Aim: Recent studies suggest that glucose-6-phosphate dehydrogenase (G6PD) deficiency, a genetically inherited condition causing hemolytic anemia, may be a risk factor for cardiovascular disease (CVD). We aimed to perform a retrospective case–control study in Sardinia taking advantage from clinical records of patients undergoing upper digestive endoscopy and screened for *H. pylori* infection.

Methods: A total of 9,604 patients with a known G6PD status and a complete clinical history, encompassing CVD, and leading CVD risk factors, including *H. pylori* infection, undergoing upper endoscopy between 2002 and 2017 were enrolled in this study.

Results: Multivariate logistic regression analysis confirmed an increased CVD risk in subjects with G6PD deficiency [odd ratio (OR), 3.24; 95% confidence interval (CI) 2.44–4.30] after adjusting for potential confounders and effect modifiers, including *H. pylori* infection. Cardiovascular risk was similar in subjects with and without G6PD deficiency before age 60 (OR, 1.26; 95% CI 0.78–2.04, *P* 0.562), whereas it increased after age 60 in the former group (OR, 3.05; 95% CI 2.22–4.19, *P*<0.0001) especially in males (OR 3.67; 95% CI 2.19–6.14) compared with females (OR, 2.96; 95% CI 1.89–4.64) by sex-specific logistic regression analysis.

Conclusion: The risk of CVD was greater in G6PD-deficient subjects after age 60, both in males and females, than those with normal enzyme activity, after adjusting for conventional CVD risk factors and *H. pylori* infection. The reduction of important protective mechanisms against oxidative stress in the elderly might explain the study findings.

Among additional risk factors, *Helicobacter pylori* infection may contribute to the progression of atherosclerosis through chronic low-grade inflammatory stimulation; therefore, this bacterial infection has been proposed as a “possible” risk factor. Chronic infection is associated with changes in the levels of serum C-reactive protein, heat shock protein, fibrinogen, triglycerides, and high-density lipoprotein, all factors related with atherosclerosis and a prothrombotic state. Moreover, *H. pylori* may increase the risk of acute cardiovascular events by promoting atherosclerotic cardiovascular disease (CVD) is a major cause of mortality and morbidity in high-resource countries. It encompasses myocardial infarction, angina pectoris, cerebrovascular disease including stroke and transient ischemic attack, peripheral artery disease, atherosclerosis, and aneurysm of the thoracic or abdominal aorta. Dyslipidemia, high blood pressure, diabetes, smoking, obesity, and a positive family history are well-known established CVD risk factors.

Key words: Glucose-6-phosphate dehydrogenase, Cardiovascular disease, Helicobacter pylori, Antioxidant defense
G6PD Deficiency in Cardiovascular Disease

rotic plaque instability and/or disruption\textsuperscript{4,6}. For example, in two studies, a cross-reactivity was observed of anti-CagA and anti-VacA antibodies with vascular wall antigens, such as endothelium, smooth muscle cells, and plaque fibroblasts in atherosclerotic arteries\textsuperscript{7-8}.

On the contrary, glucose-6-phosphate dehydrogenase (G6PD) deficiency was long considered a protective factor for CVD, via a statin-like inhibitory effect on cholesterol biosynthesis\textsuperscript{9,10}. G6PD deficiency is the most common genetically inherited enzymatic disorder in humans affecting around 400 million people worldwide\textsuperscript{11}. The enzyme catalyzes the rate-limiting step in the pentose phosphate pathway (PPP) and reduces nicotinamide adenine dinucleotide phosphate (NADP) to NADPH, necessary to protect cells from oxidative injury, especially in red blood cells where PPP is the only source of NADPH\textsuperscript{11}. The defect is X-linked, and carriers may be asymptomatic or may experience a spectrum of hemolytic disorders upon ingestion of fava bean (Vicia faba) seeds or some drugs. However, recent evidences obtained from large cohorts\textsuperscript{12-14} are in contrast with previous observations, suggesting that G6PD deficiency may actually be an independent risk factor for CVD, likely due to the impaired antioxidant defense resulting from PPP downregulation and consequential depletion of intracellular NADPH.

