Health Promotion

Prevention of cardiovascular diseases and diabetes: importance of a screening program for the early detection of risk conditions in a target population

ALESSIO FACCIOLÀ[1], GIUSEPPA VISALLI[1], GIUSEPPA D'ANDREA[2], MASSIMO VARVARÀ[2], GIUSY SANTORO[2], ROSARIA CUFFARI[2], ANGELA DI PIETRO[1]
[1] Department of Biomedical and Dental Sciences and Morphofunctional Imaging, University of Messina, Italy;
[2] Operative Unit of Epidemiology, Department of Prevention, Provincial Health Agency, Messina, Italy

Keywords

Screening • Prevention • Cardiovascular diseases • Diabetes

Summary

Introduction. *Cardiovascular diseases and diabetes are two of the main causes of morbidity and mortality worldwide. In their genesis, an important role is played by some behavioural risk factors that may induce the onset of further risk factors represented by hypertension, prediabetes, overweight and obesity. This study aimed to show the importance of the screening methodology for early detection of these risk conditions in order to reduce the burden of cardiovascular diseases and diabetes complications.*
Methods. *We carried out a screening programme involving a cohort of people aged 45-60 in which risk factors for cardiovascular diseases and diabetes were evaluated. The subjects were then classified into four groups according to the risk conditions.*
Results. *A high percentage (27.0%) of the sample had some alteration in the detected anthropometric and/or clinical-laboratory parameters but were unaware of this condition and, consequently, not under therapeutic treatment.*
Conclusions. *The screening programme allowed the early detection of hypertension and prediabetes or full-blown diabetes conditions in subjects who were unaware they had a pathological condition, and consequently to proceed with adequate investigations and start healthy lifestyles/pharmacological therapies. Overall, the results highlight the need to anticipate these screening campaigns, especially in men, to increase the effectiveness of the prevention programmes.*

Introduction

Cardiovascular diseases (CVDs) and diabetes represent the leading causes of disability and mortality worldwide and result in remarkable social and economic costs [1]. An estimated 17.9 million people died from CVDs in 2016 (31% of all global deaths), of which 85% were caused by heart attack and stroke [2, 3]. In Italy, CVDs are responsible for 44% of all deaths [4]. Moreover, according to the World Health Organization (WHO), from 1980 to 2014 the global prevalence of diabetes among those > 18 years old has risen from 4.7 to 8.5% [5].
In the onset of CVDs and diabetes, an important role is played by some behavioural risk factors such as an unhealthy diet, physical inactivity, tobacco use and harmful use of alcohol [6-10]. Particularly, the important role of healthy nutrition in the prevention of these diseases has been stressed, especially for fighting oxidative stress [11-16]. Stopping tobacco use, reducing salt intake, a healthy diet rich in fruits and vegetables, regular physical activity and restraint in the use of alcohol reduce the risk of these diseases [17-19]. Therefore, people at high risk for the onset of CVDs and diabetes need early detection and management and behavioural/pharmacological treatment [20].
Unlike many cancer types, for CVDs and diabetes there are no consolidated screening programmes to contain the disease burden. Because this public health approach needs to be expanded, we performed a screening intervention in a target population, aimed to make an early identification and treatment of possible pathological conditions and to prevent the onset of complications.

Methods

In the period January-December 2019, in a cohort of people aged 45-60 years resident in Messina, Italy, we assessed unhealthy lifestyles (smoking habits, alcohol consumption, unhealthy diet and sedentary life) and/or the presence of clinical and laboratory conditions (hypertension, hyperglycaemia, overweight/obesity). According to the plans, the programme should have lasted 3 years but, due to the COVID-19 pandemic outbreak, only the first year was carried out. A flowchart of the programme, consisting of several steps, is provided in Figure 1.

Sample enrolment

The participants were extracted from the list of the Messina Health Agency's assisted registry office and enrolled through written invitation sent to their domicile. People aged 45-60 years were invited.

