Demosthenes Panagiotakos
PhD (Med), FRSPH, FACE

Dr. Demosthenes Panagiotakos is Professor in Biostatistics, Research Methods and Epidemiology at Harokopio University of Athens and Member of the supreme Scientific Committee on Health, Environment and Emerging Risks / DG Health and Food Safety, of the European Commission (SCHEER, 2016-2026). Additionally, he is visiting Distinguished Professor at School of Arts and Sciences, Rutgers University of New Jersey, USA (since 2016), and adjunct Professor at the Faculty of Health, University of Canberra, ACT, Australia (since 2017). He is an elected Fellow of the Royal Society of Public Health (FRSPH) and the American College of Epidemiology (FACE). He has supervised as Principal Investigator 19 large-scale, epidemiological studies and research funded projects. His research interests include chronic disease epidemiology, medical research methodology, personalized medicine and risk modeling. He has published 4 books, over 900 scientific papers in peer-reviewed international journals, as well as 50 papers in national journals and Conference proceedings and has more than 40.000 citations of his work (Scopus h-index of 81). He serves as Editor-in-Chief in 2, and Associate Editor and Editorial Board member in 17, international journals. He has been included in the List of Top 1% highly cited scientists in the World (medicine and health sciences).

Επίκαιρο Άρθρο

Cardiovascular disease risk in the Greek population: 20-year experience of the ATTICA epidemiological study (2002-2022)

D. Panagiotakos and E. Damigou

ABSTRACT

Cardiovascular disease (CVD) remains the leading cause of death worldwide, however variability exists on incidence rates of CVD between different countries. The aim of the present work was to discuss CVD epidemiology in Greece, based on the ATTICA study findings; the ATTICA Study is a prospective cohort study in a sample of Greek adults from the province of Attica, Greece, with multiple follow-up examinations during a period of 20-years (2002-2022).

Key-words: *cardiovascular disease, Greece, epidemiology*

INTRODUCTION

Epidemiology of cardiovascular disease (CVD) in the world, Europe, Greece

Cardiovascular disease (CVD) is a complex disease, which may include a group of disorders of the heart and the blood vessels (i.e., coronary artery disease, cerebrovascular disease, peripheral artery disease, rheumatic heart disease, congenital heart disease, deep vein thrombosis and pulmonary embolism, heart attacks and stroke[1]). Data on CVD incidence are scarce and may vary between different regions. The Global Burden of Disease study showed that CVD burden remains high worldwide[2]. In Europe, it seems that CVD incidence is declining, but in the 57 European Society of Cardiology (ESC) member countries, 113 million people are living with CVD[3]. In Greece, according to the Panhellenic Study of Nutrition and Health with a sample of n=4.574 individuals (42.5% men) almost from every region of Greece, the prevalence of CHD was approximately 14%[4].

Established and modern CVD risk factors

Classic determinants of CVD have long been established and include diabetes mellitus, hypercholesterolemia, hypertension, smoking, unhealthy dietary habits, inflammation and atherosclerosis. Novel determinants currently studied, including psychological factors (e.g., stress), e-cigarettes, second-hand smoke, "inflamm-ageing", access to healthcare, health literacy and gender equity, offer a new more individualized perspective for managing CVD[5-11]. Thus, regarding CVD management, a new challenge has arisen; to pinpoint the pattern of factors that lead to CVD development or death. These factors are not only biological or clinical, but behavioral and psychological as well, and may need to be studied separately for men and women and/or for older and younger people. Therefore, it is imperative that each polity knows and understands this pattern –if any–, so as to be able to establish more effective preventive measures.

The increasing worldwide burden of CVD (calculated based on deaths or DALYs) seems to be parallel to the increasing prevalence of modifiable risk

✉ **Correspondence:** Prof. **Demosthenes B. Panagiotakos** • Department of Nutrition and Dietetics, School of Health Sciences and Education, Harokopio University of Athens • El. Venizelou 70, Kallithea, 176 71, Athens, Greece • Mail: dbpanag@hua.gr

factors[2]. Similarly, in Europe, the prevalence of CVD determinants (i.e., obesity, diabetes, hypertension) is increasing[12]. In Greece, 40% of mortality is attributed to behavioral risk factors (i.e., obesity, smoking status, physical inactivity)[13]. The current Greek population has been affected by unhealthy dietary habits (i.e., lower adherence to the Mediterranean diet), but smoking habits have decreased and physical activity has increased, during the last 20 years[14]. In the Panhellenic Study of Nutrition and Health the prevalence of hypertension was approximately 13%, hyperlipidemia 17%, diabetes 4%, obesity 16%, overweight 32%, approximately 50% of the participants were active smokers and 72% were regular alcohol consumers; of note sex and age differences were observed (all p_s<0.001)[4]. In the National Health Examination Survey "EMENO" (2013-2016) (n=4.822) (approximately 52% females, median age: 48 years), the prevalence of hypercholesterolemia was approximately 60% (no sex differences were observed), of hypertension 39% (men: 42% > women: 36%), of diabetes 12% (no sex differences were observed), of obesity 32% (women: 34% > men: 30%) and of current smoking 38% (men: 44% > women: 33%)[15].