The population of Sardinia, Italy, shows the highest prevalence of G6PD deficiency in the Mediterranean area, mostly due to a C→T transition at nucleotide 563 of the X-linked G6PD gene, making the island population an ideal setting to test whether enzyme activity may impact the susceptibility to develop CVD.

Aim

We aimed to perform a retrospective case–control study in Sardinia taking advantage from clinical records of patients undergoing upper digestive endoscopy and screened for \textit{H. pylori} infection.

Methods

Study Participants

Patients undergoing upper endoscopy between 2002 and 2017 with (cases) or without (controls) a clinical history of CVD were compared for G6PD status, adjusting for established CVD risk factors, such as tobacco smoking, obesity, blood hypertension, diabetes mellitus, dyslipidemia, and \textit{H. pylori} infection.

Study Design

This was a retrospective, case–control single-center study. Data of patients undergoing upper endoscopy at the Department of Medical, Surgical and Experimental Sciences (University of Sassari, Northern Sardinia, Italy) were retrieved. Patients with (cases) and without (controls) a clinical history of CVD were compared according to G6PD status and CVD risk factors, including \textit{H. pylori} infection.

Data Collection

The diagnosis of CVD was made by a cardiologist, according to national and international guidelines. Patients with only self-reported CVD diagnosis were excluded. Cardiovascular conditions considered as outcome were nonfatal acute myocardial infarction, history of effort-induced angina or coronary revascularization, stenosis ≥ 70\% of lower limb artery, and ischemic stroke. Information about established CVD risk factors, such as hypertension, cigarette smoking, obesity, dyslipidemia, and type 1 and 2 diabetes, defined according to international guidelines was also collected. More specifically, obesity was defined as a body mass index (BMI) ≥ 30 kg/m$^2$. As for smoking habits, patients were grouped into (i) never smokers and (ii) former or current smokers. Dyslipidemia was defined as elevated low-density lipoprotein cholesterol levels ≥ 100 mg/dL or low levels of high-density lipoprotein cholesterol$^\text{15}$ and categorized as a dichotomic variable. \textit{Helicobacter pylori} infection was assessed according to the presence of the bacteria in gastric specimens and/or rapid urease testing and/or$^{13}$C urea breath test and/or stool antigen test, as previously reported$^\text{16}$. Records of patients younger than 18 years or with incomplete data were excluded from the analysis. All patients signed the written informed consents and agreed to participate in a series of clinical studies including this study. The study was approved by the Local Ethics Committee “Comitato Etico ASL n° 1 di Sassari” (Prot N° 2099/CE).

Measurement of G6PD Activity

G6PD activity was determined by a semi-quantitative biochemical assay based on the G6PD/6PGD ratio in erythrocytes$^\text{17}$. A ratio <0.1 was used to define enzyme deficiency.

Statistical Analysis

Univariate and multivariate logistic regression analysis was performed using any time occurrence of CVD as outcome, and age as main predictor, adjusting for established risk factors, \textit{H. pylori} infection and G6PD status. Since G6PD is an X-linked gene, additional analyses were carried out separately in the two
A total of 9,604 patients (age, 18–95 years; 63% females) were available for the analysis. In the studied cohort, G6PD deficiency was detected in 1,123 (11.7%) subjects (7.8% men, 14.0% women), a frequency comparable with that previously reported in the general population of Northern Sardinia.\(^{19}\) (Table 1) There were 324 (3.4%) patients with a final diagnosis of CVD, and G6PD deficiency was more common among cases than controls (23.8% versus 11.3%; \(P < 0.0001\)). As expected, the frequency distribution of CVD risk factors, such as male sex, older age, high blood pressure, smoking habits, obesity, diabetes, dys-

