Association Between Pulsatile Components of Blood Pressure and Severe Tooth Loss in Rural Ecuador: The Three Villages Study

Oscar H. Del Brutto[1] ⓘD, Robertino M. Mera[2], Bettsy Y. Recalde[1],
Andrew P. Torpey[3], John P. Hill[3], Laura M. Generale[3],
Leslie D. Peralta[3], and Mark J. SedlerMPH[3]

Abstract

Background: Arterial hypertension has been associated with severe tooth loss, but differential associations with individual components of blood pressure (BP) have scarcely been investigated. We assessed the independent associations between pulsatile/steady components of BP and severe tooth loss in community-dwelling adults residing in 3 rural Ecuadorian villages. **Methods:** Individuals aged ≥40 years living in Atahualpa, El Tambo, and Prosperidad were identified during door-to-door surveys. Data collection focused on the number of remaining teeth and measurements of pulsatile/steady components of BP. Multivariate models were fitted to assess independent associations between pulsatile/steady BP components and severe tooth loss, after adjusting for relevant covariates. **Results:** A total of 1543 individuals were included. Oral exams identified 426 (28%) individuals with severe tooth loss. BP levels ≥140/90 mm Hg were determined in 481 (31%) individuals. The mean pulse pressure (PP) level was 55.3 ± 19 mm Hg. For systolic BP (SBP), the mean level was 133.1 ± 23.5 mm Hg, and for diastolic BP (DBP) it was 77.8 ± 11.5 mm Hg. Univariate models showed significant associations between severe tooth loss and SBP and PP, but not with DBP. However, the significance was taken away in fully adjusted generalized linear models. Age remained as an independent significant covariate in models using SBP and PP. Causal mediation analyses disclosed that percentages of the effect of severe tooth loss mediated by age were 99.5% for SBP and 98.9% for PP. **Conclusion:** This study shows that age captures most of the effect of the association between pulsatile components of BP and severe tooth loss.

Introduction

Nontraumatic severe tooth loss is a recognized biomarker of atherosclerosis.[1-4] It is plausible that arterial hypertension is in the path of the association between tooth loss and atherosclerosis, since several studies have found significant associations between severe tooth loss and high blood pressure (BP), a condition that predisposes to the development of atherosclerosis.[5-8] Some of these studies were confined to specific groups (eg, postmenopausal women) or limited to small sample sizes, and may not be representative of the general population. Moreover, few studies have taken into account the effect of confounders on this association or the independent association between severe tooth loss and the different components of BP, that is, pulsatile [systolic BP (SBP) and pulse pressure (PP)], and steady [diastolic BP (DBP)] components. Distinguishing the pulsatile and steady components is relevant since, theoretically, only an increase in pulsatile BP is related to stretched blood vessels and arterial stiffness, which can lead to atherosclerosis.[9,10]

[1]Universidad Espíritu Santo–Ecuador, Samborondón, Ecuador
[2]Gilead Sciences, Inc, Foster City, CA, USA
[3]Stony Brook University, New York, NY, USA

Corresponding Author:
Oscar H. Del Brutto, Air Center 3542, PO Box 522970, Miami, FL 33152-2970, USA.
Email: oscardelbrutto@hotmail.com

Recurrent nontraumatic tooth loss is a leading cause of chronic periodontitis worldwide.[11] Gram-negative anaerobic bacteria causing periodontitis may persist from 3 to 6 months after tooth extraction, and favor the release of pro-inflammatory cytokines that trigger arterial hypertension and atherosclerosis.[12,13] Atherosclerosis has long been considered an inflammatory disease.[14,15] Systolic hypertension is a biomarker for atherosclerosis,[10] and both conditions are closely linked to chronic inflammation. This supports the concept that severe tooth loss increases the risk of adverse vascular outcomes, as has been previously demonstrated by our group.[16] In this study, we aimed to assess independent associations between severe tooth loss and the different components of BP (pulsatile and steady) in community-dwelling adults enrolled in the Three Villages Study.[17]

Methods and Materials

Study Population

The study was conducted in 3 neighboring rural villages of Coastal Ecuador (Atahualpa, El Tambo, and Prosperidad). As detailed elsewhere, inhabitants of these villages share important demographic and epidemiological characteristics that include similar ethnicity (Amerindian ancestry), dietary habits, socioeconomic status, and an overall comparable cardiovascular health status.[17]

