Platelet distribution width is associated with cardiovascular mortality in an adult general population

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ABSTRACT
Platelet distribution width (PDW), a marker of platelet size heterogeneity used as a readout of processes leading to platelet production and destruction, was recently reported to tag platelet activation variability. As platelets participate in the pathogenesis of many acute and chronic diseases, we evaluated PDW as a predictor of all-cause and cause-specific mortality. Longitudinal analysis was performed on 17,334 participants (52% women, mean age 55.6±12 years) in the Moli-sani study cohort, without a history of hematological diseases. Baseline PDW measurements were categorized in tertiles, the lowest acting as the reference. A multivariable Cox-proportional hazard model was used to estimate the association between PDW and mortality. Over a median follow-up of 11.6 years (interquartile range 10.7-12.5), 1,535 deaths [37.7% cardiovascular disease (CVD) and 36.5% cancer] were ascertained. As compared to those in the first PDW tertile (14.6-16.0 fL), individuals within the highest tertile (16.6-20.4 fL) had an increased risk of all-cause [hazard ratios (HR):1.20; 1.14-1.58, P for interaction =0.028 and HR:1.37; 1.01-1.85, P=0.020, respectively]. We conclude that PDW-associated increase in CVD mortality risk could be related to accelerated/altered activation, production, or destruction of platelets, leading to several clinical conditions and death. In the elderly, PDW involvement in all-cause and cancer mortality should be further investigated.

Introduction
Number and volume changes of blood platelets have long been considered as important determinants of pathophysiological processes including athero-thrombosis and thrombo-inflammation, leading causes of cardiovascular disease. Platelet count
(Plt) and two platelet size indices, namely mean platelet volume (MPV) and platelet distribution width (PDW), are often available in routine blood analysis and are used as diagnostic support in several clinical settings. Both Plt and MPV have been largely investigated in relation to mortality in epidemiological studies focusing on general populations. Low and/or high Plt has been associated with increased all-cause, cardiovascular disease (CVD) or cancer mortality risk. Data on the relationship between MPV and mortality are more controversial and less consistent across studies: both increased and decreased mortality risk has been reported in association with MPV.

Contrary to Plt and MPV, PDW was never investigated as a marker of mortality risk in the context of general population studies, though in an Israeli cohort of 1,036 in-ward patients (age 66.4±18 years, 58.3% men) not selected for any specific pathological condition, higher PDW was associated with an increased risk of 90-day mortality and shortened survival after discharge from the hospital.

Reflecting platelet size heterogeneity, PDW is frequently used as a diagnostic marker for diseases with impaired megakaryocyte differentiation and thrombopoiesis and identified as a prognosis predictor in clinically-defined populations with several inflammatory-based conditions including CVD, cancer, metabolic syndrome, diabetes, and neurological disorders. Using an observational approach we have recently shown in the Moli-sani cohort study that PDW specifically and significantly reflects ex vivo and in vitro P-selectin-dependent platelet activation, as well as platelet involvement in in vitro coagulation. Our findings suggest that PDW might be a better marker of platelet activation and can therefore be better linked with disease outcomes where platelets are thought to play a role. Based on these findings, we aimed to investigate whether PDW variability is associated with the risk for all-cause, cardiovascular- and cancer-specific mortality in the Moli-sani study, an adult general population cohort.

Materials and Methods

Study population

The Moli-sani study is an ongoing prospective cohort study that enrolled 24,325 individuals (51.9% women, aged ≥35 years) randomly recruited from the general population of Molise region in Southern-central Italy between 2005 and 2010. The Moli-sani study complies with the Declaration of Helsinki and was approved by the Catholic University Ethical Committee, Rome, Italy. All participants enrolled provided written informed consent. Details of the Moli-sani study have been previously described.

For this study, we only included participants recruited in the center of Campobasso (n=19,211) and excluded participants in the center of Termoli (n=5,114) to avoid biases caused using a different operator and cell counter for the measurement of hematological parameters. In addition, non-Caucasian participants or participants with hematological diseases (mainly polycythemia vera, essential thrombocytopenia and myelofibrosis), missing measurements of PDW, unreliable medical questionnaire as well as individuals with an unknown cause of death were omitted from the analysis. The final study sample consisted of 17,334 individuals [51.6% women; mean age ± standard deviation (SD) 55.6±12.1 years, Supplementary Figure 1].