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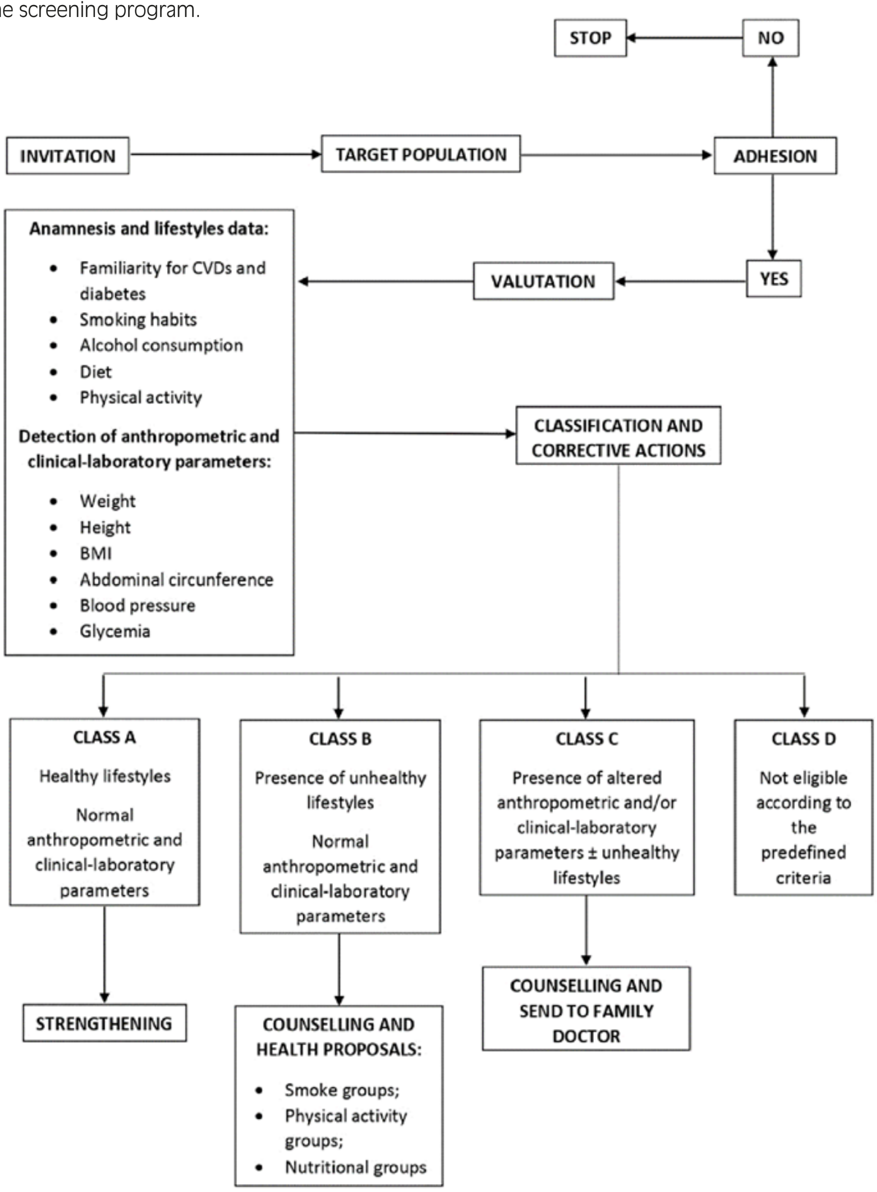
Fig. 1. Flow-chart of the screening program.



Selection of eligible subjects

Specifically trained physicians carried out a direct interview to obtain anamnesis and lifestyle variables and measure some parameters (weight, height, body mass index (BMI), abdominal circumference, blood pressure and blood glucose) in subjects who joined the programme. For the evaluation of lifestyle, we referred to the guidelines of the Italian PASSI (Progress of Healthcare Companies in Italy) Surveillance of the Istituto Superiore di Sanità (ISS) [21].

Concerning the smoking habit, we divided subjects into non-smokers (who had never smoked or had smoked fewer than 100 cigarettes in their whole life and currently do not smoke), former smokers (who currently do not smoke and who had quit smoking for at least 6 months), occasional smokers (smokers who do not smoke every day) and daily smokers (who smoke at least one cigarette every day).

The alcohol-related risk was based, for each sex, on the amount of alcohol usually ingested and the modality of alcohol consumption, which was measured in alcoholic units (AU). One AU corresponds to 12 grams of ethanol, an amount approximately contained in a can of beer (330 ml), a glass of wine (125 ml) or a small glass of liqueur (40 ml). Considering as moderate consumption the ingestion of two AUs and one AU on average per day for men and women, respectively, levels above these thresholds were classified as ‘at risk’.