The ATTICA study: 20-year (2002-2022) experience in CVD epidemiology in Greece

The ATTICA study is a prospective cohort study in a sample of Greek adults from the province of Attica, Greece (78% urban municipalities, including Athens capital city) with follow-up evaluations at 5, 10 and 20 years after the baseline examination (i.e., 2001-2: baseline, 2006: 5-year follow-up, 2012: 10-year follow-up, 2022: 20-year follow-up). The main goals of the study were to record and monitor the distribution of several socio-demographic, lifestyle, clinical, biochemical and psychological CVD risk factors, to explore the associations between the aforementioned factors and to evaluate their prognostic significance on long-term CVD risk.

The initial sample included 3.042 individuals, out of 4.056 who were randomly invited to participate from May 2001 to August 2002. Sampling was random, and stratified by sex, age group and region (for details see Pitsavos et al., 2003 and Panagiotakos et al., 2015[16,17]). Out of the 3.042 original participants, 2.169 were found and agreed to participate (71% participation rate). Of those lost to follow-up (n=873), 771 were not found due to changed, missing or incorrect addresses or telephone numbers and 102 due to refusal to be screened again. Data without any missing information were obtained from n=1.988 participants as regards to the 20-year CVD evaluation. Between the age-sex distribution of this working sample and the baseline no differences were observed (*p*'s>0.80). As regards to participants who died during the follow-up period, information was obtained from their relatives and certified vital records. The definition of the investigated outcomes was based on International Classification of Diseases (ICD)-10th version (for details see Panagiotakos et al., 2015[17]).

20-year CVD incidence, mortality and fatality

During the 20-year period, 36% (n=718) of the participants, 40% of men and 32% of women (*p for gender difference<0.001),* experienced a fatal or non-fatal CVD event. Coronary heart disease (CHD) and stroke were analyzed together, due to the small number of stroke events (i.e., 4%). Of the 718 CVD events, 13% (n=96) were fatal [man: woman (CVD fatality rate) ratio = 4:1]. The overall 20-year CVD mortality rate was 4.5% (7.3% for men and 1.8% for women).

All-cause mortality

During the 20-year period, 9.5% (n=206) of the participants, 13.3% of men and 5.7% of women, died. The causes of deaths were: 48% due to CVD (of which 72% stroke, 8% heart attacks and 20% other CVD), 18% were due to cancer, 7% due to infections (of which, 14% due to Covid-19), 4% were accidents, 1.5% due to neurological diseases, 1% due to chronic obstructive pulmonary disease and the rest due to unknown reasons. No sex differences were observed regarding the pattern of all-cause mortality (*p*=0.223).

CVD incidence according to age groups in men and women during the 20-year period

Incidence from CVD differed between the age groups of participants (*p* for trend<0.001, *Table 1*). For instance, men who were between 65-75 years old at baseline examination, experienced almost 2 times higher risk of developing CVD compared to those who were between 35-45 years. In addition, women who were between 65-75 years old at baseline, had 5 times higher risk to develop CVD, compared to those who were between 35-45 years old (*p* log-rank <0.001).

The man-to-woman ratio also differed depending on participants' age group (*p* log-rank <0.001), with

Table 1. Twenty-year incidence of cardiovascular disease (CVD) in participants of the 20-year follow-up evaluation of the ATTICA study, stratified by sex and age group (*n*= 1.988).

	Men (*n*=987)	Women (*n*=1.001)	Man-to-woman cardiovascular disease incidence ratio
Age at baseline,%	**20-year incidence of cardiovascular disease**		
<35 years old	4.3%	3.1%	1.4
35-45 years old	7.1%	3.4%	2.1
45-55 years old	41%	34%	1.2
55-65 years old	26%	35%	0.74
65-75 years old	12%	17%	0.70
75+ years old	8.8%	7.5%	1.17
Overall	40%	32%	1.25

the overall man-to-woman CVD incidence ratio being 1.25. In particular, up to the age of 45 years at baseline, men exhibited higher incidence compared to women (i.e., man-to-woman age-adjusted ratio>1). From the age of 45 years, women were approaching the CVD incidence of men of the same age, and from the age of 55 years old, women had 26% higher CVD incidence compared to men. Finally, the sex-adjusted CVD risk increased 30% per year increase of age ($p<0.001$).