Assessment of cause-specific and total mortality

The Moli-sani Study cohort was followed up for mortality until December 31st, 2018. Cause-specific mortality was assessed by the Italian mortality registry (ReNaCaM; Registro Nominativo delle Cause di Morte), validated by Italian death certificates (ISTAT form), and coded according to the International Classification of Diseases (ICD-9).

CVD mortality included deaths from diseases of the circulatory system when the underlying cause of death included ICD-9 codes 390-459. Cancer death was considered when the underlying cause of death included ICD-9 codes 140-208. Non cardiovascular/non-cancer causes of death were included in the ‘other cause mortality’ group.

Statistical analysis

The normality of continuous variables was assessed by the Shapiro-Wilk test and confirmed graphically. Normally distributed data are presented as mean [SD or standard error (SE)], skewed as geometric mean (95% CI), and categorical variables as frequencies. PDW was classified into tertiles. The difference in the distribution of baseline covariates according to tertiles of PDW was calculated using analysis of variance adjusted for age and sex (PROC MIANALYZE) to maximize data availability. Hazard ratios (HR) and 95% CI for all-cause and cause-specific mortality according to PDW tertiles were calculated using Cox Proportional Hazard (unadjusted, age- and sex-adjusted and multivariable) models with time-on-study on the time scale and considering the lowest PDW tertile as reference.

To estimate the association between PDW tertiles and all-cause and cause-specific mortality risk, a multiple imputation approach was used (SAS PROC MI, N=10 imputed datasets; and PROC MIANALYZE) to maximize data availability. Hazard ratios (HR) and 95% CI for all-cause and cause-specific mortality according to PDW tertiles were calculated using Cox Proportional Hazard (unadjusted, age- and sex-adjusted and multivariable) models with time-on-study on the time scale and considering the lowest PDW tertile as reference.

The final multivariable models included the variables associated with both outcome and exposure with a P-value (adjusted for age and sex) <0.20. Adjusted survival curves were constructed for all-cause and cause-specific mortality to show event rates during follow-up by tertiles of PDW.

The risks of all-cause and cause-specific mortality for each decrease in 1 SD of PDW (0.58 fL) were calculated in the whole sample.

Sensitivity analyses were performed: i) considering a case complete analysis for all variables (n=15,868 individuals); ii) excluding early deaths (follow-up time ≥2 years; N=17,198 individuals).

Sub-group analyses separately by sex, age classes (35-65 years, ≥65 years), CVD risk factors, and history of CVD or cancer were performed. Multiplicative interaction between PDW (modeled as tertiles) and the designed effect modifier in relation to all-cause and cause-specific mortality was tested with cross-product terms.

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<table>
<thead>
<tr>
<th>Characteristic</th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
<th>P value</th>
</tr>
</thead>
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<tr>
<td><strong>N</strong></td>
<td>5145</td>
<td>6477</td>
<td>5712</td>
<td></td>
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<tr>
<td><strong>PDW, fL</strong></td>
<td>15.8±0.21</td>
<td>16.3±0.14</td>
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<tr>
<td><strong>Min-max</strong></td>
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<td>16.1-16.5</td>
<td>16.6-20.4</td>
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<tr>
<td><strong>Men</strong></td>
<td>1971 (38.3)</td>
<td>3151 (48.7)</td>
<td>3273 (57.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Age, years</strong></td>
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<td>55.5±12.0</td>
<td>56.6±12.4</td>
<td>&lt;0.0001</td>
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<td><strong>HCT, %</strong></td>
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<td>43.4±4.0</td>
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<td><strong>PLT, x10^9/L</strong></td>
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<td>249.5±57.7</td>
<td>232.8±61.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>MPV, fL</strong></td>
<td>8.52±0.82</td>
<td>8.53±0.86</td>
<td>8.72±1.08</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>WBC, x10^9/L</strong></td>
<td>6.15 (6.11-6.19)</td>
<td>6.01 (5.98-6.05)</td>
<td>5.91 (5.87-5.95)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