Since a daily intake of 400 grams of fruit or vegetables, equivalent to five portions of 80 grams, is recommended, on this basis we discriminated between a healthy and an unhealthy diet.

Concerning physical activity, we distinguished the subjects as active, partially active or sedentary. Physically active people do a heavy job with considerable physical effort and/or do moderate activity for 30 minutes at least 5 days/week and/or intense activity for more than 20 minutes, at least 3 days a week. Partially active persons do not work physically hard but do some physical activity in their leisure time, without reaching the levels recommended by the guidelines. Sedentary persons do neither a heavy job nor perform physical activity in their leisure time.

Regarding the anthropometric parameters, we considered for both sexes a BMI value < 25 as normal, 26-30 as overweight, 31-35 as moderately obese, 36-40 as obese and > 40 as severely obese. Concerning abdominal circumference, we considered as normal a value as < 88 cm for women and < 102 cm for men.

Finally, we evaluated the blood pressure and blood glucose levels as clinical-laboratory parameters. For the methodology to correctly measure the blood pressure values, we followed the American Heart Association guidelines for the prevention, detection, evaluation and management of high blood pressure in adults [22]. We considered as normal blood pressure values < 140 mmHg for systolic and < 90 mmHg for diastolic. Considering as normal values of glycaemia < 100 mg/dl under fasting conditions and < 140 mg/dl 2 hours after a meal, values of 101-125 mg/dl under fasting conditions and 140–199 mg/dl 2 hours after a meal indicate a reduced glucose tolerance (prediabetes condition) while values ≥ 126 mg/dl under fasting conditions and ≥ 200 mg/dl were considered as full-blown diabetes.

Unfortunately, during the outpatient visit we had no possibility of performing blood collections for the evaluation of cholesterolaemia.

Sample classification

After the counselling and the physical and clinical examination, the subjects were classified into four groups, named:

- subjects with a healthy lifestyle and without any alteration in the anthropometric and clinical-laboratory parameters;
- subjects with some lifestyle risk but without alteration in the anthropometric and clinical-laboratory parameters;
- subjects with some alteration in the anthropometric and/or clinical-laboratory parameters, whether or not accompanied by unhealthy lifestyle variables, and not under therapeutic treatment as they were unaware of their unhealthy condition;
- ineligible subjects already under therapeutic treatment for hypertension and/or diabetes.

Statistical analysis

Using the Statistica program (version 10), Lilliefors and Shapiro–Wilk normality tests were used to assess data distribution patterns of continuous variables, which were expressed either as mean ± standard deviation (SD) or as median and interquartile intervals. The impact of the independent variables was evaluated using chi-square and non-parametric Mann–Whitney tests. The relationship between clinical and anthropometric parameters and independent variables was evaluated by Spearman test. Multivariate regression analysis using a priori models was performed to assess in both sexes the role of the same covariates in the variability of clinical-laboratory parameters. These included age, educational level, familiarity for hypertension and diabetes, BMI and all the behavioural variables.

Results

In the period considered, we sent 12,000 written invitations to the target population, of which 9,000 were actually delivered. Of the latter, 873 people (9.7%) joined the programme, of which 583 (66.8%) were women and 290 (33.2%) were men, with a mean age of 54.0 ± 4.1 and 54.1 ± 4.2 years, respectively (P ns). Only 1.6% were of foreign nationality.

Table I shows the socio-demographic characteristics and the anamnesis results of the entire sample.

Following anamnestic evaluation, 224 (25.7%) subjects, of which 89 were men and 135 women, were already being treated for hypertension and/or diabetes (not eligible for the screening programme: class D); 29.0 and 21.1% of the men and women were hypertensive while 5.5 and 3.8% were diabetic, respectively. Although a high percentage of the entire sample had a family predisposition to hypertension, diabetes and/or both pathologies, the percentages were higher in ineligible subjects ($P < 0.01$; data not shown).

