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Association study of APOE gene polymorphisms with diabetes and the main cardiometabolic risk factors, in the Algerian population

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Abstract

Background: Metabolic syndrome (MetS) represents a combination of at least three primary metabolic abnormalities among which obesity, hyperglycemia, dyslipidemia, and high blood pressure (HBP); once combined, they increase the cardiovascular risk significantly. APOE gene is considered as a genetic risk factor for cardiovascular diseases, and it has been linked to MetS or related disorders in several populations. Our study aimed to analyze, for the first time, the association of three APOE gene polymorphisms with MetS risk and its components in a general Algerian population sample, and to highlight the potential influence of these polymorphisms on individual susceptibility to MetS, diabetes, high blood pressure, and obesity, which has never been studied before in the Algerian population.

Results: The rs439401 showed a significant association with hypertension. The T allele confers a high risk of hypertension with an odds ratio (OR) of 1.46 (95% CI [1.12–1.9], $p = 0.006$). The rs4420638 polymorphism was significantly associated with obesity in the general population. The G allele provides protection against obesity; the resulting OR is 0.48 (95% CI [0.29–0.81], $p = 0.004$).

Conclusions: Although APOE variants were not associated with the risk of MetS, the APOE polymorphism alleles were associated with some of the metabolic parameters in Algerian subjects. The relation of APOE rs439401 alleles with high blood pressure seems indicative of a state of stress of the population.

Keywords: Genetics, High blood pressure, Diabetes, Metabolic syndrome, Obesity, Algerian population

Background

The concept of the metabolic syndrome (MetS) emerged following the increase of the risk factors associated with cardiovascular diseases and diabetes [1, 2]. MetS represents a combination of at least three primary metabolic abnormalities among which obesity, hyperglycemia, dyslipidemia, and high blood pressure (HBP); once combined, they significantly increase the risk of cardiovascular diseases [3–7].

In Algeria, the health network improvement led to a progressive aging of the population which allows for the emergence of abnormalities associated with aging and MetS. The TAHINA study (Epidemiological Transition And Health Impact in North Africa) conducted in 2005 showed a high prevalence of hypertension (24.9%) and diabetes (12.2%) in the Algerian population. Overweight has become a real public health problem, especially among women, with 66.5% overweight and 30.1% obese women. Cardiovascular disease and diabetes accounted for 26.1% and 4.4% of deaths, respectively, in 2002 [8].

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There have been at least six different published definitions for MetS; the most common definition is that of the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) [9]. The prevalence of MetS differs according to several parameters: definition, country, sex, age, and even according to the region in the same country. In Algeria, a recent study shows that the prevalence of metabolic syndrome according to the National Cholesterol Education Program - Adult Treatment Panel (NCEP-ATP) III definition was 20% in the Oran population; it was higher in women than in men (25.9 vs 13.7%) [10].

Metabolic syndrome is a multifactorial disease that implicates both environmental and genetic factors [11]. Given the importance of APOE in the metabolism of lipoproteins, indeed, APOE gene was identified as a genetic determinant of plasma lipids and lipoprotein concentrations in Caucasian and North African populations [12, 13]. We aimed to analyze the association of the APOE gene polymorphisms with MetS risk and its components, by performing case-control studies for MetS, diabetes, hypertension, and obesity in a general population sample from the city of Oran in Algeria, and to highlight the potential influence of these polymorphisms on individual susceptibility to MetS. To the best of our knowledge, the association between APOE gene and MetS and related disorders had never been studied in Algeria.

Methods

Ethical considerations

The work has been done according to Helsinki Declaration, and the study's objectives and procedures were approved by the independent ethics committee at the Algerian National Agency for the Development of Health Research (ANDRS) (since renamed as the Thematic Agency of Research in Health Sciences, ATRSS). All participants provided written informed consent prior to enrolment.

Study population

Participants were recruited during the ISOR (InSulino-résistance à ORan) study, a population-based, cross-sectional study of a representative sample of 787 individuals (378 men and 409 women, mean age 44.1 ± 10.1 years) recruited in the city of Oran, Algeria, from 2007 to 2009 [13].

