How gender influence the health state? A cross sectional study in an endocrine setting

Marta Bianchini
Istituto Regina Elena
Giulia Puliani
Universita degli Studi di Roma La Sapienza Dipartimento di Medicina Sperimentale
Alfonsina Chiefari
Istituto Regina Elena
Rosa Lauretta
Istituto Regina Elena
Marilda Mormando
Istituto Regina Elena
Agnese Barnabei
Istituto Regina Elena
Irene Terrenato
Istituto Regina Elena
Marialuisa Appetecchia (marialuisa.appetecchia@ifo.gov.it)
Istituto Regina Elena IRCCS https://orcid.org/0000-0002-2124-1335

Research article

Keywords: gender medicine, lifestyle, endocrine disease, oncological comorbidities, determinants of health.

Posted Date: November 10th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-103184/v1

Title page

How gender influence the health state? A cross sectional study in an endocrine setting

Marta Bianchini[1], Giulia Puliani[1,2], Alfonsina Chiefari[1], Rosa Lauretta[1], Marilda Mormando[1], Agnese Barnabei[1], Irene Terrenato[3] and Marialuisa Appetecchia[1]*

[1] Oncological Endocrinology Unit, IRCCS Regina Elena National Cancer Institute, Via Elio Chianesi 53, 00144, Rome, Italy;

[2] Department of Experimental Medicine, Sapienza University of Rome; Viale Regina Elena 324, 00161, Rome, Italy;

[3] Biostatistics and Bioinformatic Unit- Scientific Direction, IRCCS Regina Elena National Cancer Institute, Via Elio Chianesi 53, 00144, Rome, Italy.

*Corresponding Author: Marialuisa Appetecchia, marialuisa.appetecchia@ifo.gov.it; Via Elio Chianesi 53, 00144, Rome, Italy

Abstract

Background: Gender medicine focuses on how gender differences affect health status and diseases development and how they influence health services access and attitude to screening programmes. Endocrine diseases are influenced by many gender-related issues, some of which have not been sufficiently investigated. The aim of this study was to evaluate gender difference in determinants of health (as lifestyle, level of education, area of origin, distance from hospital) and how these elements could influence diseases prevalence in an endocrine outpatients setting, with a special focus on oncological disease.

Methods: We performed a cross-sectional study enrolling patients referring for the first time to our Oncological Endocrinology Unit, between January 2019 to December 2019.

Results: We enrolled 1107 consecutive patients. Mean age was 56.8 ± 15.0 years (77% females). The main reasons for referral were thyroid and bone diseases. We found a gender difference in some disease prevalences: malignant endocrine diseases and iatrogenic thyroid diseases were more frequent in males, while other thyroid disorders, adrenal and metabolic diseases and cancer treatment induced bone loss were higher in females. The frequency of oncological comorbidities was higher in females. No difference was found in the propensity to travel long distances to reach the hospital. In our population, women had a higher socio-cultural level and followed healthier lifestyle. In fact, alcohol and tobacco consumption was lower in females and women had lower BMI. The percentage of smokers or ex-smokers was higher in patients with any malignancy compared to patients with benign endocrine diseases.

Conclusions: the study showed the importance of considering gender as a determinant of health, able to influence also lifestyle and habits, and as an element to keep in consideration to promote a healthier lifestyle and a targeted endocrine screening especially in oncological setting.

Keywords: gender medicine; lifestyle; endocrine disease; oncological comorbidities; determinants of health.

Background

Gender medicine deals with biological, psychological and socio-cultural differences between men and women, which can affect health status and disease development(1). The term "gender" goes beyond the simple biological differences between male and female, classically defined as "sex", taking into account also environmental, social, cultural and relational factors(2).Gender medicine is therefore a complex study of how these gender differences affect the state of health, the onset and progression of diseases, the access to health services, the attitude towards prevention interventions and to therapeutic strategies(3). In fact, men and women, despite being susceptible to almost the same pathologies, could present different symptoms, disease progression and response to treatments. In addition, women have a higher propensity to consult health care providers, generally they take more medication and usually manage family health problems(4).