Table I also reports the anthropometric and clinical parameters of the eligible subjects. BMI was lower in women ($P < 0.05$) and 45.5% of them were within the normal value (< 25). Gender differences were confirmed, stratifying the sample into five classes (Tab. I). In men, the mean abdominal circumference was 96.8 ± 11.2 cm (min-max: 71-150 cm) while in women it was 87.6 ± 11.1 cm (min-max: 61-126 cm). Considering as normal values of abdominal circumference of ≤ 102 and ≤ 88 cm in men and women, respectively, a not significant higher percentage of women showed values above this limit. As expected, in both genders higher values were observed for the all anthropometric parameters in the not eligible subjects compared to the health ones, with mean BMI and abdominal circumferences equal to 29.4 ± 4.6 ($P < 0.001$) and 102.1 cm ± 10.9 ($P < 0.001$) in men and 29.5 ± 5.3 cm ($P < 0.001$) and 95.8 ± 13.8 cm ($P < 0.001$) in women.

Among lifestyle variables, differences between genders were observed in the eligible subjects for smoking and alcohol use ($P = 0.01$ and $P < 0.001$ respectively). With regard to smoking habits, 55.2% of men and 67.4% of women were non-smokers while 18.4 and 10.3%, respectively, were former smokers. The percentages of daily smokers were comparable (19.4 and 17.0% in men and women, respectively) while the significant inter-gender differences were due to higher and lower percentages of women recorded in the non- and former smoker groups, respectively. The percentages of regular drinkers were 33.0% in men and 14.5% in women and almost all were moderate drinkers in both genders. Only a very low fraction of subjects (2.1%) had an alcohol consumption above the threshold value. A difference

Tab. I. Socio-demographic characteristics of the tested sample and anthroprometric and clinical parameters of the eligible subjects (* percentages of subjects with values above the limit, fixed to 102 and 88 cm in men and women respectively).

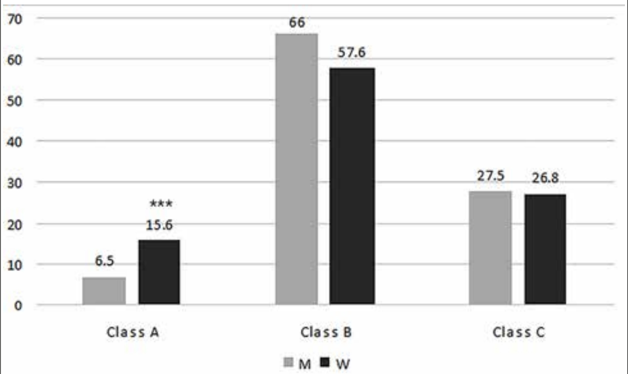
Percentages of socio-demographic characteristics and anamnestic results in the tested sample			
	Men (290)	**Women (583)**	**P value**
Age	53.6 ± 4.5	53.4 ± 4.3	ns
Educational level			
Lower school diploma	33.7	30.6	
Higher school diploma	45.8	47.0	ns
University degree	20.5	22.4	
Workers	83.5	55.7	< 0.01
Not eligible (class D)	31.3	23.5	ns
Familiarity for hypertension	57.7	66.2	< 0.05
Familiarity for diabetes	44.0	54.2	< 0.01
Familiarity for both the conditions	26.2	36.1	< 0.01
Anthropometric and clinical-laboratory parameters in the eligible subjects			
	Men (202)	**Women (448)**	**P value**
BMI	27.1 ± 4.4	26.2 ± 4.6	< 0.05
< 25 (normal weight) %	35.0	45.5%	
26-30 (overweight)	47.0	36.2	
31-35 (moderately obese)	13.0	11.9	< 0.05
36-40 (obese)	3.0	5.4	
> 40 (hyper obese)	2.0	1	
Abdominal circumference %	33.8	42.3	ns
Blood pressure (mmHg)			
Diastolic	81 (80-90)	80 (75-90)	< 0.001
Systolic	130 (120-140)	120 (115-135)	< 0.001
Fasting blood glucose (mg/dL)	102 (94-112)	98 (92-106)	ns
Post-prandial blood glucose (mg/dL)	102 (97-113)	102 (94-110)	< 0.05

was observed in dietary habits since a higher percentage of men (55.7 *vs* 45.8% of women) do not regularly eat the advised five portions/day of fruits and vegetables ($P < 0.05$). No differences were observed between genders for physical activity. Stratifying the sample into three classes, 34.3 and 30.8% were physically active, 36.8 and 32.6% were partially active and 28.9 and 36.6% were sedentary, among men and women, respectively. No differences were observed for lifestyle variables between eligible and ineligible men while, in women, the two groups differed for smoking habits and physical activity. In fact, while 67.4% of eligible women had never smoked, this percentage dropped to 47.1% in those not eligible ($P < 0.01$). The opposite was observed for sedentary lifestyle, more frequent in ineligible women (48.9 *vs* 36.6; $P < 0.01$).