Lifestyle, clinical and psychological determinants for CVD development, revealed during the 20-year follow-up period

Lifestyle, clinical and psychological trajectories of participants during the 4 examinations of the 20-year follow-up period are presented in *Table 2*. From baseline to the 20-year follow-up, the prevalence of all clinical characteristics (i.e., hypertension, diabetes, hypercholesterolemia) significantly increased, while the prevalence of current smoking decreased. In particular, compared to the baseline, history of hypertension was approximately 1.6 times higher, history of hypercholesterolemia was approximately 1.9 times higher, and history of diabetes was more than 4 times higher at the 20-year follow-up. Moreover, at the 20-year follow-up, compared to the baseline, 52% of the participants were overweight or obese (i.e., Body Mass Index>25 kg/m^2), the percent of participants that were physically active decreased, while the level of adherence to the Mediterranean diet (evaluated through the MedDietScore) remained the same (i.e., moderate to high adherence).

Table 2. Clinical and lifestyle characteristics of the ATTICA study's participants at the different evaluations (i.e., baseline and 5-, 10-, 20-year follow-up examinations).

Year of evaluation	Baseline evaluation (2001-2)	5-year follow-up (2007)	10-year follow-up (2011-12)	20-year follow-up (2022)	*p for trend*
N	3.042	2.101	2.583	1.988	
Development of CVD, %	-[1]	9	16	36	<0.001
History of hypertension, %	30	40	52	49	<0.001
History of type 2 diabetes, %	7	12	20	30	<0.001
History of hypercholesterolemia, %	39	54	62	73	<0.001
Obesity, %	18	20	30	16	0.043
MedDietScore (range 0-55)	26 (7)	25 (7)	25 (7)	26 (7)	<0.001
Smoking, %	43	38	33	27	<0.001
Low physical activity, %	60	71	75	72	<0.001

Continuous variables are presented as mean and standard deviation. Categorical variables as relative frequencies (percentages). [*]*p*-values for matched outcome derived using repeated ANOVA for normally distributed variables, the Friedman test for variables that were not normally distributed and for the rest of the comparisons using the McNemar test. [1]all participants were free of CVD at baseline according to study's entry criteria (see Methods section). **Abbreviations:** CVD: Cardiovascular disease.

Conclusion

During the last 2 decades, for the purpose of managing CVD and its determinants, various strategies and public health actions have been made. Notwithstanding, presently, CVD burden in terms of incidence, mortality and fatality is disturbingly high in the urban Greek population. Thus, it would be prudent for future public health actions to be more up-to-date with the risk factors that afflict the Greek population, so as to better monitor and manage CVD.

ACKNOWLEDGEMENTS

The authors of this work would like to thank Prof Christos Pitsavos, Dr Christina Chrysohoou, Dr Yannis Skoumas, for establishing this study in 2002, as well as the ATTICA study investigators during baseline, 1st (2006), 2nd (2012) and 3rd (2022) wave of follow-up: Elpiniki Vlachopoulou, Christina Vafia, Dimitris Dalmyras, Konstantina Kyrili, Fotios Barkas, Petros Spyridonas Adamidis, Georgia Anastasiou, Amalia Despoina Koutsogianni, Asimina Loukina, Giorgos Metzantonakis, Evrydiki Kravvariti, Manolis Kambaxis, Kyriakos Dimitriadis, Ioannis Andrikou, Amalia Sofianidi, Natalia Sinou, Aikaterini Skandali, Christina Sousouni, Ekavi N. Georgousopoulou, Natassa Katinioti, Labros Papadimitriou, Constantina Masoura, Spiros Vellas, Yannis Lentzas, Manolis Kambaxis, Konstadina Palliou, Vassiliki Metaxa, Agathi Ntzouvani, Dimitris Mpougatsas, Nikolaos Skourlis, Christina Papanikolaou, Georgia-Maria Kouli, Aimilia Christou, Adella Zana, Maria Ntertimani, Aikaterini Kalogeropoulou, Evangelia Pitaraki, Alexandros Laskaris, Mihail Hatzigeorgiou and Athanasios Grekas, Efi Tsetsekou, Carmen Vassiliadou, George Dedoussis, Marina Toutouza-Giotsa, Constadina Tselika and Sia Poulopoulou and Maria Toutouza.

