-5 in adults aged 20 and older has been estimated at 10.4% in men and 11.8% in women[[144](#_ENREF_144)], and recently it was updated upwards[[140](#_ENREF_140)]. However, the prevalence of CKD shows wide variation between and within specific geographic locations – it is higher especially in low - and middle-income countries–due to both true regional differences in CKD prevalence as well as technical and methodological issues related to measurement and definition[[145](#_ENREF_145)]. There is limited epidemiological information on the prevalence and incidence of pediatric CKD, particularly in its early stages, since it is often asymptomatic and therefore under-diagnosed and under-reported[[146](#_ENREF_146)]. The currently available data are not only limited but also imprecise, and flawed by methodological differences between the various sources[[147](#_ENREF_147)]. In Europe, the prevalence of CKD among children aged < 20 ranged from ca. 56 to 75 per million of the age-related population (registries spanning the period 1975-2008), with predominance of males (male/female ratio ranging from 1.3:1.0 to 2.0:1.0)[[146](#_ENREF_146)]. While in Latin America the corresponding prevalence is lower (~42 per million of the age-related population) and data from the Middle East are fragmented[[146](#_ENREF_146)], there is actually no comparable information available from the United States[[147](#_ENREF_147)].

Cobo *et al*[[148](#_ENREF_148)] nicely summarized the issues related to CKD and gender differences: "Men and women with CKD differ with regard to the underlying pathophysiology of the disease and its complications, present different symptoms and signs, respond differently to therapy and tolerate/cope with the disease differently". Importantly, the lack of inclusion of women in randomized clinical trials in nephrology was noted; therefore, gender differences in CKD pathophysiology, progression, management, treatment and outcome should be carefully considered[[148](#_ENREF_148)].

Several risk factors in childhood and adolescence have been associated with increased risk for future ESRD, including: persistent asymptomatic isolated microscopic hematuria[[149](#_ENREF_149)], hypertension and pre-hypertension[[150](#_ENREF_150),[151](#_ENREF_151)], overweight and obesity[[152](#_ENREF_152),[153](#_ENREF_153)], and a history of clinically evident kidney disease in childhood, even if renal function was apparently normal in adolescence[[154](#_ENREF_154)]. In all these studies, gender differences, if they existed, were not statistically significant.

Different gender trajectories of CKD progression in children and adolescents have been reported in a few studies, although the evidence is not conclusive. Among glomerular patients, faster progression of CKD was found in females[[155](#_ENREF_155)], whereas among non-glomerular patients no significant gender difference was obtained[[155](#_ENREF_155)] or even faster progression of CKD was noted in males[[156](#_ENREF_156)]. In adults, women have lower risk of CKD progression, and hence ESRD (despite men's lower prevalence of CKD), as well as lower risk of death compared with men[[157](#_ENREF_157)]. Differences in hormone levels (protective effects of estrogens and/or damaging effects of testosterone) together with unhealthier lifestyles, might cause kidney function to decline faster in men than in women[[158](#_ENREF_158),[159](#_ENREF_159)]. Furthermore, hyperuricemia has been shown to be an independent risk factor for faster CKD progression in children and adolescents, but only among males, who seem to tolerate higher levels of uric acid than females[[160](#_ENREF_160)]. Gender differences in hypertension control, particularly in the early stages of CKD, may also contribute to disparities in CKD progression, as it has been shown that African American men with CKD have poorly controlled hypertension compared with African American women[[161](#_ENREF_161)].

Gender-specific disparities have also been observed in the treatment of CKD[[148](#_ENREF_148),[158](#_ENREF_158),[159](#_ENREF_159),[162](#_ENREF_162)]. More men undergo dialysis or KRT than women, despite the fact that more women are affected by CKD, especially stage G3 CKD. Men are also referred earlier for KRT than women. The relative difference between men and women initiating and undergoing KRT has remained consistent over the last five decades and in all studied countries. Yet, the male-to-female ratios, calculated for incident and prevalent KRT patients, increase with age, showing consistency over decades and for individual countries. Although women are also less likely than men to receive kidney transplants, they are more likely to donate a kidney. Additionally, gender differences in preferences have been noticed, as elderly women seem to prefer conservative care over KRT. Although access to living donor kidneys seems equal, women have reduced access to deceased donor transplantation. Dissimilarities between the genders are also apparent in the outcomes of CKD treatment. In patients with pre-dialysis CKD, mortality is higher in men than in women; however, this difference disappears for patients on KRT. Moreover, quality of life while on KRT is poorer in women than in men, as the former report a higher burden of symptoms.

Effective CKD prevention policies begin with the identification of CKD risk factors in the population, i.e. accurately determining the incidence and prevalence of CKD while considering the distribution and burden of diverse risk factors. Then, appropriate targeted mitigation strategies should be developed, including early screening and treatment for populations or individuals with CKD risk to prevent the onset and delay the progression of the kidney disease[[163](#_ENREF_163)]. Moreover, practical clinical guidelines, a prevention program and policy for CKD management and treatment, as well as research, should stem from an approach that recognizes and addresses CKD as a national public health problem beset by inequities in incidence and prevalence, and complications across gender, as well as other risk factors such as race/ethnicity and SES[[159](#_ENREF_159),[164](#_ENREF_164)]. However, such an approach has been largely neglected[[148](#_ENREF_148)], and all aspects of CKD–from clinical guidelines, through recommendations for management, referral to a preventive program, design of health policy, and research–are made in a gender-blind manner[[148](#_ENREF_148),[159](#_ENREF_159)], despite the wide range of gender disparities related to underlying CKD pathophysiology, disease symptoms and signs, progression and complications, management, response to therapy and its outcome[[148](#_ENREF_148)].

***Severe acute respiratory syndrome COVID-19***

Policies and public health efforts have not addressed the gender-related impacts of disease outbreaks, which are both physically and socially constructed[[165](#_ENREF_165)]. The response to COVID-19 appears no different, as no global health institution or government in any affected country has conducted a gender analysis of the outbreak[[166](#_ENREF_166)].

The outburst of a pneumonia-like disease with an unknown etiology in Wuhan, China, in mid-late December 2019[[167-169](#_ENREF_167)] has become a global pandemic that poses a significant threat to global health[[170](#_ENREF_170)]. It was later found to be caused by the pathogen of the coronavirus clade termed severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)[[171-174](#_ENREF_171)]. People at risk for COVID-19, in terms of disease frequency, mortality or both, have been characterized as having pre-existing diseases such as hypertension, CVD, diabetes, chronic respiratory disease, cancer,[[175](#_ENREF_175)] and elevated BMI, mainly obesity[[176](#_ENREF_176)].

Although the disease has only recently erupted and spread, early studies have already indicated noticeable differences between males and females[[177](#_ENREF_177)]. First, there might be a gender predisposition to COVID-19, with men more prone to being affected[[178](#_ENREF_178)], as male prevalence ranges from approximately 55%[[168](#_ENREF_168),[179](#_ENREF_179),[180](#_ENREF_180)] to 67%[[181](#_ENREF_181),[182](#_ENREF_182)] and up to approximately 75%[[167](#_ENREF_167),[183](#_ENREF_183)], depending on the country, disease severity and method of diagnosis. Overall, the male to female ratio is 2.7:1[[184](#_ENREF_184)], which is quite similar to the ratio detected in the outburst of Middle East Respiratory Syndrome Coronavirus (MERS-Cov) in 2012. The reduced susceptibility of females to viral infections could be attributed to enhanced innate and adaptive immune responses in females driven by chromosome X and sex hormones[[185](#_ENREF_185)], lower density (or expression level) of angiotensin-converting enzyme 2 (ACE-2), which is the entry receptor for the COVID-19 virus, in the lungs of females compared to males[[186](#_ENREF_186)], or maybe smoking habits and their effects on increased airway expression of ACE2[[187](#_ENREF_187),[188](#_ENREF_188)], although the smoking effect should be validated[[186](#_ENREF_186)]. Of note, in a few studies the gender differences in the number of cases, if they existed, were not statistically significant[[166](#_ENREF_166),[189](#_ENREF_189),[190](#_ENREF_190)], and the differences have been shown to possibly change with age[[191](#_ENREF_191)]. In general, only a few studies have provided precise data stratified by age group and gender [[192](#_ENREF_192)]; this may be a major hurdle to evidence-based decision making and policy design[[193](#_ENREF_193)].

Regardless of susceptibility, there seem to be gender differences in mortality from and vulnerability to the disease[[166](#_ENREF_166),[176](#_ENREF_176)], as current evidence suggests that male gender is also a risk factor for a worse outcome of COVID-19. Namely, men may be more prone to higher severity and mortality, independent of age, susceptibility and pre-existing comorbid risk factors, among the general infected population[[194](#_ENREF_194)] and particularly among severely ill (or worse) patients and those who need management in intensive care units[[167](#_ENREF_167),[195](#_ENREF_195)] and invasive mechanical ventilation[[176](#_ENREF_176)]. In contrast, another study found no gender differences among patients in intensive care units or in mortality rate[[189](#_ENREF_189)]. Furthermore, patients with refractory COVID-19 were also more likely to be males, and male gender also predicted poorer treatment efficacy compared to women[[196](#_ENREF_196)].

In addition, indirect effects of COVID-19 also exhibit gender differences. For example, women in the hardest hit areas of China reported significantly higher posttraumatic stress symptoms (PTSS), compared to men, during the COVID-19 outbreak[[197](#_ENREF_197)].

Naturally, most of the research to date has focused on adults and the elderly, who are more prone to and affected by the disease. In general, children are less affected[[198](#_ENREF_198),[199](#_ENREF_199)] and tend to have a milder clinical course, yet the reported proportion of male children is approximately 55% or higher[[200-202](#_ENREF_200)]. Data on children and adolescent patients with COVID-19 have just begun to accumulate[[202](#_ENREF_202),[203](#_ENREF_203)].

Although data on gender differences are limited, and have not yet been integrated into guidelines and recommendations for disease screening, management and public policy, evidence for the consideration of gender differences has already emerged. For example, exploration of serial intervals, which refers to the time interval from symptom onset of a primary case (infecting) to that of a secondary case (infected), by regression models has accounted for gender-specific differences[[204](#_ENREF_204)]. Gender has also been integrated into a classifier prediction model to predict the status of recovered and dead COVID-19 patients[[205](#_ENREF_205)]. Nevertheless, to date, the international and national responses of countries dealing with the COVID-19 pandemic have neither considered nor addressed gender differences such as "gender norms, roles, and relations that influence women's and men's differential vulnerability to infection, exposure to pathogens, and treatment received"[[166](#_ENREF_166)]. Moreover, these factors may also differ among different groups of women and men, based on age, ethnicity/race, etc. and therefore should also be considered and integrated into guidelines and health policies.

**A BROAD AND INTEGRATIVE APPROACH TO EVIDENCE-BASED, GENDER-ORIENTED HEALTH POLICY**

Herein, we have reviewed diverse aspects of gender-specific differences related to different health conditions among adolescents, and the gap between evidence and its implementation into practical guidelines, recommendations for disease management and design of preventive strategies, and public health policies. In the next section, we provide additional evidence for this gap in diverse domains and discuss the current barriers. Then, we highlight a few emerging and influential key themes (detailed below) that should be considered and integrated into a broader approach to gender medicine to inform evidence-based, gender-oriented health policy:(1) Incorporating diverse risk factors (ethnicity, socio-demographic variables, minorities, residence, education, lifestyle habits *etc*.), in addition to gender, in order to better characterize the needs of sub-populations and properly address their needs; (2) Investigating gender-specific medical profiles of related health conditions, rather than a single disease; (3) The dynamics of gender disparities across developmental stages; and (4) The different levels of analysis: individual, communal, regional, national and global levels.

Lastly, we reflect on this broader approach, and on its application and implications.

***The overall picture: difficulties and barriers to translating medical evidence into guidelines and health policy***

Gender-specific medicine is the study of how diseases differ between men and women in terms of occurrence, clinical signs, therapeutic approach and management, prognosis, psychological and social impact, prevention and research. Despite the urgency of basic science and clinical research to increase our understanding of the gender differences of diseases, it is a neglected dimension of medicine and not included in most guidelines[[206](#_ENREF_206),[207](#_ENREF_207)]. To date, some attention to gender differences has been given mainly to certain clinical areas of medicine, many of them related to older populations, such as CVD, oncology, pharmacology, osteoporosis, pulmonary diseases, gastroenterology, hepatology, nephrology, autoimmune diseases, endocrinology, hematology, and neurology[[206-208](#_ENREF_206)]. In some of these medical fields, guidelines have been only partially adopted to include a certain degree of gender orientation. However, implementation is still far from optimal. For example, autoimmune hepatitis guidelines are considered gender-specific; however, they are driven by individual genetic fingerprints, and do not draw a clear border between men and women[[209](#_ENREF_209)]. Existing gender-adjusted treatment guidelines are still not completely applied, for example, guidelines have not been equally implemented for hypertension[[210](#_ENREF_210)], for myocardial infarction[[211](#_ENREF_211)] and for acute coronary syndrome[[212](#_ENREF_212),[213](#_ENREF_213)]. Access to dialysis treatment and the types of treatments employed for kidney diseases differ by gender[[214](#_ENREF_214),[215](#_ENREF_215)] (as well as by age, race, ethnicity and SES[[215](#_ENREF_215),[216](#_ENREF_216)]). Even if already integrated into current guidelines, such as those of CVD, guidelines still require gender-based revision[[19](#_ENREF_19)]. Only a small proportion of Canadian clinical practice guidelines contain gender-related diagnostic or management recommendations, recommendations for gender-specific laboratory reference values, or refer to differences in epidemiologic features or risk factors[[217](#_ENREF_217)]. Moreover, developers of clinical practice guidelines have yet to endorse a consistent and systematic approach for considering gender-specific information in these guidelines, such as in the case of CVD[[218](#_ENREF_218)]. In addition, epidemiological research data, which are relevant to the local population, and stratified by gender and other key variables, should be transformed from a research setting into a format that could be used by policy developers to support strategies encouraging healthy lifestyle choices and service planning within local government. For instance, data exchange supported by a population statistics company can serve as a conduit to keep regional policy makers informed by local evidence (according to age, sex and residence/suburb), rather than by a national or state health survey, in order to optimize potential intervention strategies[[219](#_ENREF_219)]. Recently, barriers to the development of sex/gender-sensitive guidelines have been identified[[220](#_ENREF_220)], including the increasing complexity of guidelines, the lack of availability and quality of gender sensitive evidence, the shortage of resources, and deficiencies in awareness/knowledge. In contrast, policies and standards from guideline organizations are conceived as facilitators. Addressing these barriers–national/social, organizational and individual ones–may create a basis for potential solutions and tools to achieve behavioral change in the development of gender-sensitive guidelines in the future[[220](#_ENREF_220)].

