

World Journal of *Clinical Cases*

World J Clin Cases 2020 September 6; 8(17): 3621-3919



Contents

Semimonthly Volume 8 Number 17 September 6, 2020

REVIEW

- 3621 Autoimmunity as the comet tail of COVID-19 pandemic
Talotta R, Robertson E
- 3645 Gender medicine: Lessons from COVID-19 and other medical conditions for designing health policy
Machluf Y, Chaïter Y, Tal O

MINIREVIEWS

- 3669 Complexities of diagnosis and management of COVID-19 in autoimmune diseases: Potential benefits and detriments of immunosuppression
Georgiev T, Angelov AK

ORIGINAL ARTICLE

Retrospective Study

- 3679 Incidental anal ¹⁸fluorodeoxyglucose uptake: Should we further examine the patient?
Moussaddaq AS, Brochard C, Palard-Novello X, Garin E, Wallenhorst T, Le Balc'h E, Merlini L'heritier A, Grainville T, Siproudhis L, Lièvre A
- 3691 Emergency surgery in COVID-19 outbreak: Has anything changed? Single center experience
D'Urbano F, Fabbri N, Koleva Radica M, Rossin E, Carcoforo P
- 3697 Somatostatin receptor scintigraphy in the follow up of neuroendocrine neoplasms of appendix
Saponjski J, Macut D, Sobic-Saranovic D, Ognjanovic S, Bozic Antic I, Pavlovic D, Artiko V
- 3708 Efficacy of stool multiplex polymerase chain reaction assay in adult patients with acute infectious diarrhea
Ahn JS, Seo SI, Kim J, Kim T, Kang JG, Kim HS, Shin WG, Jang MK, Kim HY
- 3718 Comparison of gemcitabine plus nab-paclitaxel and FOLFIRINOX in metastatic pancreatic cancer
Han SY, Kim DU, Seol YM, Kim S, Lee NK, Hong SB, Seo HI
- 3730 Shear wave elastography may be sensitive and more precise than transient elastography in predicting significant fibrosis
Yao TT, Pan J, Qian JD, Cheng H, Wang Y, Wang GQ
- 3743 Radioactive ¹²⁵I seed implantation for locally advanced pancreatic cancer: A retrospective analysis of 50 cases
Li CG, Zhou ZP, Jia YZ, Tan XL, Song YY
- 3751 Active surveillance in metastatic pancreatic neuroendocrine tumors: A 20-year single-institutional experience
Gao HL, Wang WQ, Xu HX, Wu CT, Li H, Ni QX, Yu XJ, Liu L

- 3763** Clinical efficacy of tocilizumab treatment in severe and critical COVID-19 patients

Zeng J, Xie MH, Yang J, Chao SW, Xu EL

- 3774** Phosphatidylinositol-3,4,5-trisphosphate dependent Rac exchange factor 1 is a diagnostic and prognostic biomarker for hepatocellular carcinoma

Cai Y, Zheng Q, Yao DJ

Observational Study

- 3786** Awareness and attitude of fecal microbiota transplantation through transendoscopic enteral tubing among inflammatory bowel disease patients

Zhong M, Sun Y, Wang HG, Marcella C, Cui BT, Miao YL, Zhang FM

CASE REPORT

- 3797** Cauda equina arachnoiditis – a rare manifestation of West Nile virus neuroinvasive disease: A case report

Santini M, Zupetic I, Viskovic K, Krznaric J, Kutlesa M, Krajinovic V, Polak VL, Savic V, Tabain I, Barbic L, Bogdanic M, Stevanovic V, Mrzljak A, Vilibic-Cavlek T

- 3804** Portal gas in neonates; is it always surgical? A case report

Altokhais TI

- 3808** Large lingual heterotopic gastrointestinal cyst in a newborn: A case report

Lee AD, Harada K, Tanaka S, Yokota Y, Mima T, Enomoto A, Kogo M

- 3814** Osteochondral lesion of talus with gout tophi deposition: A case report

Kim T, Choi YR

- 3821** Traumatic neuroma of remnant cystic duct mimicking duodenal subepithelial tumor: A case report

Kim DH, Park JH, Cho JK, Yang JW, Kim TH, Jeong SH, Kim YH, Lee YJ, Hong SC, Jung EJ, Ju YT, Jeong CY, Kim JY

- 3828** Autoimmune hepatitis in a patient with immunoglobulin A nephropathy: A case report

Jeon YH, Kim DW, Lee SJ, Park YJ, Kim HJ, Han M, Kim IY, Lee DW, Song SH, Lee SB, Seong EY