In 2019, Italian Ministry of Health arranged a plan for the application and the diffusion of gender medicine in the country, testifying its importance in the wider field of precision medicine(5).

Gender medicine therefore aims to achieve a "health" condition by paying attention not only to the disease itself, but also to the “determinants of health” starting from lifestyles such as alcohol, smoking, physical activity, nutrition and body weight(6). These, in fact, contribute to determining the health of women and men and have an impact on the incidence of many chronic diseases, such as cardiovascular and respiratory diseases, diabetes mellitus, and cancer diseases. Exposure to the aforementioned risk factors depends on individual choices, but it is strongly influenced by the socio-cultural and environmental context and therefore by gender(7).

In modern society, gender medicine appears essential to achieve the best diagnostic and therapeutic work-up for both men and women and to optimize health services planning(8).

Endocrinology is one of the medical disciplines most influenced by issues related to gender, as the most widespread endocrine diseases (e.g. thyroid diseases, osteoporosis and diabetes mellitus) have marked gender differences in term of prevalence. This is certainly due to hormonal differences between males and females, while the impact of gender-related determinants of health have not yet been sufficiently investigated(9).

The aims of our study were:

- to evaluate the gender difference in determinants of health as lifestyle, level of education, area of origin;
- to evaluate how and if these determinants could influence the prevalence of endocrine diseases and oncologic disease;
- to assess gender difference in availability to travel long distances in order to gain access to health services.

Methods

This is a cross-sectional study, conducted in our Oncological Endocrinology Unit at Regina Elena National Cancer Institute of Rome, between January 2019 to December 2019.

All patients (age > 18 years) referring to our endocrine center, for the first evaluation in the study frame-time, were considered potentially eligible. Patients could gain access to our center through national health system booking service or through selected waiting lists accessible by our hospital's oncologists.

The following parameters were assessed during first visit: sex, age, residence address to calculate distance from the hospital, ethnicity and nationality, level of education (grade 8 or less: elementary school and middle school; grade 12 or upper education: high school, degree or upper title),body mass index (BMI) calculated as the weight (kilograms) divided by the height (meters squared), smoking status (3 groups: smokers, non-smokers or ex-smokers), alcohol consumption (classified as yes in case of at least 0.5 UI alcohol units per day or no), physical activity (no, yes moderate or yes intense), endocrine and oncological diseases (for example: brain, breast, prostate, lung, gastrointestinal cancers, hemato-lymphoid neoplasms).

Endocrine diseases were grouped as follows: pituitary diseases, andrological diseases, neuroendocrine neoplasms, thyroid cancers, benign thyroid diseases (including thyroid nodules, thyroiditis, primary hyperthyroidism and hypothyroidism, iatrogenic thyroid disorders induced by amiodarone, tyrosine kinase inhibitors-TKI, immune checkpoint inhibitors, neck radiotherapy), bone diseases (including cancer treatment induced bone loss-CTIBL, post-menopausal osteoporosis and osteopenia, hyperparathyroidism and hypercalcemia), adrenal diseases (including adrenal hyperplasia, functioning and non-functioning adrenal adenomas and incidentalomas), diabetes mellitus and metabolic diseases (including diabetes mellitus type 2, obesity, insulin resistance). Each patient's data were collected using a standardized data collection form.

The study was done under the approval of the local ethic committee of Regina Elena National Cancer Institute and all patients gave written informed consent to participate.

2.1. Statistical analysis

100 Variables of interest were expressed as frequencies and percentage values while continuous
101 variables were expressed as mean ± standard deviation. Patients were divided in subgroups
102 according to gender and age. Associations among variables were tested with non-parametric
103 Chi-square test. Statistically significance was defined at $p<0.05$. All statistical analyses were
104 performed using Statistical Packages for Social Sciences (SPSS version 21.0).

105 **Results**

106 *3.1. Patients' characteristics*

107 In the study timeframe (one year), a total of 1180 patients referred to our endocrine center for
108 first examination. 73 patients were excluded from the study due to missing data or refusal to
109 participate, so a total of 1107 patients were enrolled in the study: 854 patients were females (77%)
110 and 253 were males (23%). Total mean age was 56.8 ± 15.0 years, with a statistically significant
111 difference between gender (male: 60 ± 16.6 years, female 56 ± 14.3 years, $p<0.001$). No gender
112 difference was found in ethnicity of patients. A higher proportion of female patients had a
113 nationality other than Italian ($p=0.008$, 29 patients from European Union, 5 from South America,
114 16 from Asia, 2 from Africa).