Gender-specific healthcare will need to cope not only with clinical-epidemiological aspects, but also with education and preparedness of hospitals, healthcare professionals and the entire healthcare ecosystem. This implies that concepts of sex and gender health should be embedded into medical curricula related to education, training and professionalism of current and future healthcare professionals[[221](#_ENREF_221)], as well as emergency medicine education[[222](#_ENREF_222)], in light of the important implications of gender for changing the clinical practice of emergency care[[223](#_ENREF_223)]. A global action initiative was convened as a workshop to assemble the available knowledge on gender-sensitive public health and identify structural influences on practice implementation, resulting in the definition of overarching implementation strategies and principles[[224](#_ENREF_224)]. Both gender norms[[225](#_ENREF_225)] and gender-equality policies[[226](#_ENREF_226)] may influence and impact approaches to gender health and women’s health throughout their lifetime and gender inequalities in health, including care demands. This may necessitate correction and redesign of gender-equality policies and effective gender-related health policies, as well as health treatment and services for women, which in turn may require additional budgets.

***Emerging themes to be integrated into a broader gender medicine approach***

Men and women are not homogeneous populations due to adverse and combined effects originating from the interplay between genetics, environmental factors and socio-cultural background. However, gender is only one of a few independent risk factors including race/ethnicity, age, and diverse socio-demographic variables (SES, parental education etc.)[[227-229](#_ENREF_227)]. Lifestyle habits and personal preferences also have an impact on both health status and the entire healthcare system, and influence the demand for healthcare services[[230](#_ENREF_230)]. Yet, gender is a pivotal risk factor, as epidemiological studies have revealed that gender remains an independent risk factor after ethnicity, age, comorbidities, and scored risk factors are taken into account[[207](#_ENREF_207)]. Interestingly, interviews with leaders of the Israeli healthcare system about their attitude towards inequity and distributed justice of healthcare services revealed the central place of age deprivation (to the elderly), geographic inaccessibility and unbalanced private-public healthcare services, in contrast to gender–that was mentioned by only one expert–among the possible threats to equity in the provision of healthcare[[231](#_ENREF_231)].

In addition, most of the literature revolves around gender differences related to a specific medical condition, providing only a narrow view of health status, rather than studying medical profiles of multiple diseases or comorbidities. As most people have more than one single medical condition, one should inspect not only a given medical condition but also its accompanying cluster of associated conditions, namely, the medical condition should be placed in the context of the other co-existing medical conditions at the individual level as well as at the population level.

Furthermore, little if any attention has been given to the interplay between risk factors such as age-related gender differences, in research and in practical guidelines. This may be due to a lack of evidence, as gender differences become pronounced during adolescence, yet evidence is mainly based on data of adults and the elderly. As physiological, morphological and behavioral and other differences between males and females become more pronounced during puberty, one should not ignore medical differences at this developmental stage. Obtaining evidence for gender differences during adolescence, and tracing these to adulthood may provide insights on the origin of these differences and on their change over the course of development. Such information may be crucial for the design of specific practical guidelines (for screening, diagnosis, continuous monitoring, and treatment) and preventive programs and health policies among males and females. It can improve individual health status, increase the impact on interventions and policies, and may assist in closing gender disparities at later stages of life.

Each individual can be observed from different angles: the genetic print, health portrait, sensitivity to exposure, and vulnerability to co-morbidity. The perspective of time over the lifespan–from childhood to old age plays a role in the presentation of health conditions, since age is a major factor in pathophysiology, pharmacodynamics, reaction to treatment and prognosis. But above all, differences between men and women may dramatically affect behavior, responses and outcomes that may be amplified if treated in a non-personalized and gender-insensitive manner.

Moreover, policy makers and caregivers should observe population trends, or rather the cumulative effect of groups of patients–at national, regional and global levels–stratified by gender, age, ethnicity and other risk factors. This approach will indicate the burden of a disease in a specific manner enabling the definition of targeted guidelines and strategies[[113](#_ENREF_113),[232](#_ENREF_232)]. For instance, a recent study demonstrated the change over time of racial and ethnic disparities in vital care practices and certain outcomes, such as hospital mortality and severe morbidities[[233](#_ENREF_233)].

In addition, demographic changes, such as aging populations, impact the entire healthcare system in terms of healthcare service utilization and cost requirements. But demographic changes are also affected by healthcare system output, such as advanced medical care and prevention measures as well as improved health behavior within the population. Forecasting future morbidity among diverse population groups is based on population projections, considering demographic changes, and the bi-directional relationship of future morbidity with the healthcare system. Such forecasting of probable trends of occurrence rates may enable determination of the measures to be taken within the healthcare system, as well as identification of priorities among population groups[[234](#_ENREF_234),[235](#_ENREF_235)].

***A broader gender medicine approach: application and implications***

Previously, we proposed a multi-step model to bridge the gap between data collection on adverse populations, research and informed health decisions and policy making[[8](#_ENREF_8)]. It would be tempting to recommend, although too easy and oversimplified, to split the model for males and females in order to generate gender-sensitive health policy. Instead, an integrative and broader approach should be applied, integrating all the above-mentioned indicators and processes in a matrix-like manner (Figure 2).

Through this approach, gender is positioned at the top of the hierarchy; below it are other risk factors such as age, race/ethnicity, SES, residence, education, minorities etc. In other words, male and female populations are subdivided by these risk factors, which reflect inequities and diversities, and thus are taken into account. For the grading of each medical condition, within each gender–and preferably also within sub-populations–a multidimensional algorithm should be utilized, while considering occurrence (prevalence, incidence, exposure), progression over time, current and future disease severity (clinical symptoms/signs) and functional disability, psychological and social impact, additional co-existing co-morbidities, medical and economic consequences, mortality rate, preference and response to diverse therapeutic approaches and management protocols, etc. This would sum up to a given score or weight, which reflects the medical condition burden.

Moreover, the interplay of the medical condition with genetic data as well as epidemiological data on lifestyle habits, environmental factors and socio-cultural background should be assessed. Optimally, this would be applied to multiple medical conditions in parallel, so the entire spectrum of medical conditions comprising the health status of a given individual is considered, placing each medical condition in its true context and unraveling the medical profiles or signatures of given sub-populations.

For each case the relevance of the data–from the local, to national or global (other countries) populations–should be indicated. Obviously, data which are collected routinely should be integrated with evidence from designated research and trials. Such a broad, in-depth and tailored evidence base that is stratified to subpopulations within each gender may enable more accurate predictions of the burden of the medical signature–comprising its co-existing comorbidities, which in turn may allow better matching and design of adapted practical guidelines and gender-sensitive health policy.

Such an integrative approach relies on complex, multi-dimensional regression models and advanced statistics tools and data analysis models (Cox proportional hazards *e.g.*), but can also rely on machine learning and artificial intelligence (AI) learning methods to produce the above-mentioned scores and direct us toward specific measures of intervention treatments and prevention strategies of various medical conditions among male and female subpopulations.

The use of AI in the analysis of big data in public health has already been discussed, and methods of approaching big data by machine learning, neural networks and pattern recognition have been suggested in constructing models[[236](#_ENREF_236)]. Key components of analytics technology and operations, data governance, change and automation, advanced analytics and insights, analytics literacy and strategy and relationship management are of importance in analyzing big data by AI[[237](#_ENREF_237)]. The use of AI in the analysis of epidemiological data related to gender, age and morbidity has been demonstrated recently for predictive purposes with implications for patient care, showcasing machine learning classification techniques in lung cancer[[238](#_ENREF_238)], as well as artificial neural network (ANN) methods in a nutritional status study[[239](#_ENREF_239)] and metabolic syndromes[[240](#_ENREF_240)]. These exemplary studies may serve as a proof-of-concept for the feasibility of using AI as a tool in the proposed integrative approach to generating evidence-based, gender-sensitive health policy. Therefore, AI and advanced analytics can provide insights into implications for patient care, assist in forecasting future morbidity among diverse population groups, and may enable determination of the measures to be taken within the healthcare system.

**CONCLUSION**

Although the growing body of evidence clearly points to gender-specific differences in diverse range of medical conditions, from chronic disease to pandemics, little has been translated into gender-oriented and adjusted medical guidelines and health policies. An integrative approach to gender medicine-which incorporates information of medical profiles of co-existing medical conditions, considering the dynamics of these profiles across developmental stages, and adjusted to diverse risk factors-was proposed, and may bridge this wide gap. Increased awareness of gender-specific differences–in basic and applied research, clinical portrayal, design of treatment regimens and procedures, guidelines, preventive strategies and public health policies-may improve individualized care, properly address the unique needs of genders and sub-populations, and hence reduce inequities, as well as reduce current and future disease burden at the individual, community, national and global levels.

**REFERENCES**

1 **Buoncervello M**, Marconi M, Carè A, Piscopo P, Malorni W, Matarrese P. Preclinical models in the study of sex differences. *Clin Sci (Lond)* 2017; **131**: 449-469 [PMID: 28265036 DOI: 10.1042/cs20160847]

2 **Alur P**. Sex Differences in Nutrition, Growth, and Metabolism in Preterm Infants. *Front Pediatr* 2019; **7**: 22 [PMID: 30792973 DOI: 10.3389/fped.2019.00022]

3 **Rezzani R**, Franco C, Rodella LF. Sex differences of brain and their implications for personalized therapy. *Pharmacol Res* 2019; **141**: 429-442 [PMID: 30659897 DOI: 10.1016/j.phrs.2019.01.030]

4 **Machluf Y**, Fink D, Farkash R, Rotkopf R, Pirogovsky A, Tal O, Shohat T, Weisz G, Ringler E, Dagan D, Chaiter Y. Adolescent BMI at Northern Israel: From Trends, to Associated Variables and Comorbidities, and to Medical Signatures. *Medicine (Baltimore)* 2016; **95**: e3022 [PMID: 27015176 DOI: 10.1097/md.0000000000003022]

5 **Gochfeld M**. Sex Differences in Human and Animal Toxicology. *Toxicol Pathol* 2017; **45**: 172-189 [PMID: 27895264 DOI: 10.1177/0192623316677327]

6 **Anderson GD**. Gender differences in pharmacological response. *Int Rev Neurobiol* 2008; **83**: 1-10 [PMID: 18929073 DOI: 10.1016/s0074-7742(08)00001-9]

7 **Bartz D**, Chitnis T, Kaiser UB, Rich-Edwards JW, Rexrode KM, Pennell PB, Goldstein JM, O'Neal MA, LeBoff M, Behn M, Seely EW, Joffe H, Manson JE. Clinical Advances in Sex- and Gender-Informed Medicine to Improve the Health of All: A Review. *JAMA Intern Med* 2020; Online ahead of print [PMID: 32040165 DOI: 10.1001/jamainternmed.2019.7194]

8 **Machluf Y**, Tal O, Navon A, Chaiter Y. From Population Databases to Research and Informed Health Decisions and Policy. *Front Public Health* 2017; **5**: 230 [PMID: 28983476 DOI: 10.3389/fpubh.2017.00230]

9 **Rich-Edwards JW**, Kaiser UB, Chen GL, Manson JE, Goldstein JM. Sex and Gender Differences Research Design for Basic, Clinical, and Population Studies: Essentials for Investigators. *Endocr Rev* 2018; **39**: 424-439 [PMID: 29668873 DOI: 10.1210/er.2017-00246]

10 **Goetz LH**, Schork NJ. Personalized medicine: motivation, challenges, and progress. *Fertil Steril* 2018; **109**: 952-963 [PMID: 29935653 DOI: 10.1016/j.fertnstert.2018.05.006]

11 **Bahcall O**. Precision medicine. *Nature* 2015; **526**: 335 [PMID: 26469043 DOI: 10.1038/526335a]

12 **Hodson R**. Precision medicine. *Nature* 2016; **537**: S49 [PMID: 27602738 DOI: 10.1038/537S49a]

13 **Corella D**, Coltell O, Portolés O, Sotos-Prieto M, Fernández-Carrión R, Ramirez-Sabio JB, Zanón-Moreno V, Mattei J, Sorlí JV, Ordovas JM. A Guide to Applying the Sex-Gender Perspective to Nutritional Genomics. *Nutrients* 2018; **11**: [PMID: 30577445 DOI: 10.3390/nu11010004]