Both diastolic and systolic pressure were higher in men ($P < 0.001$) and in 23.9% of them the values of at least one of the two parameters exceeded normal values of 90 and 140 mmHg, respectively. Instead, only 15.7% of the women showed a similar pathological condition (Tab. I). Similarly, to the blood pressure values, fasting and post-prandial blood glucose allowed us to identify, in this cohort of apparently healthy subjects, a fraction of new hyperglycaemic subjects (23.9% of men and 4.7% of women; $P < 0.001$). Although in hyperglycaemic subjects we observed mainly a prediabetes condition, 2.5% of the men and 0.7% of the women had full-blown diabetes. It should be added that in 8.6% of men, both hypertension and hyperglycaemia were observed, while in women only 3.4% had a similar pathological condition.

Figure 2 shows the classification of the eligible subjects according to the detected clinical-laboratory and anthropometric parameters.

Fig. 2. Classification of the eligible subjects according to the detected clinical-laboratory and anthropometric parameters.



Similarly to ineligible subjects, a higher familiarity for both hyperglycaemia and hypertension was observed in the subjects in class C, in comparison to classes A and B ($P < 0.01$). Only 12.7% of men and 20.8% of women in class C had no family history of either of the two pathological conditions and their inclusion in class C was mainly due to a slight alteration of diastolic and/or systolic pressure for men and high or very high anthropometric parameters for women.

Clinical and anthropometric parameters were related to lifestyle variables, socio-demographic characteristics and anamnestic data in a much-diversified manner in the two sexes (Tab. II).

Tab. II. Spearmann test performed to evaluate the role of independent variables on the clinical-laboratory and anthropometric parameters.

	Diastolic blood pressure		Sistolic blood pressure		Fasting blood glucose		Post-prandial glucose		BMI		Abdominal circumference	
	M	W	M	W	M	W	M	W	M	W	M	W
	R (p)	R (p)	R (p)	R (p)	R (p)	R (p)	R (p)	R (p)	R (p)	R (p)	R (p)	R (p)
Age		0.167 (0.0004)		0.214 (< 0.0001)								
Educational Level								-0.124 (0.0222)		-0.217 (< 0.0001)		-0.175 (0.0002)
Working Activity	0.163 (0.021)		0.163 (0.021)				-0.185 (0.045)	0.124 (0.0225)				-0.096 (0.0434)
Familiarity for hypertension												
Familiarity for diabetes	0.166 (0.018)		0.166 (0.018)							0.150 (0.0015)		0.134 (0.0047)
Familiarity for both	0.174 (0.013)		0.174 (0.013)							0.138 (0.0034)		0.138 (0.0034)
Diastolic pressure						0.318 (0.0009)			0.365 (< 0.0001)	0.361 (< 0.0001)	0.331 (< 0.0001)	0.316 (< 0.0001)
Sistolic pressure									0.289 (< 0.0001)	0.265 (< 0.0001)	0.345 (< 0.0001)	0.194 (< 0.0001)
BMI	0.289 (< 0.0001)	0.361 (< 0.0001)	0.289 (< 0.0001)	0.265 (< 0.0001)		0.316 (0.0010)	0.190 (0.037)	0.181 (0.0007)			0.849 (< 0.0001)	0.819 (< 0.0001)
Abdominal circumfe-rence	0.345 (< 0.0001)	0.316 (< 0.0001)	0.345 (< 0.0001)	0.194 (< 0.0001)		0.255 (0.0086)		0.107 (0.0473)	0.849 (< 0.0001)	0.819 (< 0.0001)		
Fasting glucose		0.318 (0.0009)										0.255 (0.0086)
Post-prandial glucose									0.190 (0.0375)	0.181 (0.0007)		0.176 (0.0011)
Smoking habit												
Physical activity		-0.118 (0.013)		-0.136 (0.004)			-0.236 (0.010)			-0.236 (< 0.0001)		-0.289 (< 0.0001)
Alchol Intake									0.306 (0.0055)		0.153 (0.03)	
Dietary habit		-0.144 (0.002)		-0.161 (0.0007)						-0.130 (0.0058)		-0.103 (0.0292)