Data collection

Data were collected using a preconceived questionnaire on socioeconomic information, physical activity (The level of physical activity was defined in quartiles as "none," "low," "medium," and "high" after summing exercise scores for sporting activities, walking, housework, and physical activity at work), tobacco use and alcohol intake, past medical history and family history, current medications, as well as anthropomorphic characteristics including height, weight, waist circumference, hip circumference, and blood pressure. Height and weight were measured while the subject was barefoot and lightly dressed. The BMI was calculated according to the Quetelet equation [14]. Systolic and diastolic blood pressure values (systolic blood pressure (SBP) and diastolic blood pressure (DBP), respectively) were measured on the right arm with the subject in the sitting position, using a standard mercury sphygmomanometer. Measurements were made before and after completion of the questionnaire, with an interval of at least 10 min. The mean value of the blood pressure readings was considered for analysis. Regarding tobacco use, participants were categorized as either smokers (i.e., individuals reporting at least one cigarette per day) or non-smokers. After a 12-h overnight fast, blood was collected aseptically via venipuncture in an EDTA tube for DNA extraction and subsequent molecular analysis, and in a heparin tube for biochemistry tests [13].

Metabolic syndrome diagnosis criteria

In this study, we have adopted the definition of metabolic syndrome according to the criteria of the "National Cholesterol Education Program - Adult Treatment Panel III" (NCEP ATPIII) [15]; the metabolic syndrome is diagnosed when a subject has three or more of the following risk factors:

- Abdominal obesity: waist circumference > 102/88 cm (men/women);
- Triglyceride level ≥ 150 mg/dL (1.69 mmol/L), fibrate treatment excluded;
- HDL cholesterol < 40/50 mg/dL (1.04/1.29 mmol/L) (men/women);
- Blood pressure ≥ 135/85 mmHg or treatment for hypertension;
- Fasting glucose ≥ 110 mg/dL (6.1 mmol/L), or treatment for diabetes.

Type 2 diabetes diagnosis criteria

The definition adopted in this study is that of the American Diabetes Association (ADA) [16]

- Fasting plasma glucose ≥ 7.0 mmol/L twice after 8 h of fasting
- Occasional blood glucose ≥ 11.1 mmol/L in the presence of symptoms of hyperglycemia (polyuria, polydipsia, unexplained weight loss)
- Diabetics declared under treatment including oral antidiabetic drugs and/or insulin

High blood pressure diagnosis criteria

Hypertension (HBP) has been defined according to the WHO criteria [17]: mean systolic blood pressure [SBP] greater than 140 mmHg and/or mean diastolic blood pressure [DBP] greater than 90 mmHg, and/or self-reported current treatment for hypertension with antihypertensive drugs.

Obesity diagnosis criteria

The body mass index (BMI) is calculated according to the Quetelet equation. A subject is considered obese if he has a BMI greater than or equal to 30 kg/m^2 [14].

Biochemistry and molecular testing

A multichannel analyzer and dedicated kits (Humastar®, HUMAN Diagnostics, Wiesbaden, Germany) were used for the colorimetric, enzymatic measurement of cholesterol (kit: monotest cholesterol with cholesterol esterase, cholesterol oxidase and peroxidase), triglycerides (kit: peridochrom triglyceride with glycerol phosphate oxidase and peroxidase), and glucose (kit: glucose, glucose oxidase, and peroxidase). Plasma LDL cholesterol levels were calculated according to the Friedewald equation. High-density lipoprotein cholesterol levels were measured after sodium phosphotungstate/magnesium chloride precipitation of chylomicrons and VLDL and LDL cholesterol and then centrifugation. Plasma insulin levels were measured using a microparticle enzyme immune assay running on an AxSYM analyzer (Abbott Laboratories, Abbott Park, Illinois, USA).

Genomic DNA was extracted from white blood cells by using the Stratagene® kit (Agilent Technologies, Les Ulis, France), according to the manufacturer's protocol. The APOE SNPs (rs429358, rs7412, rs439401, and rs4420638) were genotyped using KASPar technology (KBioscience, Hoddesdon, UK) with the following probes:

rs429358: [GACATGGAGGACGTG[C/T]GCGGCCGCCTGGTGC],

rs7412: [GATGACCTGCAGAAG[C/T]GCCTGGCAGTGTACC],

rs439401: [GCCGGCACTCTCTTC[C/T]CCTCCCACCCCCTCA],

rs4420638: [TGCTACAC TTTTCCT[A/G]GTGTGGTCTACCCGA].