14 **Ferretti MT**, Iulita MF, Cavedo E, Chiesa PA, Schumacher Dimech A, Santuccione Chadha A, Baracchi F, Girouard H, Misoch S, Giacobini E, Depypere H, Hampel H; Women’s Brain Project and the Alzheimer Precision Medicine Initiative. Sex differences in Alzheimer disease - the gateway to precision medicine. *Nat Rev Neurol* 2018; **14**: 457-469 [PMID: 29985474 DOI: 10.1038/s41582-018-0032-9]

15 **Yang W**, Warrington NM, Taylor SJ, Whitmire P, Carrasco E, Singleton KW, Wu N, Lathia JD, Berens ME, Kim AH, Barnholtz-Sloan JS, Swanson KR, Luo J, Rubin JB. Sex differences in GBM revealed by analysis of patient imaging, transcriptome, and survival data. *Sci Transl Med* 2019; **11**: [PMID: 30602536 DOI: 10.1126/scitranslmed.aao5253]

16 **Hampel H**, Vergallo A, Giorgi FS, Kim SH, Depypere H, Graziani M, Saidi A, Nisticò R, Lista S; Alzheimer Precision Medicine Initiative (APMI). Precision medicine and drug development in Alzheimer's disease: the importance of sexual dimorphism and patient stratification. *Front Neuroendocrinol* 2018; **50**: 31-51 [PMID: 29902481 DOI: 10.1016/j.yfrne.2018.06.001]

17 **Miller VM**. Why are sex and gender important to basic physiology and translational and individualized medicine? *Am J Physiol Heart Circ Physiol* 2014; **306**: H781-H788 [PMID: 24414073 DOI: 10.1152/ajpheart.00994.2013]

18 **Calabrò P**, Niccoli G, Gragnano F, Grove EL, Vergallo R, Mikhailidis DP, Patti G, Spaccarotella C, Katsiki N, Masiero G, Ueshima D, Pinar E, Chieffo A, Ussia GP, Eitel I, Tarantini G; Working Group of Interventional Cardiology of the Italian Society of Cardiology. Are we ready for a gender-specific approach in interventional cardiology? *Int J Cardiol* 2019; **286**: 226-233 [PMID: 30449695 DOI: 10.1016/j.ijcard.2018.11.022]

19 **Sciomer S**, Moscucci F, Dessalvi CC, Deidda M, Mercuro G. Gender differences in cardiology: is it time for new guidelines? *J Cardiovasc Med (Hagerstown)* 2018; **19**: 685-688 [PMID: 30239478 DOI: 10.2459/jcm.0000000000000719]

20 **Regitz-Zagrosek V**, Kararigas G. Mechanistic Pathways of Sex Differences in Cardiovascular Disease. *Physiol Rev* 2017; **97**: 1-37 [PMID: 27807199 DOI: 10.1152/physrev.00021.2015]

21 **Doumas M**, Papademetriou V, Faselis C, Kokkinos P. Gender differences in hypertension: myths and reality. *Curr Hypertens Rep* 2013; **15**: 321-330 [PMID: 23749317 DOI: 10.1007/s11906-013-0359-y]

22 **Savarese G**, D'Amario D. Sex Differences in Heart Failure. *Adv Exp Med Biol* 2018; **1065**: 529-544 [PMID: 30051405 DOI: 10.1007/978-3-319-77932-4\_32]

23 **Campesi I**, Franconi F, Seghieri G, Meloni M. Sex-gender-related therapeutic approaches for cardiovascular complications associated with diabetes. *Pharmacol Res* 2017; **119**: 195-207 [PMID: 28189784 DOI: 10.1016/j.phrs.2017.01.023]

24 **Eastwood JA**, Doering LV. Gender differences in coronary artery disease. *J Cardiovasc Nurs* 2005; **20**: 340-51; quiz 352-3 [PMID: 16141779 DOI: 10.1097/00005082-200509000-00008]

25 **Miller-Hance WC**, Tacy TA. Gender differences in pediatric cardiac surgery: the cardiologist's perspective. *J Thorac Cardiovasc Surg* 2004; **128**: 7-10 [PMID: 15224013 DOI: 10.1016/j.jtcvs.2004.04.008]

26 **Raparelli V**, Morano S, Franconi F, Lenzi A, Basili S. Sex Differences in Type-2 Diabetes: Implications for Cardiovascular Risk Management. *Curr Pharm Des* 2017; **23**: 1471-1476 [PMID: 28137219 DOI: 10.2174/1381612823666170130153704]

27 **Bairey Merz CN**, Dember LM, Ingelfinger JR, Vinson A, Neugarten J, Sandberg KL, Sullivan JC, Maric-Bilkan C, Rankin TL, Kimmel PL, Star RA; participants of the National Institute of Diabetes and Digestive and Kidney Diseases Workshop on “Sex and the Kidneys”. Sex and the kidneys: current understanding and research opportunities. *Nat Rev Nephrol* 2019; **15**: 776-783 [PMID: 31586165 DOI: 10.1038/s41581-019-0208-6]

28 **Fuseini H**, Newcomb DC. Mechanisms Driving Gender Differences in Asthma. *Curr Allergy Asthma Rep* 2017; **17**: 19 [PMID: 28332107 DOI: 10.1007/s11882-017-0686-1]

29 **Pignataro FS**, Bonini M, Forgione A, Melandri S, Usmani OS. Asthma and gender: The female lung. *Pharmacol Res* 2017; **119**: 384-390 [PMID: 28238829 DOI: 10.1016/j.phrs.2017.02.017]

30 **Zein JG**, Erzurum SC. Asthma is Different in Women. *Curr Allergy Asthma Rep* 2015; **15**: 28 [PMID: 26141573 DOI: 10.1007/s11882-015-0528-y]

31 **Ngo ST**, Steyn FJ, McCombe PA. Gender differences in autoimmune disease. *Front Neuroendocrinol* 2014; **35**: 347-369 [PMID: 24793874 DOI: 10.1016/j.yfrne.2014.04.004]

32 **Vetvik KG**, MacGregor EA. Sex differences in the epidemiology, clinical features, and pathophysiology of migraine. *Lancet Neurol* 2017; **16**: 76-87 [PMID: 27836433 DOI: 10.1016/s1474-4422(16)30293-9]

33 **Yang Y**, Wang G, He J, Ren S, Wu F, Zhang J, Wang F. Gender differences in colorectal cancer survival: A meta-analysis. *Int J Cancer* 2017; **141**: 1942-1949 [PMID: 28599355 DOI: 10.1002/ijc.30827]

34 **Ali I**, Högberg J, Hsieh JH, Auerbach S, Korhonen A, Stenius U, Silins I. Gender differences in cancer susceptibility: role of oxidative stress. *Carcinogenesis* 2016; **37**: 985-992 [PMID: 27481070 DOI: 10.1093/carcin/bgw076]

35 **Avgerinos KI**, Spyrou N, Mantzoros CS, Dalamaga M. Obesity and cancer risk: Emerging biological mechanisms and perspectives. *Metabolism* 2019; **92**: 121-135 [PMID: 30445141 DOI: 10.1016/j.metabol.2018.11.001]

36 **Olak J**, Colson Y. Gender differences in lung cancer: have we really come a long way, baby? *J Thorac Cardiovasc Surg* 2004; **128**: 346-351 [PMID: 15354089 DOI: 10.1016/j.jtcvs.2004.05.025]

37 **Rusman T**, van Vollenhoven RF, van der Horst-Bruinsma IE. Gender Differences in Axial Spondyloarthritis: Women Are Not So Lucky. *Curr Rheumatol Rep* 2018; **20**: 35 [PMID: 29754330 DOI: 10.1007/s11926-018-0744-2]

38 **Golden LC**, Voskuhl R. The importance of studying sex differences in disease: The example of multiple sclerosis. *J Neurosci Res* 2017; **95**: 633-643 [PMID: 27870415 DOI: 10.1002/jnr.23955]

39 **Goodin DS**. The epidemiology of multiple sclerosis: insights to a causal cascade. *Handb Clin Neurol* 2016; **138**: 173-206 [PMID: 27637959 DOI: 10.1016/b978-0-12-802973-2.00011-2]

40 **Nebel RA**, Aggarwal NT, Barnes LL, Gallagher A, Goldstein JM, Kantarci K, Mallampalli MP, Mormino EC, Scott L, Yu WH, Maki PM, Mielke MM. Understanding the impact of sex and gender in Alzheimer's disease: A call to action. *Alzheimers Dement* 2018; **14**: 1171-1183 [PMID: 29907423 DOI: 10.1016/j.jalz.2018.04.008]

41 **Canevelli M**, Quarata F, Remiddi F, Lucchini F, Lacorte E, Vanacore N, Bruno G, Cesari M. Sex and gender differences in the treatment of Alzheimer's disease: A systematic review of randomized controlled trials. *Pharmacol Res* 2017; **115**: 218-223 [PMID: 27913252 DOI: 10.1016/j.phrs.2016.11.035]

42 **Li R**, Singh M. Sex differences in cognitive impairment and Alzheimer's disease. *Front Neuroendocrinol* 2014; **35**: 385-403 [PMID: 24434111 DOI: 10.1016/j.yfrne.2014.01.002]

43 **Won C**, Guilleminault C. Gender differences in sleep disordered breathing: implications for therapy. *Expert Rev Respir Med* 2015; **9**: 221-231 [PMID: 25739831 DOI: 10.1586/17476348.2015.1019478]

44 **Savic I**. Sex differences in human epilepsy. *Exp Neurol* 2014; **259**: 38-43 [PMID: 24747359 DOI: 10.1016/j.expneurol.2014.04.009]

45 **Poorthuis MH**, Algra AM, Algra A, Kappelle LJ, Klijn CJ. Female- and Male-Specific Risk Factors for Stroke: A Systematic Review and Meta-analysis. *JAMA Neurol* 2017; **74**: 75-81 [PMID: 27842176 DOI: 10.1001/jamaneurol.2016.3482]

46 **Werling DM**, Geschwind DH. Sex differences in autism spectrum disorders. *Curr Opin Neurol* 2013; **26**: 146-153 [PMID: 23406909 DOI: 10.1097/WCO.0b013e32835ee548]

47 **Piccinelli M**, Wilkinson G. Gender differences in depression. Critical review. *Br J Psychiatry* 2000; **177**: 486-492 [PMID: 11102321 DOI: 10.1192/bjp.177.6.486]

48 **Asher M**, Asnaani A, Aderka IM. Gender differences in social anxiety disorder: A review. *Clin Psychol Rev* 2017; **56**: 1-12 [PMID: 28578248 DOI: 10.1016/j.cpr.2017.05.004.[]

49 **Becker JB**, McClellan ML, Reed BG. Sex differences, gender and addiction. *J Neurosci Res* 2017; **95**: 136-147 [PMID: 27870394 DOI: 10.1002/jnr.23963]

50 **McHugh RK**, Votaw VR, Sugarman DE, Greenfield SF. Sex and gender differences in substance use disorders. *Clin Psychol Rev* 2018; **66**: 12-23 [PMID: 29174306 DOI: 10.1016/j.cpr.2017.10.012]

51 **Masoli M**, Fabian D, Holt S, Beasley R; Global Initiative for Asthma (GINA) Program. The global burden of asthma: executive summary of the GINA Dissemination Committee report. *Allergy* 2004; **59**: 469-478 [PMID: 15080825 DOI: 10.1111/j.1398-9995.2004.00526.x]

52 **Asher I**, Pearce N. Global burden of asthma among children. *Int J Tuberc Lung Dis* 2014; **18**: 1269-1278 [PMID: 25299857 DOI: 10.5588/ijtld.14.0170]

53 **Bateman ED**, Jithoo A. Asthma and allergy - a global perspective. *Allergy* 2007; **62**: 213-215 [PMID: 17298336 DOI: 10.1111/j.1398-9995.2007.01324.x]

54 **Palomares O**, Akdis M, Martín-Fontecha M, Akdis CA. Mechanisms of immune regulation in allergic diseases: the role of regulatory T and B cells. *Immunol Rev* 2017; **278**: 219-236 [PMID: 28658547 DOI: 10.1111/imr.12555]

55 **Miyasaka T**, Dobashi-Okuyama K, Takahashi T, Takayanagi M, Ohno I. The interplay between neuroendocrine activity and psychological stress-induced exacerbation of allergic asthma. *Allergol Int* 2018; **67**: 32-42 [PMID: 28539203 DOI: 10.1016/j.alit.2017.04.013]

56 **Skobeloff EM**, Spivey WH, St Clair SS, Schoffstall JM. The influence of age and sex on asthma admissions. *JAMA* 1992; **268**: 3437-3440 [PMID: 1460733 DOI: 10.1001/jama.1992.03490240045034]

57 **Meurer JR**, George V, Subichin S, Yauck J, Layde P. Asthma severity among children hospitalized in 1990 and 1995. *Arch Pediatr Adolesc Med* 2000; **154**: 143-149 [PMID: 10665600 DOI: 10.1001/archpedi.154.2.143]

58 **Chen Y**, Dales R, Stewart P, Johansen H, Scott G, Taylor G. Hospital readmissions for asthma in children and young adults in Canada. *Pediatr Pulmonol* 2003; **36**: 22-26 [PMID: 12772219 DOI: 10.1002/ppul.10307]

59 **Hohmann C**, Keller T, Gehring U, Wijga A, Standl M, Kull I, Bergstrom A, Lehmann I, von Berg A, Heinrich J, Lau S, Wahn U, Maier D, Anto J, Bousquet J, Smit H, Keil T, Roll S. Sex-specific incidence of asthma, rhinitis and respiratory multimorbidity before and after puberty onset: individual participant meta-analysis of five birth cohorts collaborating in MeDALL. *BMJ Open Respir Res* 2019; **6**: e000460 [PMID: 31673365 DOI: 10.1136/bmjresp-2019-000460]