Study Design

Individuals aged ≥40 years residing in the 3 aforementioned villages were identified by means of door-to-door surveys, and those who signed a comprehensive informed consent were enrolled in the study. Baseline data were collected at the time of enrollment ensuring a complete database for all participants. Multivariate models were fitted to assess independent associations between severe tooth loss and pulsatile as well as steady components of BP. The protocol followed the standards for reporting of observational studies in epidemiology (STROBE) guidelines,[18] and was approved by the institutional review boards of Hospital-Clínica Kennedy, Guayaquil, Ecuador (FWA 00006867), and Stony Brook University, New York, NY, USA (ID: 740872_MODCR001).

Tooth Loss Assessment

A rural dentist performed an oral exam with emphasis on the number of remaining teeth. Participants were asked if they had lost teeth as the results of trauma or extraction by means of a professional, and traumatic tooth loss were not taken into account for this study. On the basis of previous studies from our group, having <10 remaining teeth is the best cutoff for identifying significant clinical correlates of severe tooth loss. Therefore, individuals were dichotomized according to whether they have <10 or ≥10 remaining teeth.[19,20]

Blood Pressure Determinations

Brachial BP was measured with a manual sphygmomanometer (Welch Allyn Tycos 7670-01), following a previously described protocol.[21] With the person in the sitting position and after resting for 10 minutes, the mean value of 3 readings taken at intervals of 2 minutes was used for analysis. Intake of caffeine, nicotine-containing products, and alcohol was not allowed in the hour before BP determinations. Also, individuals on antihypertensive medications were encouraged to stop their medications the night before BP determinations. The brachial PP was calculated by subtracting the mean DBP from the mean SBP obtained from the 3 readings. We did not use the mean arterial pressure (MAP) for analyses because, although considered a steady component of BP,[9] it includes the value of SBP in the numerator of its formula [(SBP + (DBP × 2)/3]. Therefore, increases in SBP automatically lead to increased MAP levels irrespective of DBP.

Clinical Covariates Investigated

Demographics and cardiovascular risk factors were selected as covariates, and assessed through interviews and procedures previously described in the Three Villages Study.[17] We used the American Heart Association (AHA) criteria to ascertain smoking status, physical activity, diet, the body mass index (BMI), fasting glucose, and total cholesterol blood levels.[22] BP—also included as a cardiovascular risk factor by the AHA—was not included as a covariate for collinearity, given that SBP and DBP were used together with PP determinations as dependent variables. A poor smoking status was designated if the subject was a current smoker, a poor diet if the individual had 0-1 component of the AHA healthy diet, a poor physical activity if there was no moderate/vigorous activity, a poor BMI if ≥30 kg/m^2, a poor fasting glucose if ≥126 mg/dL, and poor total cholesterol levels if ≥240 mg/dL.

Statistical Analyses

Data analyses are carried out by using STATA version 16. In univariate analyses, continuous variables were compared by linear models and categorical variables by chi-square or Fisher exact test as appropriate. Multivariate logistic regression models were fitted to evaluate whether severe tooth loss was independently associated with pulsatile and steady components of BP (as dependent variables), after adjusting for demographics and cardiovascular risk factors. In view of a presumed strong relationship between severe tooth

Table 1. Demographics and Cardiovascular Health Metrics of the Study Population Across Categories of Tooth Loss (Univariate Analyses).

Variable	Total series (n = 1543)	≥10 remaining teeth (n = 1117)	<10 remaining teeth (n = 426)	P
Age in years, mean ± SD	59.4 ± 13.1	55.6 ± 11.6	69.2 ± 11.5	<.001*
Female gender, n (%)	861 (56)	626 (56)	235 (55)	.756
Primary school education, n (%)	953 (62)	599 (54)	354 (83)	<.001*
Current smoker, n (%)	74 (5)	56 (5)	18 (4)	.517
Poor physical activity, n (%)	150 (10)	77 (7)	73 (17)	<.001*
Poor diet, n (%)	165 (11)	114 (10)	51 (12)	.316
Body mass index ≥30 kg/m^2, n (%)	453 (29)	345 (31)	108 (25)	.033*
Fasting glucose ≥126 mg/dL, n (%)	378 (24)	248 (22)	130 (31)	<.001*
Total cholesterol ≥240 mg/dL, n (%)	162 (10)	117 (10)	45 (11)	.959
Blood pressure ≥140/90 mm Hg, n (%)	481 (31)	298 (27)	183 (43)	<.001*
Systolic blood pressure, mm Hg, mean ± SD	133.1 ± 23.5	130.4 ± 21.7	140.3 ± 26.2	<.001*
Diastolic pressure, mm Hg, mean ± SD	77.8 ± 11.5	78.1 ± 11.4	77.1 ± 11.9	.128
Pulse pressure, mm Hg, mean ± SD	55.3 ± 19	52.3 ± 17	63.2 ± 21.6	<.001*