115 **Table 1. Patients' characteristics**.

	Male **N= 253 (23%)**	**Female** **N=854 (77%)**	**p value**
Age	60 ± 16.6	56 ± 14.3	<0.001*
Age ≤ 45years	50 (19.9%)	202 (23.7%)	0.209#
Age > 45 years	201 (80.1)	650 (73.6%)	
Ethnicity			
Caucasian n (%)	250 (98.8%)	839 (98.6%)	1.0#
Others n (%)	3 (1.2%)	12 (1.4%)	

Nationality			
Italian	249 (98.4%)	806 (94.4%)	0.008*#
Others	4 (1.6%)	48 (5.6%)	
Level of education			
Grade 8 or lower	86 (38.2%)	239 (30.3%)	0.024*#
Grade 12 or upper education	139 (61.8%)	551 (69.7%)	
Distance from the hospital			
≤ 10 Km	51 (20.2%)	189 (22.1%)	0.229#
10-20 Km	79 (31.2%)	223 (26.1%)	
20-30 Km	39 (15.4%)	169 (19.8%)	
>30 Km	84 (33.2%)	272 (31.9%)	
Determinants of health			
BMI	27.8 ± 5.0	26.1 ± 5.5	<0.001*
Smoking status			
Smokers or ex-smokers	150 (59.8%)	356 (42.0%)	<0.001*#
No smokers	101 (40.2%)	492 (58.0%)	
Alcohol Consumption			
No	125 (50.8%)	559 (67.0%)	<0.001*#
Yes	121 (49.2%)	275 (33.0%)	
Physical activity			
No	139 (65.0%)	468 (63.8%)	0.854#
Yes, moderate	69 (32.2%)	240 (32.7%)	
Yes, intense	6 (2.8%)	26 (3.5%)	

Legend and abbreviations: *=statistically significant differences between groups; #= chi-square test. Values are expressed as mean± standard deviation if not otherwise statedare cited.

3.2. Reason for referral

Patients of both genders referred to our center mainly for thyroid diseases. The secondary most frequent reason was bone disease. Among patients referring for benign endocrine diseases, there was a high prevalence of oncological comorbidity. In fact, at list one malignancy was present in 56.1% of patients with benign endocrine disease compared to only 14.5% of patients with endocrine malignancies, with a statistically significant difference ($p<0.001$). Considering gender,

124 malignant endocrine diseases were more frequent in males than in females (11.5% vs 5.3%,

125 p<0.001). All reasons for referral are summarized in Table 2.

126 **Table 2. Reasons for referral.**

	Male **N= 253 (23%)**	**Female** **N=854 (77%)**
Benign thyroid diseases	147 (58.1%)	476 (55.7%)
Thyroid cancers	19 (7.5%)	39 (4.6%)
Bone diseases	22 (8.7%)	247 (28.9%)
Adrenal diseases	21 (8.3%)	37 (4.3%)
Pituitary diseases	9 (3.6%)	14 (1.6%)
Neuroendocrine neoplasms	10 (4.0%)	6 (0.7%)
Diabetes mellitus and metabolic diseases	9 (3.6%)	18 (2.1%)
Andrological diseases	9 (3.6%)	NA
Others	7 (2.8%)	17 (2.0%)

127 Values are expressed as number of patients (percentage). NA= not applicable.

128 *3.3. Disease prevalence according to gender*

129 Most patients referred to our Unit for just one endocrine disease (corresponding to the reason

130 for referral), while a lower but significant percentage of patients had more than one disease: in

131 particular, 227 patients had two endocrine diseases and 23 patients had 3 endocrine

132 diseases.Global diseases prevalence is summarized in Table 3.The most frequent group of

133 disorders were benign thyroid diseases, without gender difference (p= 0.517). In a subgroup

134 analysis, percentage of iatrogenic thyroid disorders (induced by amiodarone, TKI, immune