- 3835** Diagnosis of an actively bleeding brachial artery hematoma by contrast-enhanced ultrasound: A case report

Ma JJ, Zhang B

- 3841** Lung adenocarcinoma harboring rare epidermal growth factor receptor L858R and V834L mutations treated with icotinib: A case report

Zhai SS, Yu H, Gu TT, Li YX, Lei Y, Zhang HY, Zhen TH, Gao YG

- 3847** Gastroduodenitis associated with ulcerative colitis: A case report

Yang Y, Li CQ, Chen WJ, Ma ZH, Liu G

- 3853** Majocchi's granuloma caused by *Trichophyton rubrum* after facial injection with hyaluronic acid: A case report

Liu J, Xin WQ, Liu LT, Chen CF, Wu L, Hu XP

- 3859** Novel deletion mutation in Bruton's tyrosine kinase results in X-linked agammaglobulinemia: A case report
Hu XM, Yuan K, Chen H, Chen C, Fang YL, Zhu JF, Liang L, Wang CL
- 3867** Multidisciplinary treatment of life-threatening hemoptysis and paraplegia of choriocarcinoma with pulmonary, hepatic and spinal metastases: A case report
Lin YY, Sun Y, Jiang Y, Song BZ, Ke LJ
- 3875** Diagnostic value of ultrasound in the spontaneous rupture of renal angiomyolipoma during pregnancy: A case report
Zhang T, Xue S, Wang ZM, Duan XM, Wang DX
- 3881** Gallbladder sarcomatoid carcinoma: Seven case reports
Qin Q, Liu M, Wang X
- 3890** Surgical strategy used in multilevel cervical disc replacement and cervical hybrid surgery: Four case reports
Wang XF, Meng Y, Liu H, Hong Y, Wang BY
- 3903** Diagnosis and treatment of an elderly patient with 2019-nCoV pneumonia and acute exacerbation of chronic obstructive pulmonary disease in Gansu Province: A case report
He TP, Wang DL, Zhao J, Jiang XY, He J, Feng JK, Yuan Y
- 3911** Diagnosis and treatment of mixed infection of hepatic cystic and alveolar *echinococcosis*: Four case reports
A JD, Chai JP, Wang H, Gao W, Peng Z, Zhao SY, A XR

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The WJCC is now indexed in Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports/Science Edition, PubMed, and PubMed Central. The 2020 Edition of Journal Citation Reports® cites the 2019 impact factor (IF) for WJCC as 1.013; IF without journal self cites: 0.991; Ranking: 120 among 165 journals in medicine, general and internal; and Quartile category: Q3.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: Yan-Xia Xing; Production Department Director: Yun-Xiaojuan Wu; Editorial Office Director: Jin-Lai Wang.

NAME OF JOURNAL

World Journal of Clinical Cases

ISSN

ISSN 2307-8960 (online)

LAUNCH DATE

April 16, 2013

FREQUENCY

Semimonthly

EDITORS-IN-CHIEF

Dennis A Bloomfield, Sandro Vento, Bao-Gan Peng

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/2307-8960/editorialboard.htm>

PUBLICATION DATE

September 6, 2020

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INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>



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

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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.

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.

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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.

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Manuscript source: Invited manuscript

Received: April 24, 2020

Peer-review started: April 24, 2020

First decision: May 15, 2020

Revised: May 29, 2020

Accepted: August 12, 2020

Article in press: August 12, 2020

Published online: September 6, 2020

P-Reviewer: Chou YC

S-Editor: Wang DM

L-Editor: A

P-Editor: Liu JH



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

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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.

Citation: Machluf Y, Chaite Y, Tal O. Gender medicine: Lessons from COVID-19 and other medical conditions for designing health policy. *World J Clin Cases* 2020; 8(17): 3645-3668

URL: <https://www.wjgnet.com/2307-8960/full/v8/i17/3645.htm>

DOI: <https://dx.doi.org/10.12998/wjcc.v8.i17.3645>

INTRODUCTION

The fundamentals and background of gender medicine

Buoncervello and colleagues^[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^[2,3]. 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]) to drug-related aspects (such as toxicokinetics and toxicodynamics^[5], as well as pharmacological response^[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]. 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] 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-1980 s no more than 10 articles were published each year, dozens of articles were published each year during the late 1980 s, and the annual numbers steadily grew to over a hundred during the early 1990 s, a few hundred during the 2000 s, and over one thousand during the early 2010 s, 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 1980 s, 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