The genotyping success rates ranged from 93 to 96% [13].

Statistical analysis

Statistical analysis was performed with SAS 9.1 software (SAS Institute Inc., Cary, NC, USA). The Hardy-Weinberg equilibrium was tested using a χ^2 test with one degree of freedom (d.f.). Some of the biochemical traits (fasting glucose levels, triglycerides, and insulin levels) were not normally distributed; we therefore log-transformed these parameters to obtain normal data distributions. Intergroup comparisons of means were performed with a general linear model, and multivariate logistic regression analyses were used to calculate the odds ratios for MetS, type 2 diabetes (T2D), high blood pressure (HBP), and obesity (Obes). The confounding variables were age, gender, smoking status, and physical activity. After Bonferroni correction, only associations with an uncorrected p value below 0.017 were considered to be statistically significant (i.e., 0.05 divided by the number of polymorphisms considered).

Results

Characteristics of study subjects

The main anthropometric, biochemical, and clinical characteristics have been measured; the baseline characteristics of the study population are described in Table 1.

Genotype and allele distributions

The allele and genotype distributions of the APOE polymorphisms were described in Table 2. There was no evidence of significant deviation from the Hardy-Weinberg equilibrium in any distributions.

Prevalence of the metabolic syndrome and the main cardiometabolic risk factors

These data concerning the Oran population are presented in Table 3.

Diabetes mellitus (T2D) was diagnosed in 80 participants (10.6%). The distribution of prevalence by sex shows no significant difference ($p = 0.39$); it was 11.6% for men and 9.7% for women.

The prevalence of obesity in the general population was 21.2%. It affects more women (32.5%) than men (9%), with a significant difference in the prevalence distribution between men and women ($p < 0.0001$).

The prevalence of the MetS in the Oran population is 20%; the distribution of this pathology is also significantly different between the two sexes ($p < 0.0001$). Indeed, it affects more women (25.9%) than men (13.7%).

Hypertension affects 23.1% of the study population. HBP is present in 21.2% of men and 19.6% of women; the prevalence distribution in men and women shows no significant difference ($p = 0.57$).

APOE epsilon polymorphism and cardiometabolic risk

No significant association was reported between genotypes of APOE epsilon polymorphism and the studied cardiovascular risk factors (T2D, obesity, HBP, and MetS status); the p values ranged from 0.04 to 0.92 (Table 4).

APOE rs439401 polymorphism and cardiometabolic risk

In the ISOR study, rs439401 showed a significant association with hypertension (HBP). The T allele increase the

Table 1 Anthropometric, biochemical, and clinical characteristics of the genotyped subjects

Parameters	All ($n = 787$)		Men ($n = 378$)		Women ($n = 409$)		
	Mean	SD	Mean	SD	Mean	SD	*p*
Age (years)	44.0	10.1	45.0	10.9	43.0	9.3	*0.007**
Height (cm)	165.5	9.6	172.8	6.4	158.6	6.7	$4.9 \times 10^{-135*}$
Weight (kg)	71.3	14.6	73.5	14.2	69.3	14.7	$5 \times 10^{-5*}$
BMI (kg/m^2)	26.1	5.1	24.6	4.2	27.5	5.5	$1.5 \times 10^{-16*}$
Waist (cm)	87.7	12.4	89.1	11.5	86.4	13.0	$2.2 \times 10^{-3*}$
Waist-to-hip ratio	0.86	0.09	0.90	0.07	0.83	0.09	$1.8 \times 10^{-32*}$
Fasting plasma glucose (mmol/L)	5.34	1.85	5.49	1.84	5.20	1.85	*0.001**
Total cholesterol (mmol/L)	4.45	0.91	4.45	0.76	4.44	1.03	0.92
Triglycerides (mmol/L)	1.17	0.51	1.21	0.55	1.13	0.47	*0.04**
HDL cholesterol (mmol/L)	1.25	0.31	1.27	0.30	1.23	0.32	0.10
LDL cholesterol (mmol/L)	2.68	0.87	2.64	0.73	2.72	1.10	0.19
SBP (mmHg)	123.6	18.1	125.4	17.7	122.1	18.4	*0.01**
DBP (mmHg)	76.9	9.9	77.7	9.7	76.1	10.0	*0.02**