135 checkpoint inhibitors, neck radiotherapy) was higher in males (10.6%, vs1.4% in females,

136 p<0.001), while no statistically significant difference was found in percentage of patients with

137 thyroid nodules according to gender (70% in males, 69.9% in females, p= 0.77). Consequently,

138 females had higher prevalence of remaining thyroid diseases (hypothyroidism and
139 hyperthyroidism, thyroiditis).
140 There was a statistically significant difference in the proportion of females and males affected by
141 bone diseases (respectively, 36.1% vs10.7%, p<0.001); in this group most patients had CTIBL and
142 only a minority of patients had other bone diseases not related to cancer, such as post-menopausal
143 osteoporosis or disorders of calcium metabolism in both gender. Considering CTIBL prevalence,
144 there was a statistically significant difference between males and females (27.3%vs 7.1%,
145 p<0.001).
146 In our population, there was no gender difference in the prevalence of pituitary diseases (p= 0.288),
147 while adrenal and metabolic diseases were higher in females (respectively p=0.002 and p=0.024).
148 Considering malignancies, a higher proportion of males referred for neuroendocrine neoplasms
149 (4.0% vs 0.7%, p<0.001) and thyroid cancers (7.9% vs 4.7%, p=0.047), while females had a higher
150 prevalence of oncological comorbidities than males (p=0.005). In the subgroup of patients affected
151 by oncological comorbidities, a higher percentage of women had CTIBL than men (45.0% vs
152 16.1%, p<0.001).

153 **Table 3. Diseases prevalence**

	Male **N= 253 (23%)**	**Female** **N=854 (77%)**
Benign thyroid diseases	160 (63.2%)	559 (65.5%)
Thyroid cancers	20 (7.9%)	40 (4.7%)
Bone diseases	27 (10.7%)	308 (36.1%)
Adrenal diseases	23 (9.1%)	35 (4.1%)
Pituitary diseases	9 (3.6%)	20 (2.3%)
Neuroendocrine neoplasms	10 (4.0%)	6 (0.7%)
Diabetes mellitus and metabolic diseases	27 (10.7%)	55 (6.4%)
Andrological diseases	9 (3.6%)	NA

Others	7 (2.8%)	19 (2.2%)
Oncological comorbidities	115 (45.5%)	474 (55.5%)

This Table takes in consideration all patients diseases. Values are expressed as number of patients (percentage). NA= not applicable.

3.4. Gender-related determinants of health

No difference was found in physical activities between males and females (p=0.854), and this data was confirmed also dividing patients in two age groups (under and over 45 years).

Men had a statistically significant higher BMI compared to women (27.8 ± 5.0 vs 26.1 ± 5.5 kg/m^2, p<0.001). A higher proportion of males was smokers or ex-smokers compared to females (p<0.001); accordingly, 58% of women had never smoked in their life compared to only 42% of males. Dividing the study population in two groups according to age, in younger people there was no statistically significant difference in smoking habits regarding to sex, while in people older than 45 years there was a statistically significant gender difference in the proportion of smokers (p<0.001). Also alcohol consumption was higher in males than in females (49.2 vs 33.0%, p<0.001). As smoking habits, there was a difference in alcohol habits only in older patients(p<0.001).

No difference was found in smoking status, physical activity and alcohol consumption regarding nationality (comparing Italian and foreign patients), neither between patients referring for benign and malignant endocrine diseases. However, gathering together people with any malignancies, both endocrine or non-endocrine, the percentage of smokers or ex-smokers was higher compared to the group without malignancies (p=0.041), while no difference in proportion was found regarding physical activity and alcohol consumption.

In our study population, women had a higher level of education compared to men (p=0.024), as well as not Italian people had more frequently a degree or upper title compared to Italian patients (39.1% vs 23%, p= 0.02).

Only 22% of patients lived nearby the hospital (<10 km). The prevalence of malignant endocrine disease was 7.7% in the group of patients who lived far from the hospital (>10 km) versus 3.8% in patients who lived closer (p= 0.031). No significant difference was found in the distance from the hospital according to gender, nationality or non-endocrine oncological comorbidities. Gender-related determinants of health are summarized in Table 1.