| Explanatory variables | CVD (cases, \(n = 324\)) | No CVD (controls, \(n = 9,280\)) | Unadjusted odds ratio OR (95% CI\(^\ast\)) | Adjusted odds ratio OR (95% CI\(^\ast\)) |
|-----------------------|-----------------------------|-----------------------------------|------------------------------------------|-----------------------------------------|
| Sex, \(n\) (%)        |                             |                                   |                                          |                                         |
| Female                | 145 (44.8)                  | 5,869 (63.2)                      | 1.00                                     | 1.00                                    |
| Male                  | 179 (55.2)                  | 3,411 (36.8)                      | 2.12 (1.70-2.65)**                      | 1.91 (1.49-2.43)**                      |
| Age (years)           |                             |                                   |                                          |                                         |
| < 60                  | 70 (21.6)                   | 6,047 (65.2)                      | 1.00                                     | 1.00                                    |
| ≥ 60                  | 254 (78.4)                  | 3,233 (34.8)                      | 6.79 (5.19-8.87)**                      | 3.80 (2.82-5.12)**                      |
| High blood pressure, \(n\) (%) |                      |                                   |                                          |                                         |
| No                    | 152 (46.9)                  | 7,173 (77.3)                      | 1.00                                     | 1.00                                    |
| Yes                   | 172 (53.1)                  | 2,107 (22.7)                      | 3.58 (3.08-4.82)**                      | 1.91 (1.48-2.46)**                      |
| Smoking habits, \(n\) (%) |                      |                                   |                                          |                                         |
| No                    | 165 (50.9)                  | 7,083 (76.3)                      | 1.00                                     | 1.00                                    |
| Yes                   | 159 (49.1)                  | 2,197 (23.7)                      | 3.11 (2.49-3.88)**                      | 2.33 (1.84-2.95)**                      |
| Body mass index, \(n\) (%) |                      |                                   |                                          |                                         |
| < 30 kg/m\(^2\)       | 283 (87.3)                  | 8,585 (92.5)                      | 1.00                                     | 1.00                                    |
| ≥ 30 kg/m\(^2\)       | 41 (12.7)                   | 695 (7.5)                         | 1.79 (1.28-2.51)**                      | 1.15 (0.81-1.64)                        |
| Diabetes mellitus, \(n\) (%) |                      |                                   |                                          |                                         |
| No                    | 270 (83.3)                  | 8,685 (93.6)                      | 1.00                                     | 1.00                                    |
| Yes                   | 54 (16.7)                   | 595 (6.4)                         | 2.92 (2.15-3.95)**                      | 1.57 (1.13-2.16)*                       |
| Dyslipidemia, \(n\) (%) |                      |                                   |                                          |                                         |
| No                    | 245 (75.6)                  | 8,443 (91.0)                      | 1.00                                     | 1.00                                    |
| Yes                   | 79 (24.4)                   | 837 (9.0)                         | 3.25 (2.50-4.23)**                      | 1.93 (1.45-2.56)**                      |
| Helicobacter pylori infection, \(n\) (%) |                      |                                   |                                          |                                         |
| No                    | 161 (49.7)                  | 6,378 (68.7)                      | 1.00                                     | 1.00                                    |
| Yes                   | 163 (50.3)                  | 2,902 (31.3)                      | 2.22 (1.78-2.78)**                      | 1.80 (1.42-2.28)**                      |
| G6PD\(^\#\) deficiency, \(n\) (%) |                      |                                   |                                          |                                         |
| No                    | 247 (76.2)                  | 8,234 (88.7)                      | 1.00                                     | 1.00                                    |
| Yes                   | 77 (23.8)                   | 1,046 (11.3)                      | 2.45 (1.88-3.19)**                      | 3.24 (2.44-4.30)*                       |

*\(P < 0.05\), **\(P < 0.01\)
\(^\ast\)Confidence Interval
\(^\#\)Glucose-6-phosphate dehydrogenase

Results

A total of 9,604 patients (age, 18–95 years; 63% females) were available for the analysis. In the studied cohort, G6PD deficiency was detected in 1,123 (11.7%) subjects (7.8% men, 14.0% women), a frequency comparable with that previously reported in the general population of Northern Sardinia.\(^{19}\) (Table 1). There were 324 (3.4%) patients with a final diagnosis of CVD, and G6PD deficiency was more common among cases than controls (23.8% versus 11.3%; \(P < 0.0001\)). As expected, the frequency distribution of CVD risk factors, such as male sex, older age, high blood pressure, smoking habits, obesity, diabetes, dys-

Sexes. For this reason, a considerable phenotypic discrepancy between G6PD-deficient males and females may exist. In fact, hemizygous males show a total deficiency, like homozygous females; on the other hand, heterozygous females should theoretically have a residual enzyme activity of 50% but can display large fluctuations depending on the skewed X-chromosome inactivation.\(^{18}\)

Odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated by exponentiating the regression coefficients. Statistical analyses were performed using SPSS statistical software (version 16.0, Chicago, IL). P-values lower than 0.05 were considered statistically significant.
Prevalence of cardiovascular events was substantially similar in normal subjects and carriers of G6PD deficiency, and the adjusted odds ratio for CVD was not significantly greater than unity. However, in the older subjects (age decades 60–69, 70–79, and ≥80 years), the risk associated with CVD was significantly higher in G6PD-deficient subjects than in normal ones. Moreover, sex-specific logistic regression analysis showed that beyond age 60, the CVD risk was greater in males (OR, 3.670; 95% CI 2.193–6.140) than in females (OR, 2.960; 95% CI 1.888–4.640) (Fig. 1).

Table 2. Multivariable logistic regression in patients undergoing upper endoscopy according to glucose-6-phosphate dehydrogenase (G6PD) status

The presence/absence of cardiovascular disease (CVD) was the outcome variable.

| Age (years) | G6PD normal (reference) | G6PD deficient | aOR (95% CI) |
|------------|-------------------------|---------------|--------------|
| <40        | 11 (0.5%)               | 2 (0.7%)      | 0.968 (0.188–4.974) |
| 40–49      | 18 (1.2%)               | 3 (1.6%)      | 1.260 (0.362–4.381) |
| 50–59      | 37 (2.5%)               | 8 (3.6%)      | 1.974 (0.866–4.498) |
| 60–69      | 82 (5.1%)               | 27 (12.1%)    | 3.498 (2.144–5.707)** |
| 70–79      | 67 (5.9%)               | 28 (18.3%)    | 4.770 (2.831–8.036)** |
| ≥80        | 32 (10.1%)              | 9 (24.3%)     | 3.041 (1.234–7.493)** |

*p<0.05  **p<0.01

Fig. 1. Odds ratios for cardiovascular disease (CVD) according to age decades in 9,604 patients with (1,123) and without (8,481) G6PD deficiency

Logistic regression analysis was performed with CVD as the dependent binary (presence/absence) variable and G6PD status as the main predictor variable, separately on each age decade. Odds ratios significantly diverged from unity after the sixth decade for the presence of CVD in patients with G6PD deficiency.

*p<0.0001

Lipidemia, and *H. pylori* infection, significantly differed between cases and controls. Statistically significant differences of risk persisted after adjusting for covariates, except for obesity. Interestingly, higher ORs were associated with older age (3.80, *p<0.0001*) and G6PD deficiency (3.24, *p<0.0001*) followed by smoking (2.33, *p<0.0001*), respectively (Table 1). Table 2 shows the ORs for CVD between subjects with and without G6PD deficiency, adjusting for established CVD risk factors including hypertension, cigarette smoking, obesity, dyslipidemia, type 1 and 2 diabetes, and *H. pylori* infection. Before age 60, the prevalence of cardiovascular events was substantially similar in normal subjects and carriers of G6PD deficiency, and the adjusted odds ratio for CVD was not significantly greater than unity. However, in the older subjects (age decades 60–69, 70–79, and ≥80 years), the risk associated with CVD was significantly higher in G6PD-deficient subjects than in normal ones. Moreover, sex-specific logistic regression analysis showed that beyond age 60, the CVD risk was greater in males (OR, 3.670; 95% CI 2.193–6.140) than in females (OR, 2.960; 95% CI 1.888–4.640) (Fig. 1).
Discussion

The emerging role of G6PD deficiency as a potential promoter of atherosclerosis, fostered by recent epidemiological studies, has led to a complete reappraisal of this condition among the non-modifiable cardiovascular risk factors, thus reversing the traditional opinions about its alleged protective rather than harmful effect. The findings of our study corroborate this new paradigm and suggest that the enzyme defect may be somehow able to accelerate the development of endothelial dysfunction in an age-dependent manner and, in turn, the premature onset of vascular damage.