**Continuous variables are presented as means±standard deviation and categorical variables as number and (percentage). Values for Triglycerides, d-Dimer, C-reactive protein, Cystatin C, and white blood cells are reported as geometric means with corresponding 95% confidence intervals. Means (except for age) and p values adjusted for age, sex, and hematocrit. BMI, body mass index; CVD, cardiovascular disease; DBP, diastolic blood pressure; HCT, hematocrit; HRT, hormone replacement therapy; hs-CRP, high-sensitive C-reactive protein; MPV, mean platelet volume; PDW, platelet distribution width; PLT, platelet count; SBP, systolic blood pressure; WBC, white blood cell count; PA, physical activity.**

<table>
<thead>
<tr>
<th>Table 1. Baseline characteristics according to tertiles of platelet distribution width in the Moli-sani Study cohort (N=17,334).</th>
<th>T1</th>
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<th>T3</th>
<th>P value</th>
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</thead>
<tbody>
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Results

In the Moli-sani population, the average of PDW was 16.4±0.58 fL, and its distribution displayed features of normality (Supplementary Figure 2).

Table 1 reports baseline characteristics of the Moli-sani cohort according to tertiles of PDW. Subjects in the highest PDW tertile (16.6-20.4 fL) were more frequently men and older as compared to those in the first tertile (14.6-16.0 fL). They had significantly lower Plt, hematocrit, white blood cell counts and fibrinogen levels and higher MPV. Individuals with higher PDW also had a higher waist-to-hip ratio and systolic blood pressure. They reported a greater prevalence of diabetes and atrial fibrillation and had a lower prevalence of hypercholesterolemia and adherence to the Mediterranean diet. In addition, women in the highest PDW tertile were less frequently under oral contraceptive treatment.

Over a median follow-up of 11.6 years (interquartile range 10.7 to 12.5 years; 195,521.4 person-years) 1,535 all-cause deaths were validated (579 cardiovascular and 561 cancer deaths).

Multivariable survival curves for all-cause mortality according to PDW tertiles were well separated (Figure 1, P=0.019). In a model adjusted for age, sex, hematocrit, cystatin C, systolic BP, atrial fibrillation, liver disease, hypercholesterolemia, diabetes, waist-to-hip ratio, Mediterranean diet score, physical activity/leisure time and smoking, compared to individuals within the lowest PDW tertile (14.6-16.0 fL), subjects in the highest PDW tertile (16.2-20.4 fL) had an increased risk of all-cause (HR=1.21; 95% CI 1.06-1.39 for highest vs. lowest tertile of PDW; Supplementary Table 1, Model 2), cardiovascular (HR=1.25; 95% CI 1.00-1.55; Supplementary Table 1, Model 2) and other-cause mortality (HR=1.40; 95% CI 1.07-1.86; Supplementary Table 1, Model 2). These findings remained consistent even when the model was further adjusted for Plt, MPV, and WBCs (HR=1.20; 95% CI 1.04-1.37 for all-cause mortality, HR=1.29; 95% CI 1.03-1.62 for cardiovascular mortality and HR=1.27; 95% CI 0.97-1.68 for other-cause mortality; Figure 2 and Supplementary Table 1, Model 3). No association was identified between PDW and cancer mortality (Figure 2 and Supplementary Table 1).

Analyses performed in a sub-sample (n=14,335), for which baseline fibrinogen measurements were available, showed that the associations were independent of this inflammatory and hemostatic factor (Supplementary Table 2, Model 4).

Case-complete analyses restricted to 15,868 subjects without missing values for covariates and analyses of data after exclusion of early deaths (follow-up ≥ 2 years, N=17,198 individuals), yielded very similar results (Supplementary Tables 3-4).

Sensitivity subgroup analyses were reported in Figure 3 and Supplementary Tables 5-8.

No difference in the association between PDW tertiles and all-cause and specific-cause mortality according to sex, diabetes, hypercholesterolemia, smoking habits, history of CVD, and cancer was found (Supplementary Tables 5-8, P for interaction >0.05).