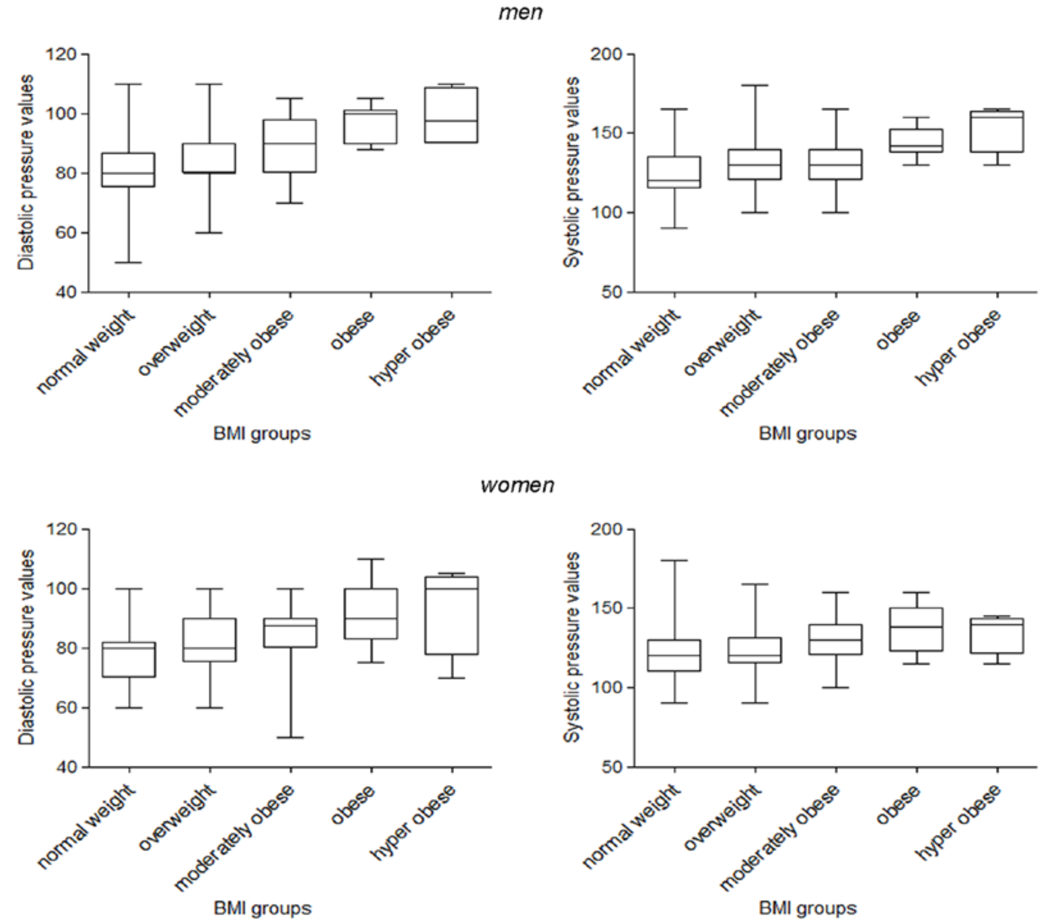
M: men; W: women.

Anthropometric parameters were an exception because in both sexes they were significantly and directly related to blood pressure values (Fig. 3).

Moreover, in men diastolic and systolic values were higher in the workers and in the presence of familiarity both for diabetes and for both pathological conditions. As expected, and surprisingly not observed in men, the blood pressure in women was related to their age in addition to familiarity for hypertension while it was negatively related to physical activity and dietary habit. In men, fasting and post-prandial blood glucose were poorly correlated with the examined variables and, limited to post-prandial glycaemia, the levels were directly related to BMI and inversely related to working and physical activity. In women, both glycaemic values were strongly related to the anthropometric parameters; in addition, fasting blood glucose was related to diastolic values while the post-prandial one was directly related to working activity and inversely related to educational level. Some anthropometric parameters were related to behavioural variables, such as alcohol consumption in men, while in women they were inversely related to physical activity and dietary habit. In the latter, a protective role was also shown by educational level and working activity.