BMI body mass index, *DBP* diastolic blood pressure, *SBP* systolic blood pressure. *p* value when comparing men with women subjects (general linear model). Data are expressed as the mean and SD, Significant *p* values are indicated in italics with an asterisk

risk of hypertension with an odds ratio (OR) of 1.46 (95% CI [1.12–1.9], $p = 0.006$). No associations with T2D, obesity, and MetS were detected in the ISOR study (Table 5).

APOE rs4420638 polymorphism and cardiometabolic risk

Logistic regression analysis showed that the rs4420638 polymorphism was significantly associated with obesity in the general population. The G allele provides protection against obesity; indeed, the G allele decreases the risk of obesity, and the resulting OR is 0.48 (95% CI [0.29–0.81], $p = 0.005$) (Table 6). No effects of rs4420638 polymorphism on T2D, MetS, and HBP were detected in the ISOR study.

The associations described for rs439401 and rs4420638 remained significant even after adjusting for the APOE epsilon polymorphism.

Discussion

To our knowledge, this is the first study that evaluates the association of APOE gene polymorphisms (epsilon, rs439401, and rs4420638), with the risk of MetS and the main cardiometabolic risk factors, within the Algerian population.

We found no association between the three polymorphisms of the APOE gene and the metabolic syndrome in the Algerian population. However, some components of the metabolic syndrome considered as cardiometabolic risk factors were significantly associated with APOE gene polymorphisms.

The logistic regression results showed that the ε2 allele increases the risk of obesity by 88% in the ISOR study. Similar results were observed in a study among the population of Croatia's Roma minority [18].

It is possible that gene-nutrition interactions are responsible for the observed association between the ε2 allele and obesity. Indeed, changes in eating habits during the last decade would be responsible for increasing the prevalence of obesity, interacting with the ε2 allele [19, 20].

The polymorphisms rs439401 and rs4420638 have been associated in some of GWAS-type studies with changes in plasma lipid concentrations. The rs439401 is reportedly associated with variations in plasma lipid concentrations in a meta-analysis of genome-wide association studies (GWAS), in 16 European cohorts [21], whereas the rs4420638 showed similar associations in Scandinavian, Europeans ancestry, and Chinese populations [22–25], but few studies have investigated the impact of these polymorphisms on metabolic and cardiovascular traits.

Our results on the Oran population report, for the first time, that the T allele of the rs439401 polymorphism increases the risk of arterial hypertension (OR 1.46, 95% CI [1.12–1.90], $p = 0.006$). No similar results were reported. In the literature, the T allele of rs439401 is significantly associated with changes in BMI, insulin concentration, waist circumference, and triglyceride concentration. The TT genotype is positively associated with an increase in the values of these parameters only in psychologically stressed individuals [26]. Our results are perhaps indicative of a state of stress of the population, resulting from the changes made in the Algerian population during the last two decades, particularly with the security crisis in the country. These hypotheses require investigations on a larger sample and, in which, the stress level must be measured accurately.

Table 2 Genotype and allele frequencies of APOE ε, rs439401, and rs4420638 in case and control groups

	MetS	Non-MetS
Epsilon		
Genotype frequency *N*(%)		
ε2/ε2	1(0.7)	5(0.9)
ε2/ε3	14(9.7)	43(7.4)
ε2/ε4	0	3(0.5)
ε3/ε3	109(75.7)	457(78.8)
ε3/ε4	16(11.1)	66(11.4)
ε4/ε4	4(2.8)	6(1)
Total	144(100)	580(100)
pEHW	0.77	0.68
Allele frequency (%)		
ε2	5.5	4.8
ε3	86.1	88.2
ε4	8.4	7
rs439401		
Genotype frequency *N*(%)		
CC	56(38.6)	228(39.1)
CT	65(44.8)	265(45.2)
TT	24(16.6)	90(15.4)
Total	145(100)	583(100)
pEHW	0.48	0.79
Allele frequency (%)		
C	61	62
T	39	38
rs4420638		
Genotype frequency *N*(%)		
AA	117(79.6)	473(79.1)
AG	27(18.4)	118(19.7)
GG	3(2)	7(1.2)
Total	147(100)	598(100)
pEHW	0.90	0.14
Allele frequency (%)		
A	88.8	89
G	11.2	11