However, subgroup analyses separately by age classes (35-65 years, ≥65 years) showed a risk trend with CVD mortality in both younger and older individuals while the association with all-cause mortality was only confirmed in the elderly (HR: 1.34; 1.14-1.58, p for interaction =0.028, Figure 3 and Supplementary Table 5). Similar results were found in the elderly for cancer mortality (age ≥65 years: HR: 1.37; 1.01-1.85, P for interaction =0.020; Figure 3 and Supplementary Table 7). In contrast, we observed an inverse association between PDW and cancer-specific mortality in the subgroup 35-65 years compared to the one observed in the elderly (HR: 0.77; 0.55-1.08, P for interaction =0.020; Figure 3 and Supplementary Table 7).

Figure 1. Multivariable survival estimates for all-cause mortality according to platelet distribution width tertiles. Multivariable survival curves were obtained from the multivariable model adjusted for age, sex, hematocrit, systolic blood pressure, atrial fibrillation, liver disease, hypercholesterolemia, Cystatin C, Mediterranean diet score, physical activity/leisure time, smoking, diabetes, waist-to-hip ratio, platelet count, mean platelet volume, white blood cell count.
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Figure 2. Hazard ratios (95% confidence intervals) for all-cause (overall), cardiovascular and cancer mortality, according to platelet distribution width tertiles. Multivariable model adjusted for age, sex, hematocrit; systolic blood pressure, atrial fibrillation, liver disease, hypercholesterolemia, Cystatin C, Mediterranean diet score, physical activity/leisure time, smoking, diabetes, waist-to-hip ratio, platelet count, mean platelet volume, white blood cell count.

Figure 3. Hazard ratios (95% confidence intervals) of subgroup analysis by age for all-cause, cardiovascular, cancer and other-cause mortality, according to platelet distribution width tertiles. Multivariable model adjusted for age, sex, hematocrit; systolic blood pressure, atrial fibrillation, liver disease, hypercholesterolemia, Cystatin C, Mediterranean diet score, physical activity/leisure time, smoking, diabetes, waist-to-hip ratio, platelet count, mean platelet volume, white blood cell count. Multiplicative interaction between platelet distribution width (modelled as tertiles) and age as the effect modifier in relation to all-cause and cause specific mortality was tested with cross-product terms.
Discussion

In a general Italian adult population, PDW was associated with cardiovascular mortality as also observed when dividing the cohort into age-based subgroups. Further age-dependent specific relationships between PDW and all-cause and cause-specific mortality were identified (Figure 4).

To the best of our knowledge, this study is the first to report data on CVD mortality risk associated with PDW in a general population. Previous studies have largely reported the association of PDW with clinical correlates as well as disease prognosis in specific pathological conditions including CVD, cancer, metabolic syndrome, diabetes, and neurological disorders, but also including pediatric and neonatal sepsis, and preterm infant mortality.

In line with our main findings, higher PDW has been previously identified as a good prognostic marker for hospital-related mortality in the context of heart failure, acute pulmonary thromboembolism, coronary syndrome, myocardial infarction, and deep venous thrombosis. In addition, in the study by Tzur et al., that showed an increased risk of 90-day mortality and shortened survival after discharge from the hospital for patients with high PDW values, it was also reported that subjects with PDW >16.7% on hospital admission were more likely to be admitted for cardio-cerebrovascular disorders and to present with several concomitant CVD-related comorbidities.

Among the major determinants of platelet influence in hemostasis, thrombosis, and inflammation, platelet size (and number) has long been considered to be one of the most relevant markers. PDW is a marker reflecting the heterogeneity of the platelet population size. Overall, all the possible processes affecting platelet volume and morphology might be responsible for PDW variability, including platelet activation, production, and destruction.