*Statistically significant result.

loss, BP and increasing age, potential interactions between severe tooth loss and age on the different investigated components of BP were explored by fitting interaction models with SBP, DBP, and PP as the dependent variables. Coefficients of association (causal mediation analysis),[23] were calculated to determine the effect of severe tooth loss on the pulsatile components of BP, which completely depend on age. Contour plots with Shepard interpolation were constructed to gain more insights on the effect of age in the association between severe tooth loss and the different components of BP.

Results

The study population consisted of 1543 community-dwelling individuals aged ≥40 years. The cohort had a mean age of 59.4 ± 13.1 years (median age: 58 years), 861 (56%) were women, and 953 (62%) had primary school education only. Seventy-four individuals (5%) were current smokers; 453 (29%) had a BMI ≥30 kg/m^2; 150 (10%) had poor physical activity; 165 (11%) had a poor diet; 378 (24%) had fasting glucose ≥126 mg/dL; and 162 (10%) had total cholesterol blood levels ≥240 mg/dL. A total of 426 (28%) individuals had severe tooth loss.

BP levels ≥140/90 mm Hg were determined in 481 (31%) individuals. The mean PP level was 55.3 ± 19 mm Hg (median: 51 mm Hg, range: 20-149 mm Hg), the mean SBP level was 133.1 ± 23.5 mm Hg (median: 129 mm Hg, range: 87-240 mm Hg), and the mean DBP level was 77.8 ± 11.5 mm Hg (median: 77 mm Hg, range: 34-123 mm Hg). Of the entire cohort, 214 (14%) were taking antihypertensive medication, many of them with current BP levels <140/90 mm Hg. Actually, several individuals with BP

≥140/90 mm Hg were unaware of their hypertensive status. Commonly used drugs were enalapril and candesartan. However, interviews revealed that these drugs were often taken irregularly and at suboptimal doses.

Characteristics of subjects across categories of tooth loss are summarized in Table 1. In univariate analyses, individuals with <10 remaining teeth were older, less educated, had worse physical activity, and fasting glucose levels ≥126 mg/dL more often than those with ≥10 remaining teeth. Obesity (BMI ≥30 kg/m^2) was significantly less common among edentulous individuals. The proportion of individuals with BP ≥140/90 mm Hg was higher among those with severe tooth loss (43% vs 27%, $P < .001$); mean (±SD) levels of SBP ($P < .001$), and PP ($P < .001$) were also higher among those with severe tooth loss. In contrast, there were no differences in the mean (±SD) levels of DBP across individuals with and without severe tooth loss ($P = .128$). When individuals were dichotomized according to the median age of the study population (58 years), the associations between severe tooth loss and SBP and PP disappeared in younger individuals, but persisted in older ones ($P = .030$ for the association with SBP, and $P = .003$ for the association with PP). Severe tooth loss was not associated with DBP in either younger or older individuals.

Results of a fully adjusted generalized linear model are shown in Table 2. The association between severe tooth loss and the pulsatile components of BP became nonsignificant due to the effect of covariates. Of interest, age remained as an independently significant covariate for the association between severe tooth loss and pulsatile but not steady components of BP. A poor BMI remained as an independently significant covariate for the association between severe

Table 2. Fully Adjusted Generalized Linear Models Showing Lack of Association Between Severe Edentulism and Different Components of Blood Pressure.[a]