H-W Hardy-Weinberg equilibrium

Table 4 APOE epsilon polymorphism and cardiometabolic risk

APOE ε	ISOR		
	APOE3	APOE2	APOE4
T2D			
No/yes	455/58	52/6	116/12
OR (95% CI)	1.00 (ref)	0.87 (0.34–2.22)	0.84 (0.42–1.68)
p		0.77	0.63
Obesity			
No/yes	414/111	47/20	115/22
OR (95% CI)	1.00 (ref)	1.88 (1.01–3.51)	0.80 (0.48–1.37)
p		0.04	0.41
MetS			
No/yes	424/96	48/18	108/28
OR (95% CI)	1.00 (ref)	1.74 (0.92–3.32)	1.29 (0.78–2.14)
p		0.09	0.33
HBP			
No/yes	413/112	54/13	110/27
OR (95% CI)	1.00 (ref)	1.18 (0.63–2.20)	0.97 (0.60–1.59)
p		0.60	0.92

T2D type 2 diabetes, *MetS* metabolic syndrome, *HBP* high blood pressure. *p* values were adjusted for age, gender, physical activity, and smoking status. Significant *p* values are indicated in italics with an asterisk

The G allele of rs4420638 seems to confer a protective effect against obesity (OR 0.48, 95% CI [0.29–0.79], $p = 0.004$).

No study was interested in measuring the association between rs4420638 polymorphism and obesity previously. No association was reported for the rs4420638 with MetS, T2D, and HBP; similar results were observed in a Tunisian population [27].

The fact that rs4420638 has low linkage disequilibrium with the epsilon polymorphism in our population gives it an advantage over European populations, where these two polymorphisms are in strong linkage disequilibrium. Thus, the study of the impact of rs4420638 would be independent of the effect of epsilon polymorphism, which makes our population very interesting from a genetic point of view for association analysis involving rs4420638 polymorphism.

Table 3 Prevalence of the metabolic syndrome and its components in the ISOR population

	Total population ($n = 787$)	Men ($n = 378$)	Women ($n = 409$)	*p*
	N(%)	*N*(%)	*N*(%)	
T2D	80(10.6%)	42(11.6%)	38(9.7%)	0.40
Obesity	167(21.2%)	34(9%)	133(32.5%)	*< 0.0001**
MetS	155(20.0%)	51(13.7%)	104(25.9%)	*< 0.0001**
HBP	160(23.1%)	80(21.2%)	80(19.6%)	0.58

T2D type 2 diabetes, *MetS* metabolic syndrome, *HBP* high blood pressure. *p* value when comparing distributions among men and women subjects. Significant *p* values are indicated in italics with an asterisk

Table 5 APOE rs439401 polymorphism and cardiometabolic risk

rs439401	Major allele/minor allele	ISOR			
		Genotypes (*N*) *p*		OR [95% CI] *p*	OR* [95% CI] *p*
T2D	C/T	Control CC (254) CT (285) TT (95) *p* = 0.13	Case CC (22) CT (38) TT (16)	CT vs CC: 1.57 [0.88–2.79] *p* = 0.13 TT vs CC: 2.12 [1.02–4.39] *p* = 0.04	1.47 [1.03–2.09] *p* = 0.03
Obesity	C/T	CC (233) CT (262) TT (89) *p* = 0.71	CC (57) CT (74) TT (26)	CA vs CC: 1.27 [0.84–1.92] *p* = 0.26 AA vs CC: 1.34 [0.76–2.35] *p* = 0.31	1.16 [0.89–1.51] *p* = 0.27
MetS	C/T	CC (228) CT (265) TT (90) *p* = 0.95	CC (56) CT (65) TT (24)	AT vs AA: 1.04 [0.68–1.59] *p* = 0.87 TT vs AA: 1.13 [0.64–2.02] *p* = 0.67	1.06 [0.80–1.40] *p* = 0.69
HBP	C/T	CC (241) CT (262) TT (86) *p* = 0.11	CC (49) CT (74) TT (29)	CT vs CC: 1.46 [0.95–2.26] *p* = 0.09 TT vs CC: 1.90 [1.07–3.36] *p* = 0.03	1.46 [1.12–1.90] *p = 0.006**