The multivariate analysis (Tab. III) confirmed these data, highlighting in men the effect of hypertension and diabetes familiarity for the respective pathological conditions. Instead, in women, blood pressure values were mainly influenced by age and BMI, while a protective role was played by dietary habit and no variable was related to blood glucose values. Only in women, the analysis underlined the effect of biological, socio-demographic and lifestyle variables and familiarity on anthropometric parameters. Diabetes familiarity was directly related, while age and educational level were inversely related, to BMI (P = 1.192, –0.066 and –0.438, respectively). Instead, abdominal circumference was directly related to age and inversely related to physical activity (P = 0.112 and –0.515, respectively),

Fig. 3. Box-plots showing the correlation between BMI groups and blood pressures values in eligible men and women.



Tab. III. Multiple regression analysis in eligible subjects.

	Men			Women	
Covariates	Diastolic	Sistolic	Fasting blood glucose	Diastolic	Sistolic
R^2 adjusted	0.272 (<0.0003)	0.312 (<0.0001)	0.158 (n.s)	0.196 (<0.0001)	0.165 (<0.0001)
Age				0,274 (0.0003)	0,180 (<0.0001)
Educational level					
Familiarity for hypertension	4.94 (0.03)	6.35 (0.005)			
Familiarity for diabetes			15.89 (0.03)		
Familiarity for both					
BMI	0,561 (0.02)	0.753 (0.002)		0,385 (<0.0001)	0.467 (<0.0001)
Smoking habits					
Alchol intake			-18.23 (0.047)		
Physical activity					
Dietary habit				-1.105 (0.010)	-1.217 (0.006)

For each covariate are reported p value and, in the bracket, p value. In the women both fasting and post-prandial blood glucose were not related to any of the examined covariates while in men this was observed for post-prandial only.

emphasizing the appropriateness of the latter in women over 40 for whom BMI can be paradoxically normal, due to the depletion of bone tissue and muscle mass.

Discussion

Because of their heavy impact on the general population worldwide in terms of burden, mortality, disability and costs, it is necessary to diagnose CVDs and diabetes and their risk factors as early as possible in order to modify unhealthy lifestyles and to treat affected people. Cancer screening programmes have been active in several countries but similar programmes for preventing the other most common chronic diseases have not yet been routinely used. Our screening programme to detect unhealthy lifestyles and/or the presence of altered clinical-laboratory conditions (principal risk factors for the onset of these diseases) highlights this deficiency. This was the first initiative in our territory about this kind of disease and it allowed us to widen the concept of screening to a large part of the population flanking the already existing oncologic screening programmes. The combination of these two fundamental prevention practices will allow a very large part of the population to be reached and the burden of chronic diseases to be reduced.

The response rate was quite low, probably because it was the first project in our territory regarding these diseases and people are only familiar with oncological screening. This result, in association with the prevalence of women in our sample, shows that awareness of this issue needs to be improved and highlights that the consolidated habit of being screened for breast and cervical cancers makes women more aware of the importance of prevention. Targeted studies should identify the reasons for not joining, considering that risk habits and unrecognized altered parameters may be present in the unresponsive subjects, to whom the percentages in classes C and D can be hypothesized as relevant by inferring our results. Moreover, it should be underlined that our results have arisen from only the first planned year of the programme. We can certainly state that the COVID-19 pandemic determined a loss of opportunity for a certain number of subjects to be diagnosed early and consequently treated with an appropriate therapeutic regimen, if the programme had been continued according to the expected times.

Female gender and a medium–high social and cultural status were the most important variables that pushed subjects to join the programme, further underlying the low awareness of poorly educated people to be responsible for their own health. An informative health campaign must increase knowledge on this topic, improving the response rate of the unresponsive subjects.