	Systolic pressure	Diastolic pressure	Pulse pressure
Severe edentulism	β: −0.43 95% CI: −3.12 to 2.26 P = .755	β: −0.31 95% CI: −1.70 to 1.08 P = .661	β: −0.12 95% CI: −2.11 to 1.88 P = .909
Age (years)	β: 0.72 95% CI: 0.62 to 0.82 P < .001*	β: −0.04 95% CI: −0.09 to 0.01 P = .144	β: 0.76 95% CI: 0.68 to 0.83 P < .001*
Female gender	β: −4.53 95% CI: −6.75 to −2.32 P < .001*	β: −6.07 95% CI: −7.21 to −4.93 P < .001*	β: 1.53 95% CI: −0.10 to 3.17 P = .066
Primary school education	β: 1.35 95% CI: −1.09 to 3.79 P = .279	β: 0.67 95% CI: −0.59 to 1.93 P = .299	β: 0.68 95% CI: −1.13 to 2.49 P = .461
Current smoker	β: 2.25 95% CI: −2.90 to 7.40 P = .392	β: 1.40 95% CI: −1.26 to 4.07 P = .303	β: 0.85 95% C.I.: -2.97 to 4.67 P = .663
Poor physical activity	β: 2.69 95% CI: −0.99 to 6.38 P = .151	β: −1.37 95% CI: −3.28 to 3.25 P = .158	β: 4.07 95% CI: 1.34 to 6.79 P = .004*
Poor diet	β: 2.83 95% CI: −0.77 to 6.44 P = .124	β: 2.31 95% CI: 0.44 to 4.17 P = .015*	β: 0.52 95% CI: −2.15 to 3.19 P = .701
Body mass index ≥30 kg/m^2	β: 4.73 95% CI: 2.38 to 7.09 P < .001*	β: 2.03 95% CI: 0.81 to 3.25 P = .001*	β: 2.71 95% CI: 0.96 to 4.46 P = .002*
Fasting glucose ≥126 mg/dL	β: 1.49 95% CI: −1.01 to 3.99 P = .242	β: 1.01 95% CI: −0.29 to 2.30 P = .127	β: 0.49 95% CI: −1.37 to 2.34 P = .606
Total cholesterol ≥240 mg/dL	β: 3.21 95% CI: −0.27 to 6.69 P = .070	β: 2.58 95% CI: 0.78 to 4.38 P = .005*	β: 0.64 95% CI: −1.94 to 3.21 P = .629

[a]Age remained as an independently significant covariate for the association between severe tooth loss and pulsatile (systolic and pulse pressure), but not steady (diastolic pressure) components of blood pressure.
*Statistically significant result.

tooth loss and all components of BP (inverse association). This inverse association could be related to the "obesity paradox" mechanism already described in subjects with atherosclerosis.[24]

Interaction models, with age partitioned by the median, showed no interaction of age on the associations between severe tooth loss and the different components of BP. β coefficients for interaction terms were: 4.15 (95% CI: −1.89 to 10.19; P = .178) for SBP; 0.21 (95% CI: −2.96 to 3.37; P = .898) for DBP; and 3.94 (95% CI: −0.69 to 8.59; P = .096) for PP. In contrast, causal mediation analyses disclosed that almost all the effects of the associations between severe tooth loss and pulsatile components of BP were mediated by age [99.5% (95% CI: 79.6% to 100%) for SBP, and 98.9% (95% CI: 83.5% to 100%) for PP] (Table 3).

Contours plots with Shepard interpolation showed the effect of age in the association between severe tooth loss and the different components of blood pressure. Plots for SBP and PP were similar and showed large clusters

of individuals with severe tooth loss among older adults irrespective of pressure levels. A cluster of individuals with severe tooth loss was noted among younger participants at higher levels of SBP and PP. In contrast, the DBP plot showed clusters of individuals with severe tooth loss at different levels of DBP and age, suggesting an unpredictable effect of age on this association (Figure 1).