60 **Raghavan D**, Jain R. Increasing awareness of sex differences in airway diseases. *Respirology* 2016; **21**: 449-459 [PMID: 26677803 DOI: 10.1111/resp.12702]

61 **Gershon AS**, Wang C, Guan J, To T. Burden of comorbidity in individuals with asthma. *Thorax* 2010; **65**: 612-618 [PMID: 20627918 DOI: 10.1136/thx.2009.131078]

62 **Zhang T**, Carleton BC, Prosser RJ, Smith AM. The added burden of comorbidity in patients with asthma. *J Asthma* 2009; **46**: 1021-1026 [PMID: 19995140 DOI: 10.3109/02770900903350473]

63 **Ferkh KE**, Nwaru BI, Griffiths C, Patel A, Sheikh A. Healthcare costs of asthma comorbidities: a systematic review protocol. *BMJ Open* 2017; **7**: e015102 [PMID: 28566366 DOI: 10.1136/bmjopen-2016-015102]

64 **de Groot EP**, Duiverman EJ, Brand PL. Comorbidities of asthma during childhood: possibly important, yet poorly studied. *Eur Respir J* 2010; **36**: 671-678 [PMID: 20930201 DOI: 10.1183/09031936.00185709]

65 **Boulet LP**, Boulay MÈ. Asthma-related comorbidities. *Expert Rev Respir Med* 2011; **5**: 377-393 [PMID: 21702660 DOI: 10.1586/ers.11.34]

66 **Cazzola M**, Calzetta L, Bettoncelli G, Novelli L, Cricelli C, Rogliani P. Asthma and comorbid medical illness. *Eur Respir J* 2011; **38**: 42-49 [PMID: 21177843 DOI: 10.1183/09031936.00140310]

67 **Ullmann N**, Mirra V, Di Marco A, Pavone M, Porcaro F, Negro V, Onofri A, Cutrera R. Asthma: Differential Diagnosis and Comorbidities. *Front Pediatr* 2018; **6**: 276 [PMID: 30338252 DOI: 10.3389/fped.2018.00276]

68 **Weatherburn CJ**, Guthrie B, Mercer SW, Morales DR. Comorbidities in adults with asthma: Population-based cross-sectional analysis of 1.4 million adults in Scotland. *Clin Exp Allergy* 2017; **47**: 1246-1252 [PMID: 28665552 DOI: 10.1111/cea.12971]

69 **Tay TR**, Hew M. Comorbid "treatable traits" in difficult asthma: Current evidence and clinical evaluation. *Allergy* 2018; **73**: 1369-1382 [PMID: 29178130 DOI: 10.1111/all.13370]

70 **Bardin PG**, Rangaswamy J, Yo SW. Managing comorbid conditions in severe asthma. *Med J Aust* 2018; **209**: S11-S17 [PMID: 30453867 DOI: 10.5694/mja18.00196]

71 **Graif Y**, Shohat T, Machluf Y, Farkash R, Chaiter Y. Association between asthma and migraine: A cross-sectional study of over 110 000 adolescents. *Clin Respir J* 2018; **12**: 2491-2496 [PMID: 30004178 DOI: 10.1111/crj.12939]

72 **Rhee H**, Love T, Groth SW, Grape A, Tumiel-Berhalter L, Harrington D. Associations between overweight and obesity and asthma outcomes in urban adolescents. *J Asthma* 2019; 1-10 [PMID: 31204534 DOI: 10.1080/02770903.2019.1633663]

73 **OÈ›elea MR,** RaÈ™cu A. The asthma obese phenotype. In: Huang K-HG Asthma diagnosis and management IntechOpen, 2018: 165-184.

74 **Haldar P**, Pavord ID, Shaw DE, Berry MA, Thomas M, Brightling CE, Wardlaw AJ, Green RH. Cluster analysis and clinical asthma phenotypes. *Am J Respir Crit Care Med* 2008; **178**: 218-224 [PMID: 18480428 DOI: 10.1164/rccm.200711-1754OC]

75 **Amelink M**, de Nijs SB, de Groot JC, van Tilburg PM, van Spiegel PI, Krouwels FH, Lutter R, Zwinderman AH, Weersink EJ, ten Brinke A, Sterk PJ, Bel EH. Three phenotypes of adult-onset asthma. *Allergy* 2013; **68**: 674-680 [PMID: 23590217 DOI: 10.1111/all.12136]

76 **Moore WC**, Fitzpatrick AM, Li X, Hastie AT, Li H, Meyers DA, Bleecker ER. Clinical heterogeneity in the severe asthma research program. *Ann Am Thorac Soc* 2013; **10 Suppl**: S118-S124 [PMID: 24313761 DOI: 10.1513/AnnalsATS.201309-307AW]

77 **Labor M**, Labor S, JuriÄ‡ I, FijaÄko V, Grle SP, Plavec D. Mood disorders in adult asthma phenotypes. *J Asthma* 2018; **55**: 57-65 [PMID: 28489959 DOI: 10.1080/02770903.2017.1306546]

78 **Ross MK**, Romero T, Sim MS, Szilagyi PG. Obese- and allergic-related asthma phenotypes among children across the United States. *J Asthma* 2019; **56**: 512-521 [PMID: 29672178 DOI: 10.1080/02770903.2018.1466317]

79 **Fischer GB**, Sarria EE, Mattiello R, Mocelin HT, Castro-Rodriguez JA. Post infectious bronchiolitis obliterans in children. *Paediatr Respir Rev* 2010; **11**: 233-239 [PMID: 21109182 DOI: 10.1016/j.prrv.2010.07.005]

80 **Machluf Y**, Farkash R, Fink D, Chaiter Y. Asthma severity and heterogeneity: Insights from prevalence trends and associated demographic variables and anthropometric indices among Israeli adolescents. *J Asthma* 2018; **55**: 826-836 [PMID: 28872935 DOI: 10.1080/02770903.2017.1373809]

81 **Machluf Y**, Farkash R, Rotkopf R, Fink D, Chaiter Y. Asthma phenotypes and associated comorbidities in a large cohort of adolescents in Israel. *J Asthma* 2020; **57**: 722-735 [PMID: 31017024 DOI: 10.1080/02770903.2019.1604743.]

82 **Tse SM**, Rifas-Shiman SL, Coull BA, Litonjua AA, Oken E, Gold DR. Sex-specific risk factors for childhood wheeze and longitudinal phenotypes of wheeze. *J Allergy Clin Immunol* 2016; **138**: 1561-1568.e6 [PMID: 27246527 DOI: 10.1016/j.jaci.2016.04.005]

83 **Koleade A**, Farrell J, Mugford G, Gao Z. Female-specific risk factors associated with risk of ACO (asthma COPD overlap) in aboriginal people. *J Asthma* 2020; **57**: 925-932 [PMID: 31106621 DOI: 10.1080/02770903.2019.1621890]

84 **Lin SC**, Lin HW. Urbanization factors associated with childhood asthma and prematurity: a population-based analysis aged from 0 to 5 years in Taiwan by using Cox regression within a hospital cluster model. *J Asthma* 2015; **52**: 273-278 [PMID: 25171433 DOI: 10.3109/02770903.2014.958854]

85 **NCD Risk Factor Collaboration (NCD-RisC).** Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128·9 million children, adolescents, and adults. *Lancet* 2017; **390**: 2627-2642 [PMID: 29029897 DOI: 10.1016/s0140-6736(17)32129-3.[]

86 **Lobstein T**, Baur L, Uauy R; IASO International Obesity TaskForce. Obesity in children and young people: a crisis in public health. *Obes Rev* 2004; **5 Suppl 1**: 4-104 [PMID: 15096099 DOI: 10.1111/j.1467-789X.2004.00133.x]

87 **Keith SW**, Redden DT, Katzmarzyk PT, Boggiano MM, Hanlon EC, Benca RM, Ruden D, Pietrobelli A, Barger JL, Fontaine KR, Wang C, Aronne LJ, Wright SM, Baskin M, Dhurandhar NV, Lijoi MC, Grilo CM, DeLuca M, Westfall AO, Allison DB. Putative contributors to the secular increase in obesity: exploring the roads less traveled. *Int J Obes (Lond)* 2006; **30**: 1585-1594 [PMID: 16801930 DOI: 10.1038/sj.ijo.0803326]

88 **Himes JH**. Agreement among anthropometric indicators identifying the fattest adolescents. *Int J Obes Relat Metab Disord* 1999; **23 Suppl 2**: S18-S21 [PMID: 10340800 DOI: 10.1038/sj.ijo.0800854]

89 **Skelton JA**, Cook SR, Auinger P, Klein JD, Barlow SE. Prevalence and trends of severe obesity among US children and adolescents. *Acad Pediatr* 2009; **9**: 322-329 [PMID: 19560993 DOI: 10.1016/j.acap.2009.04.005]

90 **Flegal KM**, Wei R, Ogden CL, Freedman DS, Johnson CL, Curtin LR. Characterizing extreme values of body mass index-for-age by using the 2000 Centers for Disease Control and Prevention growth charts. *Am J Clin Nutr* 2009; **90**: 1314-1320 [PMID: 19776142 DOI: 10.3945/ajcn.2009.28335]

91 **Koebnick C**, Smith N, Coleman KJ, Getahun D, Reynolds K, Quinn VP, Porter AH, Der-Sarkissian JK, Jacobsen SJ. Prevalence of extreme obesity in a multiethnic cohort of children and adolescents. *J Pediatr* 2010; **157**: 26-31.e2 [PMID: 20303506 DOI: 10.1016/j.jpeds.2010.01.025]

92 **Ogden CL**, Carroll MD, Fryar CD, Flegal KM. Prevalence of Obesity Among Adults and Youth: United States, 2011-2014. *NCHS Data Brief* 2015; :1-8 [PMID: 26633046]

93 **Park MH**, Falconer C, Viner RM, Kinra S. The impact of childhood obesity on morbidity and mortality in adulthood: a systematic review. *Obes Rev* 2012; **13**: 985-1000 [PMID: 22731928 DOI: 10.1111/j.1467-789X.2012.01015.x]

94 **Weiss R**, Dziura J, Burgert TS, Tamborlane WV, Taksali SE, Yeckel CW, Allen K, Lopes M, Savoye M, Morrison J, Sherwin RS, Caprio S. Obesity and the metabolic syndrome in children and adolescents. *N Engl J Med* 2004; **350**: 2362-2374 [PMID: 15175438 DOI: 10.1056/NEJMoa031049]

95 **Kelly AS**, Barlow SE, Rao G, Inge TH, Hayman LL, Steinberger J, Urbina EM, Ewing LJ, Daniels SR; American Heart Association Atherosclerosis, Hypertension, and Obesity in the Young Committee of the Council on Cardiovascular Disease in the Young, Council on Nutrition, Physical Activity and Metabolism, and Council on Clinical Cardiology. Severe obesity in children and adolescents: identification, associated health risks, and treatment approaches: a scientific statement from the American Heart Association. *Circulation* 2013; **128**: 1689-1712 [PMID: 24016455 DOI: 10.1161/CIR.0b013e3182a5cfb3]

96 **Dietz WH**. Health consequences of obesity in youth: childhood predictors of adult disease. *Pediatrics* 1998; **101**: 518-525 [PMID: 12224658]

97 **Quek YH**, Tam WWS, Zhang MWB, Ho RCM. Exploring the association between childhood and adolescent obesity and depression: a meta-analysis. *Obes Rev* 2017; **18**: 742-754 [PMID: 28401646 DOI: 10.1111/obr.12535]

98 **Caird J,** Kavanagh J, O’Mara-Eves A, Oliver K, Oliver S, Stansfield C, Thomas J. Does being overweight impede academic attainment? A systematic review. Health Education Journal 2013; 73: 497-521 [PMID: 8366901 DOI: 10.1056/NEJM199309303291406].