Discussion

Gender medicine has recently received increasing attention(10). In this perspective, we decided to design this cross-sectional study in order to provide an overview of our patients, focusing on the role of gender on endocrine diseases, risks factors and other important aspects related to health care, always in a gender perspective. Many studies in the literature have focused on the impact of gender on lifestyle(11). Men seem more prone to consume alcohol and to develop alcohol-related diseases compared to women(12). Conversely, women who physiologically tolerate lower amount of alcohol (due to the sex differences in gastric absorption and metabolism), usually drink less alcohol also for cultural reason, as society's disapproval of drinking or increased risk of physical and sexual assault(12, 13).

In our population, we confirmed a gender difference in alcohol consumption, which was lower in females. Interestingly, this difference was not statistically significant in younger people, testifying as younger women have a more similar lifestyle to males, perhaps due to female emancipation,

while in older people traditional gender differences are yet more preserved. Likewise, a higher proportion of men was smokers than women. In Italy, data from two recent tobacco use surveys show a smoking prevalence of 26% in men compared to 17.2% in women.This gender difference is reduced in young adults: in Italian adolescents (15-24 years), 21.9% of boys are smokers against 18.2% of girls(14). Therefore, these studies underline that the use of tobacco in young women is a behavior to be monitored carefully. The relevant gender difference in tobacco use has been confirmed by Italian Ministry of Health, in a Tobacco Prevention and Control Report based on ISTAT data: the estimated smoking prevalence is 19.8% (24.8% males and 15.1% females)(15). These data are consistent with our results: in the whole study population, men were more frequently smokers or ex-smokers compared to women but, considering only patients aged 45 or less (born after Italian women emancipation) this difference has not been confirmed, testifying to a change in lifestyle in new generations. Several factors should be considered in the relationship between smoking and female gender. Low sociocultural and educational levels and living in developing countries are known to be risk factors for the onset of tobacco consumption(16, 17). In the last years the proportion of women who become smoker has increased, mainly due to women's earning power and targeted marketing by tobacco companies(18).

Scientific research has also shown differences in food intake and the practice of physical activity in both sexes(19, 20). For example, in modern Western societies, the male gender seems to prefer red meat, high protein foods and sugar-sweetened beverages, while healthier foods such as vegetables, fruit, fish and dairy products are mostly eaten by women(20-22). These differences may depend on a different awareness of the relationship between food behavior and health and on a different

attention to weight control or good physical shape, in line with modern society stereotypes(23). This attitude is reflected in the nutritional pattern and body mass index. Unfortunately, we did not collect information on dietary habits of our patients, but males had a higher BMI compared to women, testifying to probably less healthy dietary habits. In our population, there were no differences in physical activity level between males and females, unlike other studies published in literature which have shown, especially in younger people, a greater propensity to physical activities in males than in females(24, 25).

Taking all these aspects together, in our study population, women seem to follow a healthier lifestyle. This data could dependon the influence of multiple factors. First, women pay greater attention to their health condition compared to men(4); secondary, it is the conditioning of society that leads women to maintain a good body shape in order to achieve beauty stereotypes; finally, the level of education of patients. Indeed, in our population, women had a higher level of education compared to men and this could have affected the lifestyle of our patients. It is demonstrated that better educated people follow a healthier lifestyle, probably due to the increased awareness of the correlation between lifestyle and health(26).

National habits also seem to influence the state ofhealth; in fact, in our study, foreign people (mainly women from European Union States) did not follow a healthier lifestyle than Italian patients, despite their higher education level.