The results for men were significantly worse than for women and 30.7% of them were ineligible. Regarding behavioural risk factors, gender differences were observed between non-smokers and former smokers, of which there was a higher and a lower percentage, respectively, of women than men. The number consuming alcohol above the recommended level was low, with no gender difference, underlining the low propensity of the Italian southern population of this age group to abuse alcohol, limiting consumption to during meals [23]. Conversely, half of the sample had an unhealthy dietary habit and more than two-thirds of the sample was sedentary or partially active. An opposite situation between sexes was observed for eating habits and physical activity, which were better and worse, respectively, in women in comparison to men.

The screening programme allowed the early detection of hypertension and prediabetes or full-blown diabetes conditions in subjects who were unaware of their condition. On the basis of the results, the physicians proposed some corrective actions. These included advice to keep a healthy lifestyle for group A, initiatives to correct the wrong lifestyle habits through participation in smoking cessation, gym and/or walking groups, and providing nutritional advice for group B, and sending to the family doctor to set up therapy for group C.

Overall, the results highlight the need to anticipate screening campaigns, especially in men, to increase the effectiveness of prevention programmes. This seems confirmed by the absence in men of age-related effects of blood pressure, underlining the earliest onset of hypertension in the men of our sample.

A further motivation to implement and anticipate prevention is the leading role of hypertension and diabetes familiarity, highly frequent in our area, which can be mitigated by a careful and constant adherence to a healthy lifestyle, started as early as possible [24, 25]. Since, surprisingly, we observed a significant inter-gender difference for these variables, data regarding this information could be affected by a recall bias. However, both bivariate and multivariate analysis highlighted that hypertension and diabetes familiarity are strongly related to risk condition, which was assessed by both early predictors as the anthropometric measures in women and later ones as higher values of diastolic and systolic pressure in men.

The high percentages of subjects with an unhealthy lifestyle, regardless of whether or not there is hypertension and/or diabetes familiarity, stressed the need to plan and frequently re-propose health education campaigns aimed to change risky behaviour and to tailor them, at least by gender, considering the inter-gender differences that can induce a lasting change in behaviour. As expected, our study confirmed that subjects, especially women, with a higher cultural level have a greater tendency to care for themselves as well as being more aware of the importance of healthier behaviours, and in the women in our cohort this independent variable was inversely related to both anthropometric measures and to post-prandial blood glucose level.

A limit of this study was that it did not assess an important and well-known risk factor for CVDs – hypercholesterolaemia – but we think that, despite this limit, the study has an important impact on the epidemiology and prevention of the chronic diseases considered.

Conclusions

Our study confirms the importance of the presence, in national prevention plans, of screening programmes for early detection of the risk factors for CVDs and diabetes and to act promptly in their diagnosis and treatment. However, the non-negligible number of subjects in whom there was early recognition of hypertension and/or diabetes and that ignored their conditions highlights the need to target screening programmes on a younger population, i.e. under the age of 50, especially for men. Due to the COVID-19 pandemic, our programme was stopped but, according to the results of the first year of the project, it is crucial to resume it as soon as possible in order to reduce the burden of these important public health concerns. We can assume that the blockade or in any case the remarkable slowdown in screening

campaigns, such as the one discussed here, is a further damage in terms of health that humanity has suffered from the COVID-19 pandemic.
Our Provincial Health Agency has already performed some investigations to evaluate the spread of infectious diseases in our territory [26-28] and to determine the attitudes and spread the culture of prevention regarding sexually transmitted infections and vaccine prevention [29-31]. Following these results, we intend to extend our field of action by including chronic diseases.

Ethics declarations

The study protocol was promoted and approved by the Sicily Region as part of the 2014-2018 Regional Prevention Plan and by the Messina Provincial Health Agency as part of the 2014-2018 Prevention Plan in the project 2.1-Objectives 1.2.1. All humans research procedures were in accordance with the standards set forth in the Declaration of Helsinki principles of 1975, as revised in 2013. An informed consent was priority obtained by the subjects enrolled in the research. No animals were used in this research.

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Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

Conceptualization: ADP, GDA and RC. Methodology: MV and GS. Formal analysis, data curation and writing - original draft: GV and AF. All Authors revised the manuscript and gave their contribution to improve the paper. All authors read and approved the final manuscript.

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Correspondence: Alessio Facciolà, Department of Biomedical and Dental Sciences and Morphofunctional Imaging, University of Messina, via Consolare Valeria 1, 98125 Messina, Italy - E-mail: afacciola@unime.it

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