Discussion

This population-based study shows that age captures most of the effect of the association between pulsatile components of BP and severe tooth loss. However, univariate analyses reveal a differential association between severe tooth loss and some individual components of BP. Severe tooth loss is significantly associated with SBP and PP levels, but not with DBP. These associations are significant only in individuals above the median age of the study population. Indeed, the association vanished in multivariate models due

Table 3. Causal Mediation Analyses Showing That Almost All the Effects of the Associations Between Severe Tooth Loss and Pulsatile Components of Blood Pressure Are Mediated by Age.[a]

Effect	Mean	95% confidence interval
Systolic blood pressure		
ACME (coefficient of association)	9.91	8.39 to 11.62
Direct effect	0.04	−2.43 to 2.63
Total effect	9.95	7.59 to 12.44
Percentage of total effect mediated by age	99.5%	79.6% to 100%
Pulse pressure		
ACME (coefficient of association)	10.79	9.49 to 12.33
Direct effect	0.11	−1.73 to 2.04
Total effect	10.91	8.95 to 12.93
Percentage of total effect mediated by age	98.9%	83.5% to 100%

Abbreviation: ACME, average causal mediation effect.
[a]Steady component of blood pressure was not considered for this analysis because of lack of association in univariate models.

to the effect of confounders (mostly age), and causal mediation analysis confirms that age captures almost all the effect of the association between severe tooth loss and pulsatile components of BP. This is related to the fact that both conditions (severe tooth loss and pulsatile components of BP) increase with advancing age.

As previously mentioned, atherosclerosis is an inflammatory disease. However, there are other hypotheses besides chronic inflammation that seek to explain the association between severe tooth loss and arterial hypertension. One is the apparent worse nutritional status of edentulous when compared with non-edentulous individuals.[25,26] However, this is less likely to account for the findings of this study, since the percentage of individuals with poor dietary habits was similar across groups. In these villages, vitamin B–enriched white rice is an important component of the diet and almost all individuals eat—irrespective of the number of remaining teeth–1 or 2 servings of white rice per day. In addition, the major source of proteins from the diet is oily fish, which is easier to chew than other meat varieties by edentulous individuals.[27] Another theory suggest the effect of smoking habits. However, smoking is not applicable to the current study population, since only a few participants are current or past smokers, and the prevalence of smoking does not differ across edentulous and non-edentulous individuals.

Other studies have shown a differential association of gender in the relationship between severe tooth loss and arterial hypertension. A German series found this association to be significant only in males.[28] The same investigators also argued that higher degrees of osteoporosis in women may lead to early tooth extraction, thus reducing the risk of long-lasting periodontitis.[29] Yet, other studies (including only women) have found an association between severe tooth loss and arterial hypertension.[6,7,30] Therefore, the literature to date does not support a clear conclusion about gender-related differences in the association between severe tooth loss and arterial hypertension.

There are very few studies evaluating differential associations between severe tooth loss and arterial hypertension across pulsatile and steady components of BP. Our results support a previous study showing a direct association between severe tooth loss (and periodontitis) and pulsatile components of BP; in that study, the authors used the same cutoff for defining severe tooth loss as did the present study, and they found that having <10 remaining teeth was associated with increased SBP.[5] Other studies have shown a direct association between missing teeth and high DBP. One of these is a small case-control study limited to post-menopausal women, where mean (±SD) levels of DBP were 78.9 ± 1.5 mm Hg in 67 individuals with a mean of 22 remaining teeth *versus* 73.1 ± 1.7 mm Hg in 31 with a mean of 28 remaining teeth (*P* = .021).[6] Besides the small sample size and the restricted demographics of the study population, none of the 2 groups represented true cases of severe tooth loss; therefore, the results should be interpreted with caution. In another, much larger, study that used <20 remaining teeth as the cutoff for defining severe tooth loss, the relationship between severe tooth loss and DBP followed a nonlinear pattern that increased in individuals with 20 to 27 teeth and decreased in those with <19 teeth.[8] Possible mechanisms responsible for the apparent lack of association between severe tooth and DBP are still unclear. However, it has been suggested that lower levels of inflammation are found in individuals with isolated diastolic hypertension when compared to those with systolic/diastolic or isolated systolic hypertension.[31]