REFERENCES

1. Cardiovascular diseases (CVDs) [Internet]. [cited 2022 Dec 14]. Available from: https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds)
2. Roth GA, Mensah GA, Johnson CO, et al. Global Burden of Cardiovascular Diseases and Risk Factors, 1990-2019: Update From the GBD 2019 Study. *J Am Coll Cardiol* 2020 Dec 22; 76(25): 2982-3021.
3. Visseren FLJ, Mach F, Smulders YM, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice: Developed by the Task Force for cardiovascular disease prevention in clinical practice with representatives of the European Society of Cardiology and 12 medical societies With the special contribution of the European Association of Preventive Cardiology (EAPC). *European Heart Journal* 2021 Sep 7; 42(34): 3227-337.
4. Magriplis E, Panagiotakos D, Mitsopoulou AV, et al. Prevalence of hyperlipidaemia in adults and its relation to the Mediterranean diet: the Hellenic National Nutrition and Health Survey (HNNHS). *Eur J Prev Cardiol* 2019 Dec; 26(18): 1957-67.
5. Wu H, Li C, Li B, Zheng T, Feng K, Wu Y. Psychological factors and risk of atrial fibrillation: A meta-analysis and systematic review. *Int J Cardiol* 2022 Sep 1; 362: 85-92.
6. Sharma A, Gupta I, Venkatesh U, Singh AK, Golamari R, Arya P. E-cigarettes and myocardial infarction: A systematic review and Meta-analysis. *Int J Cardiol* 2022 Sep 7; S0167-5273(22)01315-8.
7. Critselis E, Panagiotakos DB, Georgousopoulou EN, Katsaounou P, Chrysohoou C, Pitsavos C. Exposure to second hand smoke and 10-year (2002-2012) incidence of cardiovascular disease in never smokers: The ATTICA cohort study. *International Journal of Cardiology* 2019 Nov 15; 295: 29-35.
8. Liberale L, Montecucco F, Tardif JC, Libby P, Camici GG. Inflamm-ageing: the role of inflammation in age-dependent cardiovascular disease. *Eur Heart J* 2020 Aug 14; 41(31): 2974-82.
9. Mannoh I, Hussien M, Commodore-Mensah Y, Michos ED. Impact of social determinants of health on cardiovascular disease prevention. *Curr Opin Cardiol* 2021 Sep 1; 36(5): 572-9.
10. O'Neil A, Scovelle AJ, Milner AJ, Kavanagh A. Gender/Sex as a Social Determinant of Cardiovascular Risk. *Circulation* 2018 Feb 20; 137(8): 854-64.
11. Kouvari M, Yannakoulia M, Souliotis K, Panagiotakos DB. Challenges in Sex- and Gender-Centered Prevention and Management of Cardiovascular Disease: Implications of Genetic, Metabolic, and Environmental Paths. *Angiology* 2018 Nov; 69(10): 843-53.
12. Timmis A, Townsend N, Gale CP, et al. European Society of Cardiology: Cardiovascular Disease Statistics 2019. *Eur Heart J* 2020 Jan 1; 41(1): 12-85.
13. OECD/European Observatory on Health Systems and Policies (2019), Greece: Country Health Profile 2019, State of Health in the EU, OECD Publishing, Paris/European Observatory on Health Systems and Policies, Brussels. [cited 2022 Nov 18]. Available from: https://www.oecd.org/greece/greece-country-health-profile-2019-d87da56a-en.htm
14. Michas G, Karvelas G, Trikas A. Cardiovascular disease in Greece; the latest evidence on risk factors. Hellenic *Journal of Cardiology* 2019 Sep 1; 60(5): 271-5.
15. Touloumi G, Karakosta A, Kalpourtzi N, et al. High prevalence of cardiovascular risk factors in adults living in Greece: the EMENO National Health Examination Survey. *BMC Public Health* 2020 Nov 7; 20(1): 1665.
16. Pitsavos C, Panagiotakos DB, Chrysohoou C, Stefanadis C. Epidemiology of cardiovascular risk factors in Greece: aims, design and baseline characteristics of the ATTICA study. *BMC Public Health.* 2003 Oct 20; 3(1): 32.
17. Panagiotakos DB, Georgousopoulou EN, Pitsavos C, et al. Ten-year (2002–2012) cardiovascular disease incidence and all-cause mortality, in urban Greek population: The ATTICA Study. *International Journal of Cardiology* 2015 Feb 1; 180: 178-84.