On one hand, our findings of PDW being associated with an increased risk for cardiovascular mortality might be suggestive of progressive platelet activation in individuals with higher PDW, with subsequent changes in the morphology of platelets and pseudopodia formation. We and others have observed that PDW variability is linked to platelet function/activation measured cross-sectionally both in vitro and ex vivo in thrombo-inflammation and coagulation-dependent assays, specifically, even better than MPV. Even if the association identified between PDW and platelet activation observed cross-sectionally in the Moli-family cohort had an inverse sign compared to the association we observed for cardiovascular-specific mortality in the Moli-sani study, both cases, PDW appeared to explain these associations better than MPV variability.

On the other hand, greater platelet heterogeneity might also be the result of an increased hypercoagulability after the initiation of thrombotic events, which would stimulate thrombopoiesis alongside increased platelet consumption/destruction. The latter is supported by the evidence in our cohort that individuals within the third PDW tertile also showed higher MPV and lower Plt (Table 1). In addition, increased platelet consumption/destruction might also depend upon an altered bone marrow activity of which the acquisition of somatic

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**Figure 4.** Graphical abstract.
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mutations causing clonal expansion advantage [clonal hematopoiesis of indeterminate potential (CHIP)] is one of the causes and an emerging risk factor for CVD
and all-cause mortality. Indeed, a recent large study conducted in 200,453 UK Biobank participants showed highly significant associations between the presence of clonal hematopoiesis of indeterminate potential (CHIP) mutations and PDW, the most significantly associated blood trait among others including Plt and Pct.

As a surrogate of platelet production/turnover, PDW might also indirectly reflect the presence of reticulated or larger platelets. A number of preclinical studies as well as studies conducted in healthy donors point to striking biological differences in both the transcriptome and the proteome of larger platelets or RNA-rich reticulated platelets. The latter, in particular, represents a specific platelet subpopulation with a higher thrombogenic potential and has found to be significantly elevated in patients with coronary artery disease and acute coronary syndrome and have been associated with adverse cardiovascular events.

Finally, we also observed a significantly increased cancerspecific mortality by PDW in the elderly (age ≥65 years, Figure 3) showing an opposite direction of the one observed in the younger subjects. This association appeared to drive most of the association identified with all-cause mortality, which, in fact, was only confirmed in the elderly. Despite PDW has been shown to be a good cancer prognosis biomarker, also as predictor of mortality in cancer patients, data on PDW variability in relation to cancer mortality in elderly cohorts of the general population are not available. Further studies on elderly cohorts with adequate numbers of incident cancer events should be conducted to substantiate these findings.

Strengths and limitations

The major strengths of this study are its prospective design on a large general adult population and the availability of a wide number of lifestyle, anthropometric, and biological variables, allowing for a better understanding of the predictive role of PDW levels controlling for their possible confounding effects. A limitation is the lack of longitudinal PDW measurements, which makes it unlikely to fully capture exposure over the life course. Additionally, PDW measures are partially dependent on the technology used to record them. However, all PDW measurements were performed using the same instrument and by the same operators, virtually excluding all pre-analytical and analytical variables. Finally, the findings here reported derive from an observational study, thus causality cannot be inferred.

Conclusions

Up to now, PDW had never been investigated as a potential predictor of mortality risk in general populations. The PDW-associated increase in CVD mortality risk reported in this study could be related to accelerated/altered platelet activation, production, or destruction, all age-dependent processes leading to CVD and CVD-related comorbidities and death. Further studies in general populations should be undertaken to better clarify the PDW involvement in all-cause and cancer mortality in the elderly.

References


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53. Li BY, He SZ, Li WH. Heterogeneity of human platelet density subpopulations in aggregation, secretion of ATP, and cytosolic-free calcium concentration. Zhongguo Yao Li Xue Bao 1996;17:152-5.