99 **Gortmaker SL**, Must A, Perrin JM, Sobol AM, Dietz WH. Social and economic consequences of overweight in adolescence and young adulthood. *N Engl J Med* 1993; **329**: 1008-1012 [PMID: 8366901 DOI: 10.1056/NEJM199309303291406]

100 **Must A**, Jacques PF, Dallal GE, Bajema CJ, Dietz WH. Long-term morbidity and mortality of overweight adolescents. A follow-up of the Harvard Growth Study of 1922 to 1935. *N Engl J Med* 1992; **327**: 1350-1355 [PMID: 1406836 DOI: 10.1056/nejm199211053271904]

101 **Abdullah A**, Wolfe R, Stoelwinder JU, de Courten M, Stevenson C, Walls HL, Peeters A. The number of years lived with obesity and the risk of all-cause and cause-specific mortality. *Int J Epidemiol* 2011; **40**: 985-996 [PMID: 21357186 DOI: 10.1093/ije/dyr018]

102 **Turer CB**, Skinner CS, Barlow SE. Algorithm to detect pediatric provider attention to high BMI and associated medical risk. *J Am Med Inform Assoc* 2019; **26**: 55-60 [PMID: 30445547 DOI: 10.1093/jamia/ocy126]

103 **Andreeva VA**, Fezeu LK, Hercberg S, Galan P. Obesity and Migraine: Effect Modification by Gender and Perceived Stress. *Neuroepidemiology* 2018; **51**: 25-32 [PMID: 29843127 DOI: 10.1159/000489663]

104 **Tronieri JS**, Wurst CM, Pearl RL, Allison KC. Sex Differences in Obesity and Mental Health. *Curr Psychiatry Rep* 2017; **19**: 29 [PMID: 28439762 DOI: 10.1007/s11920-017-0784-8]

105 **Jonikas JA**, Cook JA, Razzano LA, Steigman PJ, Hamilton MM, Swarbrick MA, Santos A. Associations Between Gender and Obesity Among Adults with Mental Illnesses in a Community Health Screening Study. *Community Ment Health J* 2016; **52**: 406-415 [PMID: 26711093 DOI: 10.1007/s10597-015-9965-2]

106 **BaHammam AS**, Pandi-Perumal SR, Piper A, Bahammam SA, Almeneessier AS, Olaish AH, Javaheri S. Gender differences in patients with obesity hypoventilation syndrome. *J Sleep Res* 2016; **25**: 445-453 [PMID: 26990045 DOI: 10.1111/jsr.12400]

107 **Hu L**, Huang X, You C, Li J, Hong K, Li P, Wu Y, Wu Q, Bao H, Cheng X. Prevalence and Risk Factors of Prehypertension and Hypertension in Southern China. *PLoS One* 2017; **12**: e0170238 [PMID: 28095471 DOI: 10.1371/journal.pone.0170238]

108 **Macia E**, Gueye L, Duboz P. Hypertension and Obesity in Dakar, Senegal. *PLoS One* 2016; **11**: e0161544 [PMID: 27622534 DOI: 10.1371/journal.pone.0161544]

109 **Asad Z**, Abbas M, Javed I, Korantzopoulos P, Stavrakis S. Obesity is associated with incident atrial fibrillation independent of gender: A meta-analysis. *J Cardiovasc Electrophysiol* 2018; **29**: 725-732 [PMID: 29443438 DOI: 10.1111/jce.13458]

110 **Chaiter Y**, Machluf Y, Pirogovsky A, Palma E, Yona A, Shohat T, Yitzak A, Tal O, Ash N. Quality control and quality assurance of medical committee performance in the Israel Defense Forces. *Int J Health Care Qual Assur* 2010; **23**: 507-515 [PMID: 20845680 DOI: 10.1108/09526861011050538]

111 **Furer A**, Afek A, Orr O, Gershovitz L, Landau Rabbi M, Derazne E, Pinhas-Hamiel O, Fink N, Leiba A, Tirosh A, Kark JD, Twig G. Sex-specific associations between adolescent categories of BMI with cardiovascular and non-cardiovascular mortality in midlife. *Cardiovasc Diabetol* 2018; **17**: 80 [PMID: 29871640 DOI: 10.1186/s12933-018-0727-7]

112 **Ladhani M**, Craig JC, Wong G. Obesity and gender-biased access to deceased donor kidney transplantation. *Nephrol Dial Transplant* 2020; **35**: 184-189 [PMID: 31203364 DOI: 10.1093/ndt/gfz100]

113 **GBD 2015 Obesity Collaborators.**, Afshin A, Forouzanfar MH, Reitsma MB, Sur P, Estep K, Lee A, Marczak L, Mokdad AH, Moradi-Lakeh M, Naghavi M, Salama JS, Vos T, Abate KH, Abbafati C, Ahmed MB, Al-Aly Z, Alkerwi A, Al-Raddadi R, Amare AT, Amberbir A, Amegah AK, Amini E, Amrock SM, Anjana RM, Ärnlöv J, Asayesh H, Banerjee A, Barac A, Baye E, Bennett DA, Beyene AS, Biadgilign S, Biryukov S, Bjertness E, Boneya DJ, Campos-Nonato I, Carrero JJ, Cecilio P, Cercy K, Ciobanu LG, Cornaby L, Damtew SA, Dandona L, Dandona R, Dharmaratne SD, Duncan BB, Eshrati B, Esteghamati A, Feigin VL, Fernandes JC, Fürst T, Gebrehiwot TT, Gold A, Gona PN, Goto A, Habtewold TD, Hadush KT, Hafezi-Nejad N, Hay SI, Horino M, Islami F, Kamal R, Kasaeian A, Katikireddi SV, Kengne AP, Kesavachandran CN, Khader YS, Khang YH, Khubchandani J, Kim D, Kim YJ, Kinfu Y, Kosen S, Ku T, Defo BK, Kumar GA, Larson HJ, Leinsalu M, Liang X, Lim SS, Liu P, Lopez AD, Lozano R, Majeed A, Malekzadeh R, Malta DC, Mazidi M, McAlinden C, McGarvey ST, Mengistu DT, Mensah GA, Mensink GBM, Mezgebe HB, Mirrakhimov EM, Mueller UO, Noubiap JJ, Obermeyer CM, Ogbo FA, Owolabi MO, Patton GC, Pourmalek F, Qorbani M, Rafay A, Rai RK, Ranabhat CL, Reinig N, Safiri S, Salomon JA, Sanabria JR, Santos IS, Sartorius B, Sawhney M, Schmidhuber J, Schutte AE, Schmidt MI, Sepanlou SG, Shamsizadeh M, Sheikhbahaei S, Shin MJ, Shiri R, Shiue I, Roba HS, Silva DAS, Silverberg JI, Singh JA, Stranges S, Swaminathan S, Tabarés-Seisdedos R, Tadese F, Tedla BA, Tegegne BS, Terkawi AS, Thakur JS, Tonelli M, Topor-Madry R, Tyrovolas S, Ukwaja KN, Uthman OA, Vaezghasemi M, Vasankari T, Vlassov VV, Vollset SE, Weiderpass E, Werdecker A, Wesana J, Westerman R, Yano Y, Yonemoto N, Yonga G, Zaidi Z, Zenebe ZM, Zipkin B, Murray CJL. Health Effects of Overweight and Obesity in 195 Countries over 25 Years. *N Engl J Med* 2017; **377**: 13-27 [PMID: 28604169 DOI: 10.1056/NEJMoa1614362]

114 **Chu DT**, Minh Nguyet NT, Dinh TC, Thai Lien NV, Nguyen KH, Nhu Ngoc VT, Tao Y, Son LH, Le DH, Nga VB, JurgoÅ„ski A, Tran QH, Van Tu P, Pham VH. An update on physical health and economic consequences of overweight and obesity. *Diabetes Metab Syndr* 2018; **12**: 1095-1100 [PMID: 29799416 DOI: 10.1016/j.dsx.2018.05.004]

115 **Apovian CM**. Obesity: definition, comorbidities, causes, and burden. *Am J Manag Care* 2016; **22**: s176-s185 [PMID: 27356115]

116 **Runge CF**. Economic consequences of the obese. *Diabetes* 2007; **56**: 2668-2672 [PMID: 17601989 DOI: 10.2337/db07-0633]

117 **Tremmel M**, Gerdtham UG, Nilsson PM, Saha S. Economic Burden of Obesity: A Systematic Literature Review. *Int J Environ Res Public Health* 2017; **14**: [PMID: 28422077 DOI: 10.3390/ijerph14040435]

118 **August GP**, Caprio S, Fennoy I, Freemark M, Kaufman FR, Lustig RH, Silverstein JH, Speiser PW, Styne DM, Montori VM; Endocrine Society. Prevention and treatment of pediatric obesity: an endocrine society clinical practice guideline based on expert opinion. *J Clin Endocrinol Metab* 2008; **93**: 4576-4599 [PMID: 18782869 DOI: 10.1210/jc.2007-2458]

119 **Nittari G**, Scuri S, Petrelli F, Pirillo I, di Luca NM, Grappasonni I. Fighting obesity in children from European World Health Organization member states. Epidemiological data, medical-social aspects, and prevention programs. *Clin Ter* 2019; **170**: e223-e230 [PMID: 31173054 DOI: 10.7417/ct.2019.2137]

120 **Martin A**, Saunders DH, Shenkin SD, Sproule J. Lifestyle intervention for improving school achievement in overweight or obese children and adolescents. *Cochrane Database Syst Rev* 2014; CD009728 [PMID: 24627300 DOI:10.1002/14651858.CD009728.pub2.]

121 **Doak CM**, Visscher TL, Renders CM, Seidell JC. The prevention of overweight and obesity in children and adolescents: a review of interventions and programmes. *Obes Rev* 2006; **7**: 111-136 [PMID: 16436107 DOI: 10.1111/j.1467-789X.2006.00234.x]

122 **Katz DL**, O'Connell M, Njike VY, Yeh MC, Nawaz H. Strategies for the prevention and control of obesity in the school setting: systematic review and meta-analysis. *Int J Obes (Lond)* 2008; **32**: 1780-1789 [PMID: 19079319 DOI: 10.1038/ijo.2008.158]

123 **Mead E**, Brown T, Rees K, Azevedo LB, Whittaker V, Jones D, Olajide J, Mainardi GM, Corpeleijn E, O'Malley C, Beardsmore E, Al-Khudairy L, Baur L, Metzendorf MI, Demaio A, Ells LJ. Diet, physical activity and behavioural interventions for the treatment of overweight or obese children from the age of 6 to 11 years. *Cochrane Database Syst Rev* 2017; **6**: CD012651 [PMID: 28639319 DOI: 10.1002/14651858.cd012651]

124 **Al-Khudairy L**, Loveman E, Colquitt JL, Mead E, Johnson RE, Fraser H, Olajide J, Murphy M, Velho RM, O'Malley C, Azevedo LB, Ells LJ, Metzendorf MI, Rees K. Diet, physical activity and behavioural interventions for the treatment of overweight or obese adolescents aged 12 to 17 years. *Cochrane Database Syst Rev* 2017; **6**: CD012691 [PMID: 28639320 DOI: 10.1002/14651858.cd012691]

125 **Mayerhofer E**, Ratzinger F, Kienreich NE, Stiel A, Witzeneder N, Schrefl E, Greiner G, Wegscheider C, Graf I, Schmetterer K, Marculescu R, Szekeres T, Perkmann T, Fondi M, Wagner O, Esterbauer H, Mayerhofer M, Holocher-Ertl S, Wojnarowski C, Hoermann G. A Multidisciplinary Intervention in Childhood Obesity Acutely Improves Insulin Resistance and Inflammatory Markers Independent From Body Composition. *Front Pediatr* 2020; **8**: 52 [PMID: 32154197 DOI: 10.3389/fped.2020.00052]

126 **Stice E**, Shaw H, Marti CN. A meta-analytic review of obesity prevention programs for children and adolescents: the skinny on interventions that work. *Psychol Bull* 2006; **132**: 667-691 [PMID: 16910747 DOI: 10.1037/0033-2909.132.5.667]

127 **Doyle S**, Lloyd A, Birt J, Curtis B, Ali S, Godbey K, Sierra-Johnson J, Halford JC. Willingness to pay for obesity pharmacotherapy. *Obesity (Silver Spring)* 2012; **20**: 2019-2026 [PMID: 22301901 DOI: 10.1038/oby.2011.387]

128 **Himes JH**, Dietz WH. Guidelines for overweight in adolescent preventive services: recommendations from an expert committee. The Expert Committee on Clinical Guidelines for Overweight in Adolescent Preventive Services. *Am J Clin Nutr* 1994; **59**: 307-316 [PMID: 8310979 DOI: 10.1093/ajcn/59.2.307]

129 **Barlow SE**, Dietz WH. Obesity evaluation and treatment: Expert Committee recommendations. The Maternal and Child Health Bureau, Health Resources and Services Administration and the Department of Health and Human Services. *Pediatrics* 1998; **102**: E29 [PMID: 9724677 DOI: 10.1542/peds.102.3.e29]

130 **Barlow SE**; Expert Committee. Expert committee recommendations regarding the prevention, assessment, and treatment of child and adolescent overweight and obesity: summary report. *Pediatrics* 2007; **120 Suppl 4**: S164-S192 [PMID: 18055651 DOI:10.1542/peds.2007-2329C.]

131 **Acosta A**, Streett S, Kroh MD, Cheskin LJ, Saunders KH, Kurian M, Schofield M, Barlow SE, Aronne L. White Paper AGA: POWER - Practice Guide on Obesity and Weight Management, Education, and Resources. *Clin Gastroenterol Hepatol* 2017; **15**: 631-649.e10 [PMID: 28242319 DOI: 10.1016/j.cgh.2016.10.023]

132 **Wolfenstetter SB**. [Juvenile obesity and comorbidity type 2 diabetes mellitus (T2 DM) in Germany: development and cost-of-illness analysis]. *Gesundheitswesen* 2006; **68**: 600-612 [PMID: 17099820 DOI: 10.1055/s-2006-927181]

133 **Kouris-Blazos A**, Wahlqvist ML. Health economics of weight management: evidence and cost. *Asia Pac J Clin Nutr* 2007; **16 Suppl 1**: 329-338 [PMID: 17392129]

134 **Shamseddeen H**, Getty JZ, Hamdallah IN, Ali MR. Epidemiology and economic impact of obesity and type 2 diabetes. *Surg Clin North Am* 2011; **91**: 1163-1172, vii [PMID: 22054146 DOI: 10.1016/j.suc.2011.08.001]

135 **Fontaine KR**, Redden DT, Wang C, Westfall AO, Allison DB. Years of life lost due to obesity. *JAMA* 2003; **289**: 187-193 [PMID: 12517229 DOI: 10.1001/jama.289.2.187]

136 **Wang G**, Dietz WH. Economic burden of obesity in youths aged 6 to 17 years: 1979-1999. *Pediatrics* 2002; **109**: E81-E81 [PMID: 11986487 DOI: 10.1542/peds.109.5.e81]

137 **Ryan JG**. Cost and policy implications from the increasing prevalence of obesity and diabetes mellitus. *Gend Med* 2009; **6 Suppl 1**: 86-108 [PMID: 19318221 DOI: 10.1016/j.genm.2009.01.002]

138 **Esposito L**, Villaseñor A, Rodríguez EC, Millett C. The economic gradient of obesity in Mexico: Independent predictive roles of absolute and relative wealth by gender. *Soc Sci Med* 2020; **250**: 112870 [PMID: 32146237 DOI: 10.1016/j.socscimed.2020.112870]