During a year, the percentage of women referring for a first endocrine visit was significantly higher than men. This fact could be explained by the more common prevalence of endocrine diseases in

236 females(27), but also by the higher attention paid to personal health status typical of women and
237 their higher propensity to refer to health care centers(1).
238 One of the aims of our study was to ascertain if women were more willing than men to travel long
239 distances for obtaining medical care. The willingness to move from own home area to reach
240 tertiary center health care was the same in both sexes and did not change according to nationality;
241 in fact, most patients decided to go to a qualified cancer endocrinology center, even if it was not
242 close to their residences. This was particularly true for patients with endocrine tumors who showed
243 a higher propensity to travel long distances. It is important to consider that a relevant part of the
244 first access to our center was allowed regardless of the reported disease, considering that the
245 booking service of the Italian public health system does not indicate to the patients the most
246 suitable hospital. According to this, the reason for referral to our center was only partially biased
247 by the type of center (Oncological Endocrine Unit).
248 The most common reason for referral to our center was an endocrine malignancy or a benign
249 endocrine disease associated to other oncological comorbidities, probably because our center is a
250 national reference hospital for neoplastic diseases. In our population, women had a higher
251 prevalence of oncological comorbidities: a high percentage of these patients referred to the
252 Endocrine Unit for prevention and treatment of cancer induced bone loss, mainly due to the intake
253 of aromatase inhibitors or gonadotropin-releasing hormone analogs for breast cancers.
254 Benign thyroid diseases were the most common endocrine disorders in both sexes; this finding
255 could be explained by the high prevalence of thyroid nodules. The increased prevalence in our
256 population could be caused by the fact that oncological patients undergo multiple and deepened

257 whole body radiological examinations (such as computed tomography and magnetic resonance
258 imaging) and functional procedures (such as positron emission tomography), therefore thyroid
259 nodules can be an accidental finding(28), and patients have been referred to our Unit for
260 subsequent tests, such as the fine needle aspiration diagnostic biopsy of the thyroid nodule.
261 Furthermore, there was no gender difference in the prevalence of benign thyroid disease, although
262 some disorders, such as Hashimoto's thyroiditis or thyroid nodules, are known to be more frequent
263 in females(27). However, this finding could be explained considering that in our population this
264 group of diseases also contains drug related thyroid dysfunction (e.g. due to TKI or amiodarone
265 intake) or subclinical thyroid disease due to age or chronic diseases, which usually do not showed
266 significant gender differences(29, 30).
267 Probably, the high incidence of adrenal incidentalomas could be explained by the high number of
268 radiological and functional tests performed in our Hospital for the cancer diagnosis and for
269 patients' follow-up.
270 In our study, thyroid malignancies were more frequent in males than females.The risk of
271 malignancy of the thyroid nodules is known to be greater in males(31, 32), and that male gender is
272 an independent prognostic factors in papillary thyroid carcinoma, which influences staging and
273 risk of recurrence(33, 34). These factors together could explain the propensity to refer to a national
274 cancer center in male patients.
275 We therefore sought to evaluate the impact of common gender-influenced risk factors in the higher
276 prevalence of endocrine malignancies found in males.

In patients with at least one tumor (endocrine or non-endocrine), the percentage of smokers and ex-smokers was higher compared to patients without neoplasms.

This finding has not been confirmed considering only patients with endocrine malignancies, probably due to the low number of patients affected and also considering that for some of these malignancies (for example thyroid cancer) other risk factors are of considerable importance, such as family history or previous radiation exposure(32, 35).

In a gender medicine perspective, it should be also interesting to evaluate possible differences between men and women in terms of inclination in carrying out periodic follow-up visits and adherence to the treatment proposed by physician, with possible impact on progression and outcomes of the endocrine disorders. Unfortunately, we do not have data on these aspects in our population, as only one visit per patient has been analysed, but this topic is of a great interest for further studies.

Conclusions

Biological and sociocultural aspects are known to influence lifestyle, patient health, disease development and treatment adherence. The study highlights and confirms the importance of considering gender and gender-related health determinants as key factors for health, even in patients affected by endocrine diseases, in which this approach has not been widely used.

Our study demonstrated that smoking and alcohol consumption are more common in males and younger women. Therefore, in the approach to the patient, doctors should pay special attention to female and male lifestyle, in order to discourage voluptuous habits and to encourage physical activity and healthy eating habits.This is particularly important mainly in subjects who, nowadays,

298 seem to be less careful to these aspects, as men, younger women or patients with lower
299 socio-cultural level.
300 Our study confirmed, as already known in the literature, that women were more affected by
301 endocrine disorders but, in our cohort, the proportion of endocrine malignancies was higher in
302 men. Therefore, from a precision medicine perspective, all efforts must be made to raise
303 awareness, in oncological patients and health care providers, on the risk of endocrine diseases
304 development in order to promote targeted screening in both genders.