Online supplementary material:
Supplementary methods: “Blood and biochemical parameters” and “Covariate assessment”.
Supplementary Figure S1. Flow chart of selection of the studied population among Moli-sani participants. The groups of eliminated participants (out of the 24,325 recruited at baseline) are overlaid. The final study sample cannot be calculated as a subtraction of the sum of eliminated groups out of the recruited subjects at baseline.
Supplementary Figure S2. Platelet distribution width (fL) distribution in the Moli-sani cohort.
Supplementary Figure S3. Multivariable survival estimates for cardiovascular disease (panel A, P=0.058), cancer (panel B, P=0.73) and other-cause (panel C, P=0.19) mortality according to platelet distribution width tertiles. Multivariable survival curves were obtained from the multivariable model adjusted for age, sex, hematocrit; systolic blood pressure, atrial fibrillation, liver disease, hypercholesterolemia, Cystatin C, Mediterranean diet score, physical activity/leisure time, smoking, diabetes, waist-to-hip ratio, platelet count, mean platelet volume, white blood cell count by using the first imputed dataset. The other imputed datasets are similar and thus omitted.
Supplementary Table S1. Hazard ratios (95% confidence intervals) for all-cause, cardiovascular, cancer and other-cause mortality, according to platelet distribution width tertiles (17,334).
Supplementary Table S2. Hazard ratios (95% confidence intervals) for all-cause, cardiovascular and cancer mortality, according to platelet distribution width tertiles excluding subjects with missing value for plasmatic fibrinogen (n=14,335).
Supplementary Table S3. Sensitivity analyses for the association of platelet distribution width with all-cause and cause specific mortality considering a case complete approach (n=15,868).
Supplementary Table S4. Sensitivity analyses for the association of platelet distribution width with all-cause mortality excluding early deaths (follow-up >2 years, n=17,198).
Supplementary Table S5. Subgroup analyses for the association of platelet distribution width with all-cause mortality.
Supplementary Table S6. Subgroup analyses for the association of platelet distribution width with cardiovascular disease mortality.
Supplementary Table S7. Subgroup analyses for the association of platelet distribution width with cancer mortality.
Supplementary Table S8. Subgroup analyses for the association of platelet distribution width with other-cause mortality.

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Appendix: Moli-sani investigators

The enrolment phase of the Moli-sani study was conducted at the Research Laboratories of the Catholic University in Campobasso (Italy), the follow-up of the Moli-sani cohort is being conducted at the Department of Epidemiology and Prevention of the IRCCS Neuromed, Pozzilli, Italy.

Steering committee: Licia Iacoviello*° (Chairperson), Giovanni de Gaetano* and Maria Benedetta Donati*.


Safety and ethical committee: Jos Vermyle (Catholic University, Leuven, Belgio) (Chairperson), Renzo Pegoraro (Pontificia Accademia per la Vita, Roma, Italy), Antonio Spagnolo (Catholic University, Roma, Italy).

External event adjudicating committee: Deodato Assanelli (Brescia, Italy), Livia Rago (Campobasso, Italy).

Baseline and follow-up data management: Simona Costanzo* (Coordinator), Marco Olivieri (Campobasso, Italy), Teresa Panzera*.


Biobank, molecular and genetic laboratory: Amalia De Curtis* (Coordinator), Sara Magnacca¹, Fabrizia Noro*, Alfonsina Tirozzi*.

Recruitment staff: Mariarosaria Persichillo* (Coordinator), Francesca Braccone*, Teresa Panzera*.

Communication and press office: Americo Bonanni*.

Regional institutions: Direzione Generale per la Salute - Regione Molise; Azienda Sanitaria Regionale del Molise (ASReM, Italy); Agenzia Regionale per la Protezione Ambientale del Molise (ARPA Molise, Italy); Molise Dati Spa (Campobasso, Italy); Offices of vital statistics of the Molise region.

Hospitals: Presidi Ospedalieri ASReM: Ospedale A. Cardarelli, Campobasso; Ospedale F. Veneziale, Isernia; Ospedale San Timoteo, Termoli (CB); Ospedale Ss. Rosario, Venafro (IS); Ospedale Vietri, Larino (CB); Ospedale San Francesco Caracciolo, Agnone (IS); Casa di Cura Villa Maria, Campobasso; Ospedale Gemelli Molise, Campobasso; IRCCS Neuromed, Pozzilli (IS), Italy.

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°Department of Medicine and Surgery, University of Insubria, Varese, Italy.
¹Mediterranea Cardiocentro, Napoli, Italy.

Moli-sani Study Past Investigators are available at https://www.moli-sani.org/?page_id=173

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