139 **Delles C**, Vanholder R. Chronic kidney disease. *Clin Sci (Lond)* 2017; **131**: 225-226 [PMID: 28057893 DOI: 10.1042/cs20160624]

140 **Lv JC**, Zhang LX. Prevalence and Disease Burden of Chronic Kidney Disease. *Adv Exp Med Biol* 2019; **1165**: 3-15 [PMID: 31399958 DOI: 10.1007/978-981-13-8871-2\_1[]

141 **Fishbane S**, Spinowitz B. Update on Anemia in ESRD and Earlier Stages of CKD: Core Curriculum 2018. *Am J Kidney Dis* 2018; **71**: 423-435 [PMID: 29336855 DOI: 10.1053/j.ajkd.2017.09.026]

142 **Stompór T**, ZabÅ‚ocki M, Åesiów M. Osteoporosis in mineral and bone disorders of chronic kidney disease. *Pol Arch Med Wewn* 2013; **123**: 314-320 [PMID: 23711558 DOI: 10.20452/pamw.1782]

143 **Drew DA**, Weiner DE, Sarnak MJ. Cognitive Impairment in CKD: Pathophysiology, Management, and Prevention. *Am J Kidney Dis* 2019; **74**: 782-790 [PMID: 31378643 DOI: 10.1053/j.ajkd.2019.05.017]

144 **Mills KT**, Xu Y, Zhang W, Bundy JD, Chen CS, Kelly TN, Chen J, He J. A systematic analysis of worldwide population-based data on the global burden of chronic kidney disease in 2010. *Kidney Int* 2015; **88**: 950-957 [PMID: 26221752 DOI: 10.1038/ki.2015.230]

145 **Glassock RJ**, Warnock DG, Delanaye P. The global burden of chronic kidney disease: estimates, variability and pitfalls. *Nat Rev Nephrol* 2017; **13**: 104-114 [PMID: 27941934 DOI: 10.1038/nrneph.2016.163]

146 **Harambat J**, van Stralen KJ, Kim JJ, Tizard EJ. Epidemiology of chronic kidney disease in children. *Pediatr Nephrol* 2012; **27**: 363-373 [PMID: 21713524 DOI: 10.1007/s00467-011-1939-1]

147 **Warady BA**, Chadha V. Chronic kidney disease in children: the global perspective. *Pediatr Nephrol* 2007; **22**: 1999-2009 [PMID: 17310363 DOI: 10.1007/s00467-006-0410-1]

148 **Cobo G**, Hecking M, Port FK, Exner I, Lindholm B, Stenvinkel P, Carrero JJ. Sex and gender differences in chronic kidney disease: progression to end-stage renal disease and haemodialysis. *Clin Sci (Lond)* 2016; **130**: 1147-1163 [PMID: 27252402 DOI: 10.1042/cs20160047]

149 **Vivante A**, Afek A, Frenkel-Nir Y, Tzur D, Farfel A, Golan E, Chaiter Y, Shohat T, Skorecki K, Calderon-Margalit R. Persistent asymptomatic isolated microscopic hematuria in Israeli adolescents and young adults and risk for end-stage renal disease. *JAMA* 2011; **306**: 729-736 [PMID: 21846854 DOI: 10.1001/jama.2011.1141]

150 **Leiba A**, Twig G, Vivante A, Skorecki K, Golan E, Derazne E, Tzur D, Grossman E, Dichtiar R, Kark JD, Shohat T. Prehypertension among 2.19 million adolescents and future risk for end-stage renal disease. *J Hypertens* 2017; **35**: 1290-1296 [PMID: 28169886 DOI: 10.1097/hjh.0000000000001295]

151 **Leiba A**, Fishman B, Twig G, Gilad D, Derazne E, Shamiss A, Shohat T, Ron O, Grossman E. Association of Adolescent Hypertension With Future End-stage Renal Disease. *JAMA Intern Med* 2019; **179**: 517-523 [PMID: 30801616 DOI: 10.1001/jamainternmed.2018.7632]

152 **Vivante A**, Golan E, Tzur D, Leiba A, Tirosh A, Skorecki K, Calderon-Margalit R. Body mass index in 1.2 million adolescents and risk for end-stage renal disease. *Arch Intern Med* 2012; **172**: 1644-1650 [PMID: 23108588 DOI: 10.1001/2013.jamainternmed.85]

153 **Silverwood RJ**, Pierce M, Hardy R, Thomas C, Ferro C, Savage C, Sattar N, Kuh D, Nitsch D; National Survey of Health and Development Scientific and Data Collection Teams. Early-life overweight trajectory and CKD in the 1946 British birth cohort study. *Am J Kidney Dis* 2013; **62**: 276-284 [PMID: 23714172 DOI: 10.1053/j.ajkd.2013.03.032]

154 **Calderon-Margalit R**, Golan E, Twig G, Leiba A, Tzur D, Afek A, Skorecki K, Vivante A. History of Childhood Kidney Disease and Risk of Adult End-Stage Renal Disease. *N Engl J Med* 2018; **378**: 428-438 [PMID: 29385364 DOI: 10.1056/NEJMoa1700993]

155 **Bonnéric S**, Karadkhele G, Couchoud C, Patzer RE, Greenbaum LA, Hogan J. Sex and Glomerular Filtration Rate Trajectories in Children. *Clin J Am Soc Nephrol* 2020; **15**: 320-329 [PMID: 32111703 DOI: 10.2215/cjn.08420719]

156 **Warady BA**, Abraham AG, Schwartz GJ, Wong CS, Muñoz A, Betoko A, Mitsnefes M, Kaskel F, Greenbaum LA, Mak RH, Flynn J, Moxey-Mims MM, Furth S. Predictors of Rapid Progression of Glomerular and Nonglomerular Kidney Disease in Children and Adolescents: The Chronic Kidney Disease in Children (CKiD) Cohort. *Am J Kidney Dis* 2015; **65**: 878-888 [PMID: 25799137 DOI: 10.1053/j.ajkd.2015.01.008]

157 **Ricardo AC**, Yang W, Sha D, Appel LJ, Chen J, Krousel-Wood M, Manoharan A, Steigerwalt S, Wright J, Rahman M, Rosas SE, Saunders M, Sharma K, Daviglus ML, Lash JP; CRIC Investigators. Sex-Related Disparities in CKD Progression. *J Am Soc Nephrol* 2019; **30**: 137-146 [PMID: 30510134 DOI: 10.1681/asn.2018030296]

158 **Carrero JJ**, Hecking M, Chesnaye NC, Jager KJ. Sex and gender disparities in the epidemiology and outcomes of chronic kidney disease. *Nat Rev Nephrol* 2018; **14**: 151-164 [PMID: 29355169 DOI: 10.1038/nrneph.2017.181]

159 **Brar A**, Markell M. Impact of gender and gender disparities in patients with kidney disease. *Curr Opin Nephrol Hypertens* 2019; **28**: 178-182 [PMID: 30652978 DOI: 10.1097/mnh.0000000000000482]

160 **Rodenbach KE**, Schneider MF, Furth SL, Moxey-Mims MM, Mitsnefes MM, Weaver DJ, Warady BA, Schwartz GJ. Hyperuricemia and Progression of CKD in Children and Adolescents: The Chronic Kidney Disease in Children (CKiD) Cohort Study. *Am J Kidney Dis* 2015; **66**: 984-992 [PMID: 26209544 DOI: 10.1053/j.ajkd.2015.06.015]

161 **Duru OK**, Li S, Jurkovitz C, Bakris G, Brown W, Chen SC, Collins A, Klag M, McCullough PA, McGill J, Narva A, Pergola P, Singh A, Norris K. Race and sex differences in hypertension control in CKD: results from the Kidney Early Evaluation Program (KEEP). *Am J Kidney Dis* 2008; **51**: 192-198 [PMID: 18215697 DOI: 10.1053/j.ajkd.2007.09.023]

162 **Antlanger M**, Noordzij M, van de Luijtgaarden M, Carrero JJ, Palsson R, Finne P, Hemmelder MH, Aresté-Fosalba N, Reisæter AV, Cases A, Traynor JP, Kramar R, Massy Z, Jager KJ, Hecking M; ERA-EDTA Registry. Sex Differences in Kidney Replacement Therapy Initiation and Maintenance. *Clin J Am Soc Nephrol* 2019; **14**: 1616-1625 [PMID: 31649071 DOI: 10.2215/cjn.04400419]

163 **Luyckx VA**, Tuttle KR, Garcia-Garcia G, Gharbi MB, Heerspink HJL, Johnson DW, Liu ZH, Massy ZA, Moe O, Nelson RG, Sola L, Wheeler DC, White SL. Reducing major risk factors for chronic kidney disease. *Kidney Int Suppl (2011)* 2017; **7**: 71-87 [PMID: 30675422 DOI: 10.1016/j.kisu.2017.07.003]

164 **Norris K**, Nissenson AR. Race, gender, and socioeconomic disparities in CKD in the United States. *J Am Soc Nephrol* 2008; **19**: 1261-1270 [PMID: 18525000 DOI:10.1681/asn.2008030276]

165 Smith J. Overcoming the ‘tyranny of the urgent’: Integrating gender into disease outbreak preparedness and response. Gender & Development 2019; 27: 355-369 [PMID: DOI: 10.1080/13552074.2019.1615288]

166 **Wenham C**, Smith J, Morgan R; Gender and COVID-19 Working Group. COVID-19: the gendered impacts of the outbreak. *Lancet* 2020; **395**: 846-848 [PMID: 32151325 DOI: 10.1016/s0140-6736(20)30526-2]

167 **Huang C**, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; **395**: 497-506 [PMID: 31986264 DOI: 10.1016/s0140-6736(20)30183-5]

168 **Guan WJ**, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC, Du B, Li LJ, Zeng G, Yuen KY, Chen RC, Tang CL, Wang T, Chen PY, Xiang J, Li SY, Wang JL, Liang ZJ, Peng YX, Wei L, Liu Y, Hu YH, Peng P, Wang JM, Liu JY, Chen Z, Li G, Zheng ZJ, Qiu SQ, Luo J, Ye CJ, Zhu SY, Zhong NS; China Medical Treatment Expert Group for Covid-19. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med* 2020; **382**: 1708-1720 [PMID: 32109013 DOI: 10.1056/NEJMoa2002032]

169 **Lake MA**. What we know so far: COVID-19 current clinical knowledge and research. *Clin Med (Lond)* 2020; **20**: 124-127 [PMID: 32139372 DOI: 10.7861/clinmed.2019-coron]

170 **Du Toit A**. Outbreak of a novel coronavirus. *Nat Rev Microbiol* 2020; **18**: 123 [PMID: 31988490 DOI: 10.1038/s41579-020-0332-0]

171 **Lu R**, Zhao X, Li J, Niu P, Yang B, Wu H, Wang W, Song H, Huang B, Zhu N, Bi Y, Ma X, Zhan F, Wang L, Hu T, Zhou H, Hu Z, Zhou W, Zhao L, Chen J, Meng Y, Wang J, Lin Y, Yuan J, Xie Z, Ma J, Liu WJ, Wang D, Xu W, Holmes EC, Gao GF, Wu G, Chen W, Shi W, Tan W. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet* 2020; **395**: 565-574 [PMID: 32007145 DOI: 10.1016/s0140-6736(20)30251-8]

172 **Zhu N**, Zhang D, Wang W, Li X, Yang B, Song J, Zhao X, Huang B, Shi W, Lu R, Niu P, Zhan F, Ma X, Wang D, Xu W, Wu G, Gao GF, Tan W; China Novel Coronavirus Investigating and Research Team. A Novel Coronavirus from Patients with Pneumonia in China, 2019. *N Engl J Med* 2020; **382**: 727-733 [PMID: 31978945 DOI: 10.1056/NEJMoa2001017]

173 **Wu F,** Zhao S, Yu B, Chen Y-M, Wang W, Song Z-G, Hu Y, Tao Z-W, Tian J-H, Pei Y-Y, Yuan M-L, Zhang Y-L, Dai F-H, Liu Y, Wang Q-M, Zheng J-J, Xu L, Holmes EC, Zhang Y-Z. A new coronavirus associated with human respiratory disease in china. Nature 2020; 579: 265-269 [PMID: DOI: 10.1038/s41586-020-2008-3]

174 **Zhou P**, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, Si HR, Zhu Y, Li B, Huang CL, Chen HD, Chen J, Luo Y, Guo H, Jiang RD, Liu MQ, Chen Y, Shen XR, Wang X, Zheng XS, Zhao K, Chen QJ, Deng F, Liu LL, Yan B, Zhan FX, Wang YY, Xiao GF, Shi ZL. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature* 2020; **579**: 270-273 [PMID: 32015507 DOI: 10.1038/s41586-020-2012-7]

175 **Zhou F**, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Y, Chen H, Cao B. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020; **395**: 1054-1062 [PMID: 32171076 DOI: 10.1016/s0140-6736(20)30566-3]

176 **Simonnet A**, Chetboun M, Poissy J, Raverdy V, Noulette J, Duhamel A, Labreuche J, Mathieu D, Pattou F, Jourdain M; LICORN and the Lille COVID-19 and Obesity study group. High Prevalence of Obesity in Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) Requiring Invasive Mechanical Ventilation. *Obesity (Silver Spring)* 2020; **28**: 1195-1199 [PMID: 32271993 DOI: 10.1002/oby.22831]

177 **Cai H**. Sex difference and smoking predisposition in patients with COVID-19. *Lancet Respir Med* 2020; **8**: e20 [PMID: 32171067 DOI: 10.1016/S2213-2600(20)30117-X]