T2D type 2 diabetes, *MetS* metabolic syndrome, *HBP* high blood pressure. *OR* adjusted on age, gender, physical activity, and smoking status. *OR** obtained for additive model. *p* values were adjusted for age, gender, physical activity, and smoking status. Significant *p* values are indicated in italics with an asterisk

Table 6 APOE rs4420638 polymorphism and cardiometabolic risk

rs4420638	Major allele/minor allele	ISOR			
		Genotypes (*N*) *p*		OR [95% CI] *p*	OR* [95% CI] *p*
T2D	A/G	Control AA (515) AG(124) GG (9) *p* = 0.56	Case AA (63) AG(16) GG (0)	AG vs AA: 1.20 [0.65–2.22] *p* = 0.56	0.99 [0.56–1.75] *p* = 0.98
Obesity	A/G	AA (463) AG (128) GG (10) *p* = 0.02	AA (136) AG (21) GG (0)	AG vs AA: 0.51 [0.30–0.85] *p = 0.01**	0.48[0.29–0.79] *p = 0.004**
MetS	A/G	AA (473) AG (118) GG (7) *p* = 0.68	AA (117) AG (27) GG (3)	AG vs AA: 0.93 [0.57–1.53] *p* = 0.78 GG vs AA: 3.19 [0.73–13.89] *p* = 0.12	1.10 [0.71–1.70] *p* = 0.66
HBP	A/G	AA (469) AG (128) GG (7) *p* < 0.001	AA (20) AG (127) GG (3)	AG vs AA: 0.56 [0.33–0.96] *p* = 0.03 GG vs AA: 2.24 [0.51–9.84] *p* = 0.29	0.73 [0.47–1.14] *p* = 0.17

T2D type 2 diabetes, *MetS* metabolic syndrome, *HBP* high blood pressure. *OR* adjusted on age, gender, physical activity, and smoking status. *OR** obtained for additive model. *p* values were adjusted for age, gender, physical activity, and smoking status. Significant *p* values are indicated in italics with an asterisk

Conclusion

Although APOE variants were not associated with the risk of MetS, the APOE polymorphism alleles were associated with some of the metabolic parameters in Algerian subjects. The relation of APOE rs439401 alleles with HBP seems indicative of a state of stress of the population. These hypotheses require in the future investigations on a larger sample and, in which, the stress level must be measured accurately.

The interaction of gene nutrition must be investigated in the future; the Algerian population shows many changes in eating habits during the last decade, which could be responsible for the increasing prevalence of obesity in our population and which can influence the effect of APOE polymorphism on the studied parameters.

Abbreviations

ANDRS: Agence Nationale De Recherche en Santé; APOE: Apolipoprotein E; ATRSS: Agence Thématique de Recherche en Science de la Santé; BMI: Body mass index; d.f.: Degree of freedom; DBP: Diastolic blood pressure; DNA: Deoxyribonucleic acid; HDL: High-density lipoprotein; ISOR: InSulino-résistance à ORan; LDL: Low-density lipoprotein; MetS: Metabolic syndrome; SBP: Systolic blood pressure; SNP: Single nucleotide polymorphism; T2D: Type 2 diabetes

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Authors' contributions

SMB and LH designed the research; SMB, LH, and IHM conducted the research; HOD, SLH, IHM, SMB, and LH participated in the recruitment of subjects; HB built the database; HB performed the DNA extraction; HB and SMB performed the statistical analyses; HB and SMB interpreted the results. IHM assayed biochemical parameters; HB wrote the paper under the supervision of SMB; HB and SMB had primary responsibility for the final content. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The work has been done according to Helsinki Declaration and the study's objectives and procedures were approved by the independent ethics committee at the Algerian National Agency for the Development of Health Research (ANDRS) (reference n°02/07/01/01/076), (since renamed as the Thematic Agency of Research in Health Sciences, ATRSS). All participants provided written informed consent prior to enrolment.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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