305 **List of abbreviations:**

306 TKI: tyrosine kinase inhibitors; CTIBL: cancer treatment induced bone loss; BMI: body mass
307 index.

308 Declarations

309 **Ethics approval and consent to participate**

310 The study has been approved by the local ethic committee of Regina Elena National Cancer
311 Institute (reference number: 1370/20). All patients give written informed consent to study
312 participation.

313 **Availability of data and materials**

314 The datasets generated during the current study are available in the GARR repository,
315 [https://www.garr.it/it/]

316 **Competing interests**

317 The authors declare they have no competing interests.

Funding

Not applicable

Author Contributions

MB: Study conduction, data collecting, initial data analysis, writing – original draft. GP: Data control, initial data analysis, writing – original draft. AC, RL, MM, AB: Data collecting. IT: Statistical analysis. M.A.: study conception and design, supervision, writing – review & editing. All authors have read and agreed to the published version of the manuscript.

References

1. McGregor AJ, Templeton K, Kleinman MR, Jenkins MR. Advancing sex and gender competency in medicine: sex & gender women's health collaborative. Biol Sex Differ. 2013;4(1):11.
2. Ristvedt SL. The evolution of gender. JAMA Psychiatry. 2014;71(1):13-4.
3. Legato M. Principles of Gender-Specific Medicine. 2nd Edition. Elsevier. 2011.
4. Cortese DA. A vision of individualized medicine in the context of global health. Clin Pharmacol Ther. 2007;82(5):491-3.
5. http://www.salute.gov.it/imgs/C_17_pubblicazioni_2860_allegato.pdf.
6. Vlassoff C. Gender differences in determinants and consequences of health and illness. J Health Popul Nutr. 2007;25(1):47-61.
7. Legato MJ, Johnson PA, Manson JE. Consideration of Sex Differences in Medicine to Improve Health Care and Patient Outcomes. JAMA. 2016;316(18):1865-6.
8. Peres A. Gender-specific medicine in clinical research and health policy implications. Italian Journal of Gender-Specific Medicine. 2018;4(2):45-6.
9. Lauretta R, Sansone M, Sansone A, Romanelli F, Appetecchia M. Gender in Endocrine Diseases: Role of Sex Gonadal Hormones. Int J Endocrinol. 2018;2018:4847376.
10. Baggio G. [Gender medicine: a interdisciplinary approach to medicine.]. G Ital Med Lav Ergon. 2017;39(3):196-8.
11. Vari R, Scazzocchio B, D'Amore A, Giovannini C, Gessani S, Masella R. Gender-related differences in lifestyle may affect health status. Ann Ist Super Sanita. 2016;52(2):158-66.
12. Erol A, Karpyak VM. Sex and gender-related differences in alcohol use and its consequences: Contemporary knowledge and future research considerations. Drug Alcohol Depend. 2015;156:1-13.
13. Agabio R, Pisanu C, Gessa GL, Franconi F. Sex Differences in Alcohol Use Disorder. Curr Med Chem. 2017;24(24):2661-70.