178 **Li LQ**, Huang T, Wang YQ, Wang ZP, Liang Y, Huang TB, Zhang HY, Sun W, Wang Y. COVID-19 patients' clinical characteristics, discharge rate, and fatality rate of meta-analysis. *J Med Virol* 2020; **92**: 577-583 [PMID: 32162702 DOI: 10.1002/jmv.25757]

179 **Zheng F**, Liao C, Fan QH, Chen HB, Zhao XG, Xie ZG, Li XL, Chen CX, Lu XX, Liu ZS, Lu W, Chen CB, Jiao R, Zhang AM, Wang JT, Ding XW, Zeng YG, Cheng LP, Huang QF, Wu J, Luo XC, Wang ZJ, Zhong YY, Bai Y, Wu XY, Jin RM. Clinical Characteristics of Children with Coronavirus Disease 2019 in Hubei, China. *Curr Med Sci* 2020; **40**: 275-280 [PMID: 32207032 DOI: 10.1007/s11596-020-2172-6]

180 **Han Q**, Lin Q, Jin S, You L. Coronavirus 2019-nCoV: A brief perspective from the front line. *J Infect* 2020; **80**: 373-377 [PMID: 32109444 DOI: 10.1016/j.jinf.2020.02.010]

181 **Yang X**, Yu Y, Xu J, Shu H, Xia J, Liu H, Wu Y, Zhang L, Yu Z, Fang M, Yu T, Wang Y, Pan S, Zou X, Yuan S, Shang Y. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med* 2020; **8**: 475-481 [PMID: 32105632 DOI: 10.1016/s2213-2600(20)30079-5]

182 **Chen N**, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, Xia J, Yu T, Zhang X, Zhang L. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 2020; **395**: 507-513 [PMID: 32007143 DOI: 10.1016/s0140-6736(20)30211-7]

183 **Chang**, Lin M, Wei L, Xie L, Zhu G, Dela Cruz CS, Sharma L. Epidemiologic and Clinical Characteristics of Novel Coronavirus Infections Involving 13 Patients OutsideWuhan, China. *JAMA* 2020; Online ahead of print [PMID: 32031568 DOI: 10.1001/jama.2020.1623]

184 **Wang C**, Horby PW, Hayden FG, Gao GF. A novel coronavirus outbreak of global health concern. *Lancet* 2020; **395**: 470-473 [PMID: 31986257 DOI: 10.1016/S0140-6736(20)30185-9]

185 **Jaillon S**, Berthenet K, Garlanda C. Sexual Dimorphism in Innate Immunity. *Clin Rev Allergy Immunol* 2019; **56**: 308-321 [PMID: 28963611 DOI: 10.1007/s12016-017-8648-x]

186 **Lukassen S**, Chua RL, Trefzer T, Kahn NC, Schneider MA, Muley T, Winter H, Meister M, Veith C, Boots AW, Hennig BP, Kreuter M, Conrad C, Eils R. SARS-CoV-2 receptor ACE2 and TMPRSS2 are primarily expressed in bronchial transient secretory cells. *EMBO J* 2020; **39**: e105114 [PMID: 32246845 DOI: 10.15252/embj.20105114]

187 **Leung JM**, Yang CX, Tam A, Shaipanich T, Hackett TL, Singhera GK, Dorscheid DR, Sin DD. ACE-2 expression in the small airway epithelia of smokers and COPD patients: implications for COVID-19. *Eur Respir J* 2020; **55**: [PMID: 32269089 DOI: 10.1183/13993003.00688-2020]

188 **Cai G.** Bulk and single-cell transcriptomics identify tobacco-use disparity in lung gene expression of ace2, the receptor of 2019-ncov. medRxiv 2020 [DOI: 10.1101/2020.02.05.20020107]

189 **Wang D**, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, Zhao Y, Li Y, Wang X, Peng Z. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA* 2020; Online ahead of print [PMID: 32031570 DOI: 10.1001/jama.2020.1585]

190 **Zhang JJ**, Dong X, Cao YY, Yuan YD, Yang YB, Yan YQ, Akdis CA, Gao YD. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. *Allergy* 2020; **75**: 1730-1741 [PMID: 32077115 DOI: 10.1111/all.14238]

191 **Lian J**, Jin X, Hao S, Cai H, Zhang S, Zheng L, Jia H, Hu J, Gao J, Zhang Y, Zhang X, Yu G, Wang X, Gu J, Ye C, Jin C, Lu Y, Yu X, Yu X, Ren Y, Qiu Y, Li L, Sheng J, Yang Y. Analysis of Epidemiological and Clinical Features in Older Patients With Coronavirus Disease 2019 (COVID-19) Outside Wuhan. *Clin Infect Dis* 2020; **71**: 740-747 [PMID: 32211844 DOI: 10.1093/cid/ciaa242]

192 **Dudley JP**, Lee NT. Disparities in Age-specific Morbidity and Mortality From SARS-CoV-2 in China and the Republic of Korea. *Clin Infect Dis* 2020; **71**: 863-865 [PMID: 32232322 DOI: 10.1093/cid/ciaa354]

193 **Bhopal R**. Covid-19 worldwide: we need precise data by age group and sex urgently. *BMJ* 2020; **369**: m1366 [PMID: 32245830 DOI: 10.1136/bmj.m1366]

194 **Jin JM,** Bai P, He W, Wu F, Liu XF, Han DM, Liu S, Yang JK. Gender differences in patients with covid-19: Focus on severity and mortality. medRxiv 2020 [DOI: 10.1101/2020.02.23.20026864]

195 **Chen T**, Wu D, Chen H, Yan W, Yang D, Chen G, Ma K, Xu D, Yu H, Wang H, Wang T, Guo W, Chen J, Ding C, Zhang X, Huang J, Han M, Li S, Luo X, Zhao J, Ning Q. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. *BMJ* 2020; **368**: m1091 [PMID: 32217556 DOI: 10.1136/bmj.m1091]

196 **Mo P**, Xing Y, Xiao Y, Deng L, Zhao Q, Wang H, Xiong Y, Cheng Z, Gao S, Liang K, Luo M, Chen T, Song S, Ma Z, Chen X, Zheng R, Cao Q, Wang F, Zhang Y. Clinical characteristics of refractory COVID-19 pneumonia in Wuhan, China. *Clin Infect Dis* 2020; Online ahead of print [PMID: 32173725 DOI: 10.1093/cid/ciaa270]

197 **Liu N**, Zhang F, Wei C, Jia Y, Shang Z, Sun L, Wu L, Sun Z, Zhou Y, Wang Y, Liu W. Prevalence and predictors of PTSS during COVID-19 outbreak in China hardest-hit areas: Gender differences matter. *Psychiatry Res* 2020; **287**: 112921 [PMID: 32240896 DOI: 10.1016/j.psychres.2020.112921]

198 **Wu Z**, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. *JAMA* 2020; Online ahead of print [PMID: 32091533 DOI: 10.1001/jama.2020.2648]

199 **She J**, Liu L, Liu W. COVID-19 epidemic: Disease characteristics in children. *J Med Virol* 2020; **92**: 747-754 [PMID: 32232980 DOI: 10.1002/jmv.25807]

200 **Lu X**, Zhang L, Du H, Zhang J, Li YY, Qu J, Zhang W, Wang Y, Bao S, Li Y, Wu C, Liu H, Liu D, Shao J, Peng X, Yang Y, Liu Z, Xiang Y, Zhang F, Silva RM, Pinkerton KE, Shen K, Xiao H, Xu S, Wong GWK; Chinese Pediatric Novel Coronavirus Study Team. SARS-CoV-2 Infection in Children. *N Engl J Med* 2020; **382**: 1663-1665 [PMID: 32187458 DOI: 10.1056/NEJMc2005073]

201 **Wei M**, Yuan J, Liu Y, Fu T, Yu X, Zhang ZJ. Novel Coronavirus Infection in Hospitalized Infants Under 1 Year of Age in China. *JAMA* 2020; : [PMID: 32058570 DOI: 10.1001/jama.2020.2131]

202 **Dong Y**, Mo X, Hu Y, Qi X, Jiang F, Jiang Z, Tong S. Epidemiology of COVID-19 Among Children in China. *Pediatrics* 2020; **145**: e20200702 [PMID: 32179660 DOI: 10.1542/peds.2020-0702]

203 **Sun D**, Li H, Lu XX, Xiao H, Ren J, Zhang FR, Liu ZS. Clinical features of severe pediatric patients with coronavirus disease 2019 in Wuhan: a single center's observational study. *World J Pediatr* 2020; **16**: 251-259 [PMID: 32193831 DOI: 10.1007/s12519-020-00354-4]

204 **Zhao S**, Cao P, Chong MKC, Gao D, Lou Y, Ran J, Wang K, Wang W, Yang L, He D, Wang MH. COVID-19 and gender-specific difference: Analysis of public surveillance data in Hong Kong and Shenzhen, China, from January 10 to February 15, 2020. *Infect Control Hosp Epidemiol* 2020; **41**: 750-751 [PMID: 32146921 DOI: 10.1017/ice.2020.64]

205 **Al-Najjar H**, Al-Rousan N. A classifier prediction model to predict the status of Coronavirus COVID-19 patients in South Korea. *Eur Rev Med Pharmacol Sci* 2020; **24**: 3400-3403 [PMID: 32271458 DOI: 10.26355/eurrev\_202003\_20709]

206 **Baggio G**, Corsini A, Floreani A, Giannini S, Zagonel V. Gender medicine: a task for the third millennium. *Clin Chem Lab Med* 2013; **51**: 713-727 [PMID: 23515103 DOI: 10.1515/cclm-2012-0849]

207 **Regitz-Zagrosek V**, Seeland U. Sex and gender differences in clinical medicine. *Handb Exp Pharmacol* 2012; **(214)**: 3-22 [PMID: 23027443 DOI: 10.1007/978-3-642-30726-3\_1]

208 **Kim YS**, Kim N. Sex-Gender Differences in Irritable Bowel Syndrome. *J Neurogastroenterol Motil* 2018; **24**: 544-558 [PMID: 30347934 DOI: 10.5056/jnm18082]

209 **Lowe D**, John S. Autoimmune hepatitis: Appraisal of current treatment guidelines. *World J Hepatol* 2018; **10**: 911-923 [PMID: 30631396 DOI: 10.4254/wjh.v10.i12.911]

210 **Reckelhoff JF**. Gender differences in hypertension. *Curr Opin Nephrol Hypertens* 2018; **27**: 176-181 [PMID: 29406364 DOI: 10.1097/mnh.0000000000000404]

211 **Roffi M**, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, Bax JJ, Borger MA, Brotons C, Chew DP, Gencer B, Hasenfuss G, Kjeldsen K, Lancellotti P, Landmesser U, Mehilli J, Mukherjee D, Storey RF, Windecker S; ESC Scientific Document Group . 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2016; **37**: 267-315 [PMID: 26320110 DOI: 10.1093/eurheartj/ehv320]

212 **Jortveit J**, Govatsmark RE, Langørgen J, Hole T, Mannsverk J, Olsen S, Risøe C, Halvorsen S. Gender differences in the assessment and treatment of myocardial infarction. *Tidsskr Nor Laegeforen* 2016; **136**: 1215-1222 [PMID: 27554562 DOI: 10.4045/tidsskr.16.0224]

213 **Poon S**, Goodman SG, Yan RT, Bugiardini R, Bierman AS, Eagle KA, Johnston N, Huynh T, Grondin FR, Schenck-Gustafsson K, Yan AT. Bridging the gender gap: Insights from a contemporary analysis of sex-related differences in the treatment and outcomes of patients with acute coronary syndromes. *Am Heart J* 2012; **163**: 66-73 [PMID: 22172438 DOI: 10.1016/j.ahj.2011.09.025]

214 **McKercher C**, Jose MD, Grace B, Clayton PA, Walter M. Gender differences in the dialysis treatment of Indigenous and non-Indigenous Australians. *Aust N Z J Public Health* 2017; **41**: 15-20 [PMID: 27960225 DOI: 10.1111/1753-6405.12621]

215 **Australian Institute of Health.** Dialysis and kidney transplantation in australia: 1991-2010. AIHW, 2012

216 **Patzer RE**, McClellan WM. Influence of race, ethnicity and socioeconomic status on kidney disease. *Nat Rev Nephrol* 2012; **8**: 533-541 [PMID: 22735764 DOI: 10.1038/nrneph.2012.117]

217 **Tannenbaum C**, Clow B, Haworth-Brockman M, Voss P. Sex and gender considerations in Canadian clinical practice guidelines: a systematic review. *CMAJ Open* 2017; **5**: E66-E73 [PMID: 28401121 DOI: 10.9778/cmajo.20160051]

218 **Norris CM**, Tannenbaum C, Pilote L, Wong G, Cantor WJ, McMurtry MS. Systematic Incorporation of Sex-Specific Information Into Clinical Practice Guidelines for the Management of ST -Segment-Elevation Myocardial Infarction: Feasibility and Outcomes. *J Am Heart Assoc* 2019; **8**: e011597 [PMID: 30929545 DOI: 10.1161/jaha.118.011597]

219 **Pasco JA**, Foulkes C, Doolan B, Brown K, Holloway KL, Brennan-Olsen SL. A conduit between epidemiological research and regional health policy. *Aust N Z J Public Health* 2016; **40**: 250-254 [PMID: 27027274 DOI: 10.1111/1753-6405.12520]

220 **Zeitler J**, Babitsch B. [Barriers and facilitators for the development of sex/gender sensitive clinical practice guidelines: A qualitative interview study]. *Z Evid Fortbild Qual Gesundhwes* 2018; **135-136**: 65-71 [PMID: 30049655 DOI: 10.1016/j.zefq.2018.05.002]