The present study has limitations, including the cross-sectional design. However, biological plausibility suggests that the relationship goes from severe tooth loss to arterial hypertension, since reverse causation in unlikely, although it has been suggested that arterial hypertension might facilitate tooth loss.[6] The study population is limited to individuals of Amerindian ancestry, and our findings might not be extrapolated to other races/ethnic groups. It is also possible
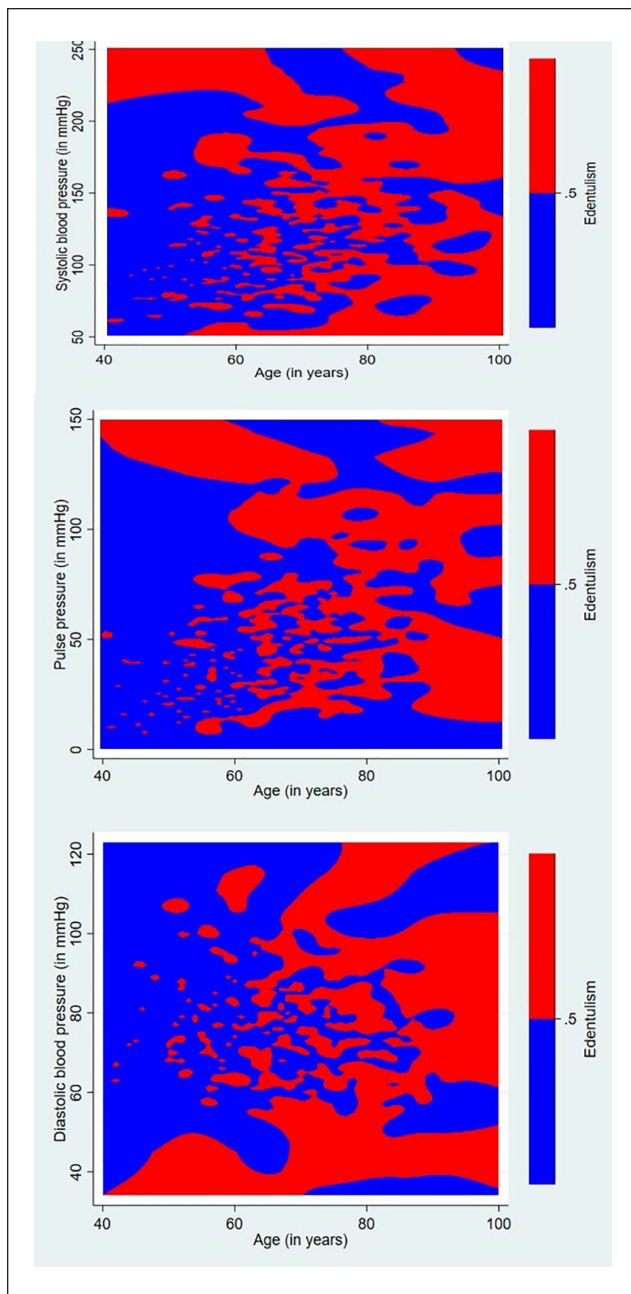
Figure 1. Contours plots with Shepard interpolation showing the effect of age in the association between severe tooth loss and the different components of blood pressure. Upper panel corresponds to systolic blood pressure (SBP), central panel to pulse pressure (PP) and lower panel to diastolic blood pressure (DBP). Upper and central panel plots show large clusters of individuals with severe tooth loss (in red) among older adults irrespective of SBP and PP levels. In addition, a cluster of individuals with severe tooth loss is noted among younger adults at higher levels of SBP and PP. In contrast, the lower panel suggests an unpredictable effect of age in the association between severe tooth loss and DBP by showing clusters of individuals with severe tooth loss at different levels of DBP and age.

that some unmeasured biomarkers (particularly inflammatory cytokines) were in the path of the association between severe tooth loss and pulsatile components of BP. In addition, we cannot rule out the possibility that some of our subjects with severe tooth loss who currently do not have increased SBP or PP, may develop them in the future. On the other hand, the population-based design with unbiased recruitment of study participants, together with statistical models used for the assessment of the effect modification of age in the association between severe tooth loss and pulsatile components of BP, represent major strengths of this study. Another advantage is the paucity of current or past smokers in the study population, which reduces the confounding effects of smoking in the association between severe tooth loss and arterial hypertension.[32]

Conclusion

This population-based study suggests that severe tooth loss is linked to pulsatile—but not steady—components of BP, and that this association is strongly mediated by age. Further longitudinal studies, which should also include the assessment of atherosclerosis biomarkers, are needed to confirm these findings.

Author Contributions

OHD: Study design, manuscript drafting; RMM: Statistical analyses; BYR, APT, JPH, LMG, LDP: Data collection and analysis; MJS: Significant intellectual contribution to manuscript content.

Declaration of Conflicting Interests

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ORCID iD

Oscar H. Del Brutto ![iD] https://orcid.org/0000-0003-1917-8805

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