14. Lugo A, Zuccaro P, Pacifici R, Gorini G, Colombo P, La Vecchia C, et al. Smoking in Italy in 2015-2016: prevalence, trends, roll-your-own cigarettes, and attitudes towards incoming regulations. Tumori. 2017;103(4):353-9.
15. http://www.istat.it/it/files/2016/12/Asi-2016.pdf.
16. Giskes K, Kunst AE, Benach J, Borrell C, Costa G, Dahl E, et al. Trends in smoking behaviour between 1985 and 2000 in nine European countries by education. J Epidemiol Community Health. 2005;59(5):395-401.
17. Harrell JS, Bangdiwala SI, Deng S, Webb JP, Bradley C. Smoking initiation in youth: the roles of gender, race, socioeconomics, and developmental status. J Adolesc Health. 1998;23(5):271-9.
18. Shafey O, Fernandez E, Thun M, Schiaffino A, Dolwick S, Cokkinides V. Cigarette advertising and female smoking prevalence in Spain, 1982-1997: case studies in International Tobacco Surveillance. Cancer. 2004;100(8):1744-9.
19. Li KK, Concepcion RY, Lee H, Cardinal BJ, Ebbeck V, Woekel E, et al. An examination of sex differences in relation to the eating habits and nutrient intakes of university students. J Nutr Educ Behav. 2012;44(3):246-50.
20. Rolls BJ, Fedoroff IC, Guthrie JF. Gender differences in eating behavior and body weight regulation. Health Psychol. 1991;10(2):133-42.
21. Fagerli RA, Wandel M. Gender differences in opinions and practices with regard to a "healthy diet". Appetite. 1999;32(2):171-90.
22. Yahia N, Wang D, Rapley M, Dey R. Assessment of weight status, dietary habits and beliefs, physical activity, and nutritional knowledge among university students. Perspect Public Health. 2016;136(4):231-44.
23. Ferguson C, Winegard B, Winegard B. Who Is the Fairest One of All? How Evolution Guides Peer and Media Influences on Female Body Dissatisfaction. Rev Gen Psychol 2011;15(1):11-28.
24. Salles-Costa R, Heilborn ML, Werneck GL, Faerstein E, Lopes CS. [Gender and leisure-time physical activity]. Cad Saude Publica. 2003;19 Suppl 2:S325-33.
25. Solmon MA. Physical education, sports, and gender in schools. Adv Child Dev Behav. 2014;47:117-50.
26. Brobeck E, Bergh H, Odencrants S, Hildingh C. Lifestyle advice and lifestyle change: to what degree does lifestyle advice of healthcare professionals reach the population, focusing on gender, age and education? Scand J Caring Sci. 2015;29(1):118-25.
27. Vanderpump MP. The epidemiology of thyroid disease. Br Med Bull. 2011;99:39-51.
28. Russ G, Leboulleux S, Leenhardt L, Hegedus L. Thyroid incidentalomas: epidemiology, risk stratification with ultrasound and workup. Eur Thyroid J. 2014;3(3):154-63.
29. Maqdasy S, Benichou T, Dallel S, Roche B, Desbiez F, Montanier N, et al. Issues in amiodarone-induced thyrotoxicosis: Update and review of the literature. Ann Endocrinol (Paris). 2019;80(1):54-60.
30. Waring AC, Arnold AM, Newman AB, Buzkova P, Hirsch C, Cappola AR. Longitudinal changes in thyroid function in the oldest old and survival: the cardiovascular health study all-stars study. J Clin Endocrinol Metab. 2012;97(11):3944-50.
31. Mettler J, Armefti S, Schmidt M, Faust M, Engels M, Chiapponi C. Benign Thyroid Diseases: Are There Gender-Specific Differences for Diagnosis and Treatment of Nontoxic Thyroid

Nodules? Results from a 4-Year Retrospective Analysis of an Endocrine Tumor Board. Visc Med. 2020;36(1):28-33.
32. Gharib H, Papini E, Garber JR, Duick DS, Harrell RM, Hegedus L, et al. American Association of Clinical Endocrinologists, American College of Endocrinology, and Associazione Medici Endocrinologi Medical Guidelines for Clinical Practice for the Diagnosis and Management of Thyroid Nodules--2016 Update. Endocr Pract. 2016;22(5):622-39.
33. Kao YH, Gan HK, Zaheer S, Lam WW, Loke KS, Wong WY, et al. Gender, Race, and Age at Diagnosis as Risk Factors for Metastasis or Recurrence among 1,657 Thyroid Cancer Patients Treated with Radioiodine across 40 Years in Singapore. Oncol Res Treat. 2015;38(12):679-82.
34. Ding J, Wu W, Fang J, Zhao J, Jiang L. Male sex is associated with aggressive behaviour and poor prognosis in Chinese papillary thyroid carcinoma. Sci Rep. 2020;10(1):4141.
35. Su X, Li Z, He C, Chen W, Fu X, Yang A. Radiation exposure, young age, and female gender are associated with high prevalence of RET/PTC1 and RET/PTC3 in papillary thyroid cancer: a meta-analysis. Oncotarget. 2016;7(13):16716-30.