221 **Miller VM**, Rice M, Schiebinger L, Jenkins MR, Werbinski J, Núñez A, Wood S, Viggiano TR, Shuster LT. Embedding concepts of sex and gender health differences into medical curricula. *J Womens Health (Larchmt)* 2013; **22**: 194-202 [PMID: 23414074 DOI: 10.1089/jwh.2012.4193]

222 **Ashurst JV**, McGregor AJ, Safdar B, Weaver KR, Quinn SM, Rosenau AM, Goyke TE, Roth KR, Greenberg MR. Emergency Medicine Gender-specific Education. *Acad Emerg Med* 2014; **21**: 1453-1458 [PMID: 25491708 DOI: 10.1111/acem.12545]

223 **McGregor AJ**, Beauchamp GA, Wira CR 3rd, Perman SM, Safdar B. Sex as a Biological Variable in Emergency Medicine Research and Clinical Practice: A Brief Narrative Review. *West J Emerg Med* 2017; **18**: 1079-1090 [PMID: 29085541 DOI: 10.5811/westjem.2017.8.34997]

224 **Oertelt-Prigione S**, Dalibert L, Verdonk P, Stutz EZ, Klinge I. Implementation Strategies for Gender-Sensitive Public Health Practice: A European Workshop. *J Womens Health (Larchmt)* 2017; **26**: 1255-1261 [PMID: 28937841 DOI: 10.1089/jwh.2017.6592]

225 **Weber AM**, Cislaghi B, Meausoone V, Abdalla S, Mejía-Guevara I, Loftus P, Hallgren E, Seff I, Stark L, Victora CG, Buffarini R, Barros AJD, Domingue BW, Bhushan D, Gupta R, Nagata JM, Shakya HB, Richter LM, Norris SA, Ngo TD, Chae S, Haberland N, McCarthy K, Cullen MR, Darmstadt GL; Gender Equality, Norms and Health Steering Committee. Gender norms and health: insights from global survey data. *Lancet* 2019; **393**: 2455-2468 [PMID: 31155273 DOI: 10.1016/s0140-6736(19)30765-2]

226 **Palència L**, De Moortel D, Artazcoz L, Salvador-Piedrafita M, Puig-Barrachina V, Hagqvist E, Pérez G, Ruiz ME, Trujillo-Alemán S, Vanroelen C, Malmusi D, Borrell C. Gender Policies and Gender Inequalities in Health in Europe: Results of the SOPHIE Project. *Int J Health Serv* 2017; **47**: 61-82 [PMID: 27530991 DOI: 10.1177/0020731416662611]

227 **Tillmann B**, Wunsch H. Epidemiology and Outcomes. *Crit Care Clin* 2018; **34**: 15-27 [PMID: 29149936 DOI: 10.1016/j.ccc.2017.08.001]

228 **Violan C**, Foguet-Boreu Q, Flores-Mateo G, Salisbury C, Blom J, Freitag M, Glynn L, Muth C, Valderas JM. Prevalence, determinants and patterns of multimorbidity in primary care: a systematic review of observational studies. *PLoS One* 2014; **9**: e102149 [PMID: 25048354 DOI: 10.1371/journal.pone.0102149]

229 **Takele K**, Zewotir T, Ndanguza D. Risk factors of morbidity among children under age five in Ethiopia. *BMC Public Health* 2019; **19**: 942 [PMID: 31307433 DOI: 10.1186/s12889-019-7273-4]

230 **Biswas A**, Oh PI, Faulkner GE, Bajaj RR, Silver MA, Mitchell MS, Alter DA. Sedentary time and its association with risk for disease incidence, mortality, and hospitalization in adults: a systematic review and meta-analysis. *Ann Intern Med* 2015; **162**: 123-132 [PMID: 25599350 DOI: 10.7326/m14-1651]

231 **Bar-oz A,** Bin Nun G, Shvarts S. The israeli healthcare system on the operating table: 25 years since implementation of the national health insurance law. The National Institute for Health Services Researh and Health Policy 2019:

232 **GBD 2015 LRI Collaborators**. Estimates of the global, regional, and national morbidity, mortality, and aetiologies of lower respiratory tract infections in 195 countries: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet Infect Dis* 2017; **17**: 1133-1161 [PMID: 28843578 DOI: 10.1016/s1473-3099(17)30396-1]

233 **Boghossian NS**, Geraci M, Lorch SA, Phibbs CS, Edwards EM, Horbar JD. Racial and Ethnic Differences Over Time in Outcomes of Infants Born Less Than 30 Weeks' Gestation. *Pediatrics* 2019; **144**: e20191106 [PMID: 31405887 DOI: 10.1542/peds.2019-1106]

234 **Nowossadeck E**. [Forecasts of morbidity based on population projections: what can health monitoring contribute?]. *Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz* 2010; **53**: 427-434 [PMID: 20354667 DOI: 10.1007/s00103-010-1048-5]

235 **Frank J**, Ryll A. [In Process Citation]. *Gesundheitswesen* 2015; **77**: 932-938 [PMID: 25531156 DOI: 10.1055/s-0034-1390417]

236 **Benke K**, Benke G. Artificial Intelligence and Big Data in Public Health. *Int J Environ Res Public Health* 2018; **15**: [PMID: 30544648 DOI: 10.3390/ijerph15122796]

237 **Caesar MCW**, Hakim Z, Ierasts T. Connecting Data to Value: An Operating Model for Healthcare Advanced Analytics. *Healthc Q* 2020; **23**: 20-27 [PMID: 32249735 DOI: 10.12927/hcq.2020.26143]

238 **Lynch CM**, Abdollahi B, Fuqua JD, de Carlo AR, Bartholomai JA, Balgemann RN, van Berkel VH, Frieboes HB. Prediction of lung cancer patient survival via supervised machine learning classification techniques. *Int J Med Inform* 2017; **108**: 1-8 [PMID: 29132615 DOI: 10.1016/j.ijmedinf.2017.09.013]

239 **Kupusinac A**, StokiÄ‡ E, SukiÄ‡ E, Rankov O, KatiÄ‡ A. What kind of Relationship is Between Body Mass Index and Body Fat Percentage? *J Med Syst* 2017; **41**: 5 [PMID: 27826765 DOI: 10.1007/s10916-016-0636-9]

240 **Ivanović D**, Kupusinac A, Stokić E, Doroslovački R, Ivetić D. ANN Prediction of Metabolic Syndrome: a Complex Puzzle that will be Completed. *J Med Syst* 2016; **40**: 264 [PMID: 27730390 DOI: 10.1007/s10916-016-0601-7]

**Footnotes**

**Conflict-of-interest statement:** The authors declare that there are no commercial or financial or any other relationships that could be construed or perceived by the academic or medical communities as representing a potential conflict of interest. The opinions expressed in this manuscript represent the consensus of the authors and do not necessarily reflect the formal position of the affiliated institutions.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

**Manuscript source:** Invited manuscript

**Peer-review started:** April 24, 2020

**First decision:** May 15, 2020

**Article in press:**

**Specialty type:** Public, environmental and occupational health

**Country/Territory of origin:** Israel

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): B

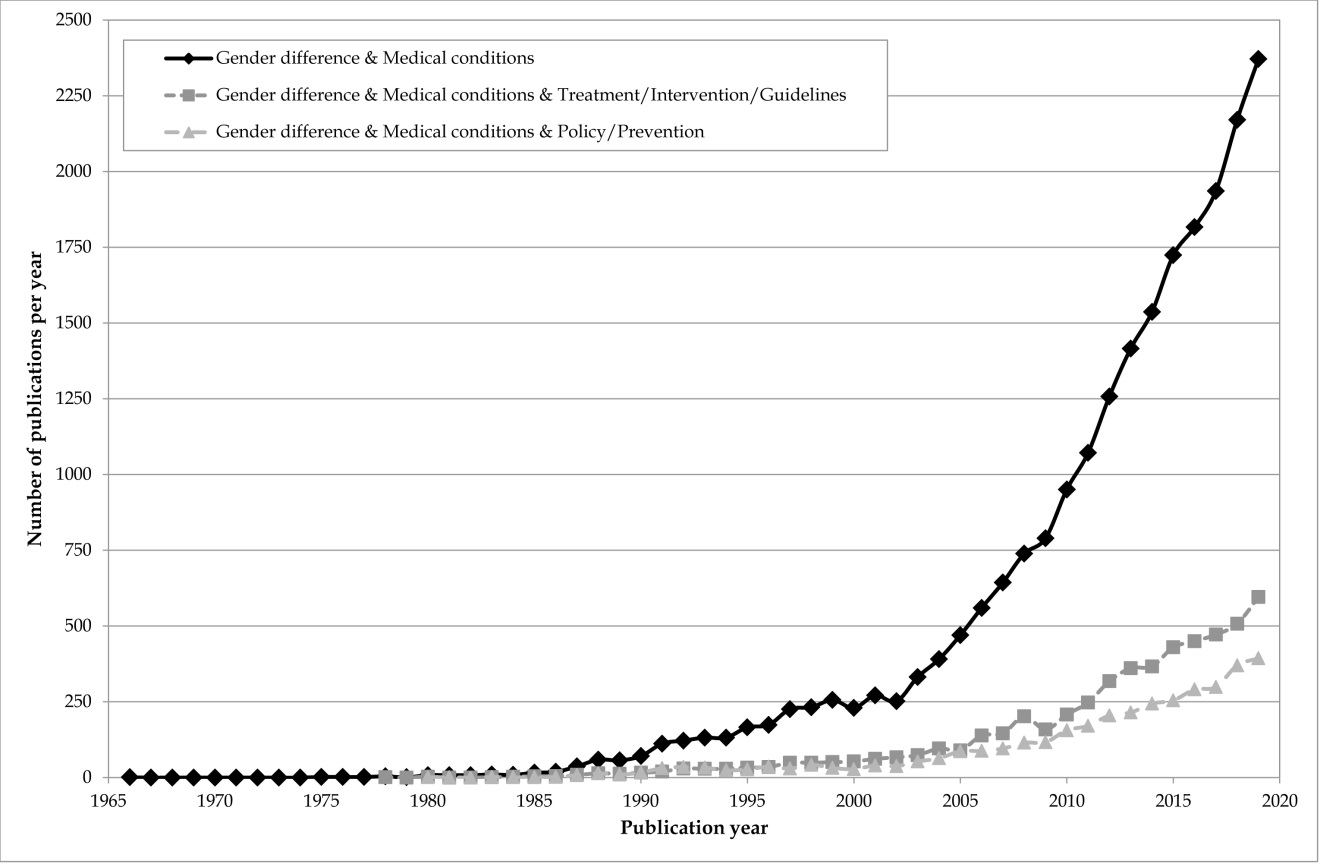
Grade C (Good): 0

Grade D (Fair): 0

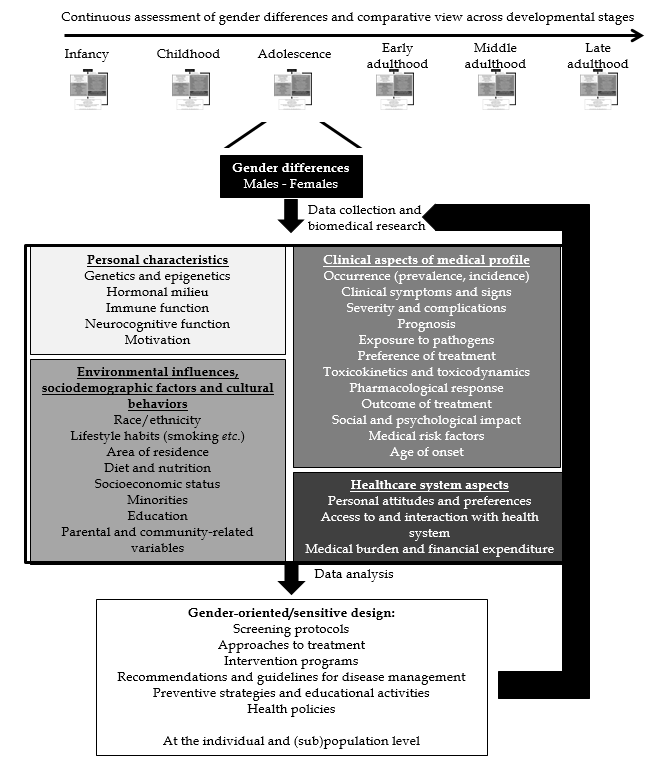
Grade E (Poor): 0

**P-Reviewer:** Chou YC **S-Editor:** Wang DM **L-Editor: P-Editor:**

**Figure Legends**

****

**Figure 1 The annual number or articles publishes in PubMed on gender differences and medical conditions.** The annual number of articles on gender differences and medical conditions1 (black rhombus, continuous line), and the subsets on treatment/intervention/guidelines2 (dark gray square, dotted line) or health policy/prevention strategies3 (light gray, dashed line). 1The exact query searched for the following terms in either the “Title” or the “Abstract” of the articles: [(“Gender difference” OR “sex difference” OR [(“sex” OR “gender”) AND “risk factors”)] AND (“health” OR “comorbidities” OR “medical conditions”) NOT (“transgender” OR “identity” OR “orientation”)]; 2The exact query is similar to the first one, including an additional condition: (“Treatment” OR “intervention” OR “guidelines”); 3The exact query is similar to the first one, including an additional condition: (“Policy” OR “prevention”).



**Figure 2 A broad and integrative approach to generating data on gender differences related to medical profiles across developemental stages and translating the evidence into age-adjusted and gender-oriented clinical guidelines and health policy.**