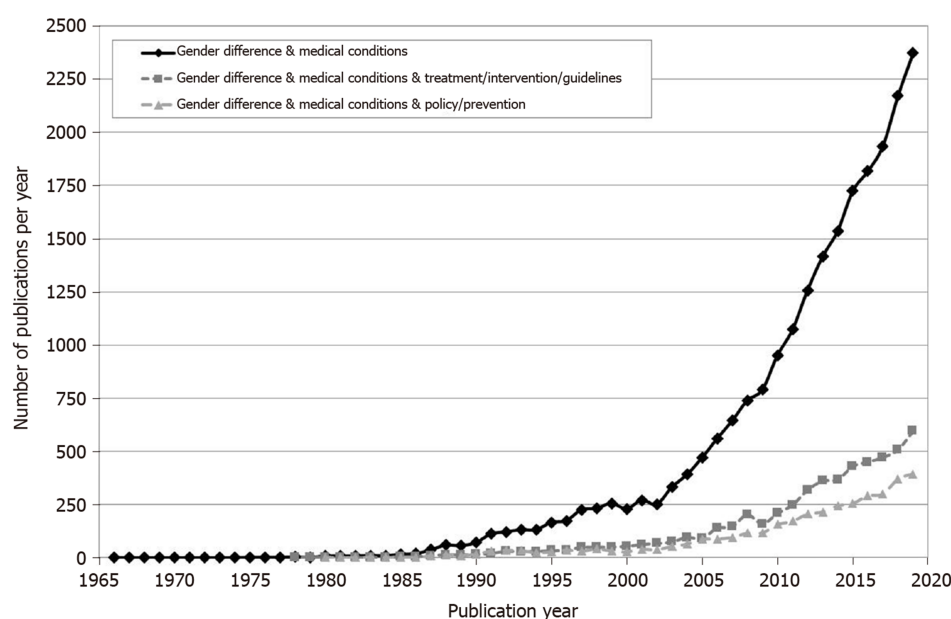


Figure 1 The annual number of articles publishes in PubMed on gender differences and medical conditions. The annual number of articles on gender differences and medical conditions¹ (black rhombus, continuous line), and the subsets on treatment/intervention/guidelines² (dark gray square, dotted line) 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").

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], as well as the consideration of sex disparities in preclinical studies including *in vitro* and *in vivo* approaches^[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].

Yet, almost simultaneously the premise of personalized medicine^[10] or precision medicine^[11,12] 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] and translational medicine^[17], or into epidemiological and pathophysiological data as well as into information on treatment options and clinical outcomes^[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], diabetes^[23-26], renal diseases^[27], asthma^[28-30], autoimmune diseases^[31], migraine^[32], cancer^[33-36], spondyloarthritis^[37], multiple sclerosis^[38,39], Alzheimer's disease^[40-42], sleep apnea and sleep disordered breathing^[43], epilepsy^[44], stroke^[45], autism^[46], depression^[47], anxiety^[48], addiction and substance use^[49,50], 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]. Its pathophysiology includes abnormalities of the immune regulation of allergic, inflammatory and neuroendocrine responses^[54,55]. 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]. The role of sex hormones, genetic predisposition and comorbidities in airway inflammation, smooth muscle contraction, mucus production and airway mechanics has been demonstrated^[28,60]. 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^[29,30].

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]. Cross-sectional surveys and small cohorts support the relationship of asthma^[64-68], particularly the severe asthma phenotype^[69,70], with diverse comorbidities such as upper airway diseases, neurologic disorders including migraine^[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^[72,73], 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]. 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^[70,77,78], as such comorbidities may be coincidental findings or they may contribute directly to asthma severity^[79] and to the difficult-to-treat phenotype^[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], as well as coexisting medical conditions^[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]. Additionally, identifying gender-specific risk factors for asthma among both young and adult populations^[80-84] 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^[85,86]. 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]. 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]. It seems that regardless of the threshold or definition, the estimates of severe obesity are higher among boys than among girls^[89-91], although the evidence is not conclusive^[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^[86,93-95], including hyperlipidemia, hypertension, and abnormal glucose tolerance^[96]. Moreover, childhood and adolescent obesity, mainly among girls, is associated with adverse psychosocial consequences^[86], social exclusion and depression^[96,97], as well as lower educational attainment^[98,99], lower income and increased rates of household poverty^[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]. Furthermore, the number of years living with obesity is directly associated with the risk of mortality^[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].