In our study, the risk of cardiovascular events, starting from age 60, was greater in G6PD-deficient subjects, both males and females, than in those with normal enzyme activity, after adjusting for conventional CVD risk factors and *H. pylori* infection. It could be argued that the increased susceptibility to CVD in older G6PD-deficient subjects might result from a less frequent prescription by doctors of low-dose aspirin (well-known G6PD inhibitor potentially capable of inducing hemolytic episodes) as antiplatelet agent. However, the percentage of patients exposed to antiplatelet medications for primary prevention was similar in cases and controls (12.4% versus 9.7%) and was independent of the G6PD status. In line with previous studies, our findings indicated *H. pylori* infection as an additional risk factor for CVD with an OR of 1.80 (*P*<0.0001), similar to that of dyslipidemia and high blood pressure. This may be explained considering the elegant experiments carried out by Xia *et al.* in human and animal models. In this study, young patients and mice infected with *H. pylori* showed significantly impaired endothelial function. Moreover, infection treatment improved significantly endothelium-dependent vasodilation in both patients and mice. However, among all risk factors, such as *H. pylori* infection, G6PD deficiency, following age, demonstrated to be the strongest.

It cannot be entirely excluded, albeit unlikely, a selection bias leading to increased proportion of elderly people with CVD; however, this potential confounder likely impacted on G6PD-deficient and normal patients in a similar manner.

A biologically plausible explanation for these findings could be the crucial role of G6PD enzyme in the PPP. During aging, a progressive imbalance occurs between the production of free radicals and the antioxidant defenses, which tends to be worse in people with a less efficient antioxidant endowment due to genetic causes. As a consequence, a pathological process such as atherosclerosis, due, at least in part, to free radical damage, is likely to develop faster in those elderly subjects who have inherited defects in antioxidant mechanisms. In younger subjects, organ damage has not yet reached a critical threshold to reveal the presence of genetically weaker mechanisms against reactive oxygen species. During senescence, a reduction in antioxidant defense has been documented for glutathione and nitric oxide (NO). The glutathione rate of synthesis declines in elderly humans, as demonstrated by stable-isotope techniques, resulting in an increased pro-oxidizing status. This phenomenon may be reversed by treating elderly subjects with oral supplementation of L-cysteine and L-glycine, both precursors of reduced glutathione. In addition, in vitro studies demonstrated that G6PD deficiency depletes NO in endothelial cells, thereby increasing the level of reactive oxygen species acting as powerful inducers of vascular inflammation and, in turn, endothelial dysfunction. Parsanathan and colleagues recently found that cell adhesion molecules (ICAM-1, VCAM-1) in human umbilical vein endothelial cells treated with G6PD inhibitors are upregulated, providing a further mechanistic pathway hinged on inflammatory cell recruitment within the peri-endothelial milieu. In addition, they found that this effect was reversed by L-cysteine, pointing again to a major role of glutathione and the antioxidant defense. Protection of endothelium is critical in the elderly where NO bioavailability decreases compared to younger subjects. Thus, the lack of important protective pathways against oxidative stress might explain the findings of our study.

There are scattered reports in the literature of an increased frequency of G6PD deficiency in long-lived individuals. These data, if accurate, are clearly in contrast with our findings, reinforcing the hypothesis that this condition represents a cardiovascular risk factor, the effect of which is amplified by age. However, a recent study conducted in a large cohort has excluded an increased frequency of G6PD deficiency at extreme ages.

The main limitation of our study is the cross-sectional design; therefore, age-related increase in ORs for CVD in G6DP deficiency may have been confounded by several uncontrolled factors, such as family history of CVD, lifestyle factors, diet, exercise, and alcohol intake, among others, which may significantly impact the CVD risk. Therefore, the findings of this study should be confirmed in a longitudinal study. Moreover, the study recruited only patients who underwent endoscopy, which might limit generalizability of the findings.

Nonetheless, some strengths need to be underlined in this study. First, the large size cohort analyzed...
belonged to the same ethnic group with a homogeneous genetic background. Data were retrieved from structured records duly filled out in the same fashion throughout the study period. Moreover, blood hypertension, diabetes mellitus, dyslipidemia, \textit{H. pylori} infection, and CVD, with the exception of tobacco smoking that was self-reported, were definitive diagnosis performed by the specialist, making our results reliable.

**Conclusion**

A conclusion about the ultimate significance of G6PD deficiency among the other established non-modifiable cardiovascular risk factors needs to be confirmed by large, prospective studies. However, our results add evidence to this new research field that is going to interest a large section of the world population.

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**Conflict of Interests**

The authors declare that they have no conflicts of interest.

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