The associations between obesity and a wide range of comorbidities differ between genders, for example: Migraine^[103], depression, eating disorders, anxiety and other mental disorders^[104,105], sleep apnea^[106], hypertension^[107,108], atrial fibrillation^[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]. 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]. Recently, the gender-specific associations between obese adolescents with cardiovascular and non-cardiovascular mortality in midlife were investigated^[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].

Altogether, the rising prevalence of elevated BMI and its burden^[113]—in terms of health, social and economic consequences^[99,114-117]—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]. 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]. There is more evidence that obesity prevention programs produce larger effects for females than males^[126], although this difference is usually non-significant^[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]. 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]. 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], and recommendations that provide practical guidance to pediatric clinicians who evaluate, treat and prevent overweight and obesity in children and adolescents have been developed^[129,130]. 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^[118,131]. 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] and Australia^[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]. Gender differences in the economic impact of obesity have been estimated by quality of life, years of life lost^[135] and hospitalization costs^[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], low income countries^[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]. 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]. Additionally, CKD, especially in later stages, may cause chronic anemia^[141], mostly due to a lack of erythropoietin, osteoporosis^[142] and cognitive impairment^[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], and recently it was updated upwards^[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]. 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]. The currently available data are not only limited but also imprecise, and flawed by methodological differences between the various sources^[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]. While in Latin America the corresponding prevalence is lower (approximately 42 per million of the age-related population) and data from the Middle East are fragmented^[146], there is actually no comparable information available from the United States^[147].

Cobo *et al*^[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].

Several risk factors in childhood and adolescence have been associated with increased risk for future ESRD, including: Persistent asymptomatic isolated microscopic hematuria^[149], hypertension and pre-hypertension^[150,151], overweight and obesity^[152,153], and a history of clinically evident kidney disease in childhood, even if renal function was apparently normal in adolescence^[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], whereas among non-glomerular patients no significant gender difference was obtained^[155] or even faster progression of CKD was noted in males^[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]. 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^[158,159]. 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]. 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].

Gender-specific disparities have also been observed in the treatment of CKD^[148,158,159,162]. 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]. 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^[159,164]. However, such an approach has been largely neglected^[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^[148,159], 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].

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, also known as 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]. 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].

The outburst of a pneumonia-like disease with an unknown etiology in Wuhan, China, in mid-late December 2019^[167-169] has become a global pandemic that poses a significant threat to global health^[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]. 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], and elevated BMI, mainly obesity^[176].

Although the disease has only recently erupted and spread, early studies have already indicated noticeable differences between males and females^[177]. First, there might be a gender predisposition to COVID-19, with men more prone to being affected^[178], as male prevalence ranges from approximately 55%^[168,179,180] to 67%^[181,182] and up to approximately 75%^[167,183], depending on the country, disease severity and method of diagnosis. Overall, the male to female ratio is 2.7:1^[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], 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], or maybe smoking habits and their effects on increased airway expression of ACE2^[187,188], although the smoking effect should be validated^[186]. Of note, in a few studies the gender differences in the number of cases, if they existed, were not statistically significant^[166,189,190], and the differences have been shown to possibly change with age^[191]. In general, only a few studies have provided precise data stratified by age group and gender^[192]; this may be a major hurdle to evidence-based decision making and policy design^[193].

Regardless of susceptibility, there seem to be gender differences in mortality from and vulnerability to the disease^[166,176], 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] and particularly among severely ill (or worse) patients and those who need management in intensive care units^[167,195] and invasive mechanical ventilation^[176]. In contrast, another study found no gender differences among patients in intensive care units or in mortality rate^[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].

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].

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^[198,199] and tend to have a milder clinical course, yet the reported proportion of male children is approximately 55% or higher^[200-202]. Data on children and adolescent patients with COVID-19 have just begun to accumulate^[202,203].

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]. Gender has also been integrated into a classifier prediction model to predict the status of recovered and dead COVID-19 patients^[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]. 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^[206,207]. 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]. 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]. Existing gender-adjusted treatment guidelines are still not completely applied, for example, guidelines have not been equally implemented for

hypertension^[210], for myocardial infarction^[211] and for acute coronary syndrome^[212,213]. Access to dialysis treatment and the types of treatments employed for kidney diseases differ by gender^[214,215] (as well as by age, race, ethnicity and SES^[215,216]). Even if already integrated into current guidelines, such as those of CVD, guidelines still require gender-based revision^[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]. 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]. 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]. Recently, barriers to the development of sex/gender-sensitive guidelines have been identified^[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].

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], as well as emergency medicine education^[222], in light of the important implications of gender for changing the clinical practice of emergency care^[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]. Both gender norms^[225] and gender-equality policies^[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]. 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]. 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]. 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].

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^[113,232]. 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].

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^[234,235].

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]. 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

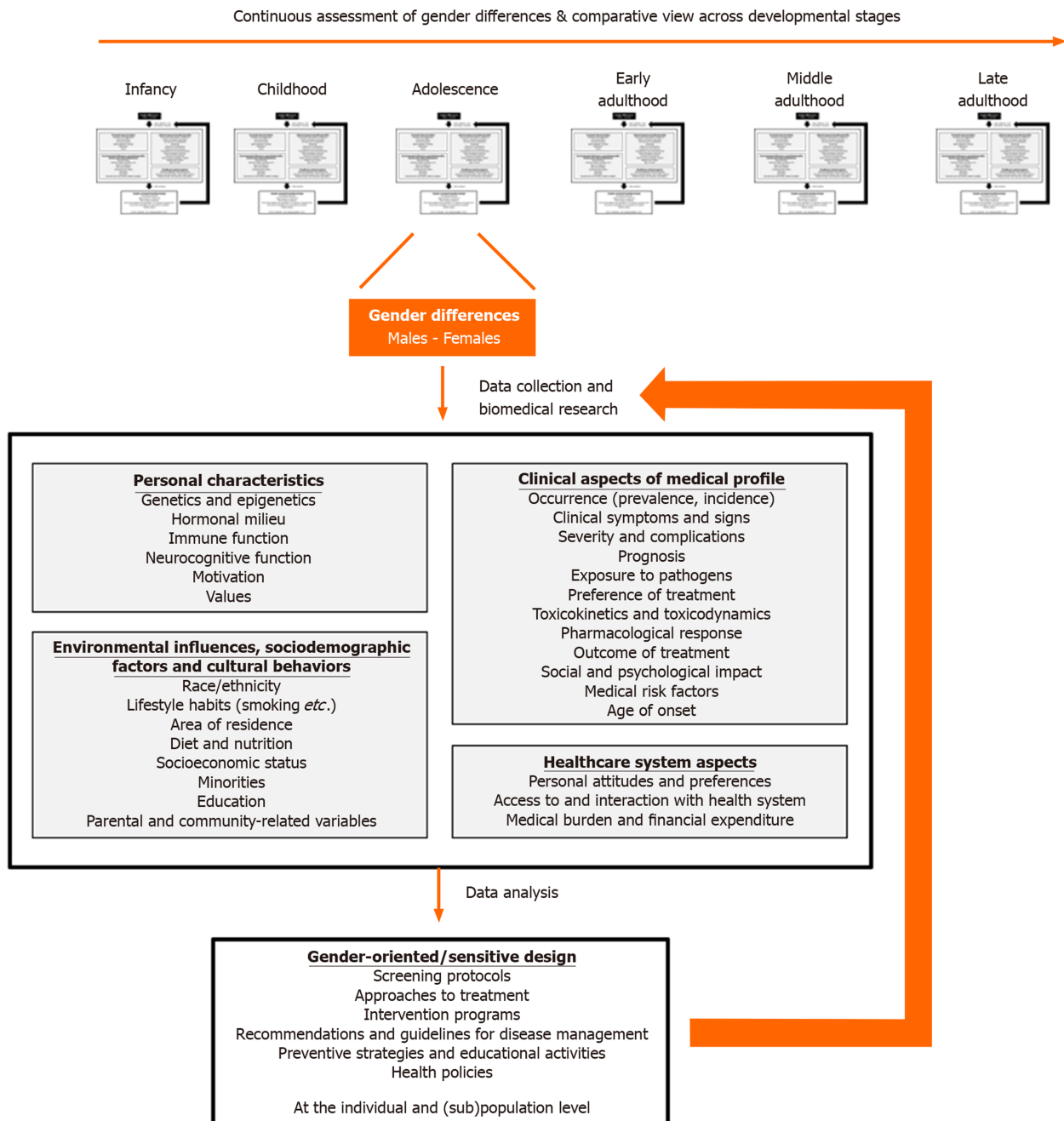


Figure 2 A broad and integrative approach to generating data on gender differences related to medical profiles across developmental stages and translating the evidence into age-adjusted and gender-oriented clinical guidelines and health policy.

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]. 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]. 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], as well as artificial neural network (ANN) methods in a nutritional status study^[239] and metabolic syndromes^[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.

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