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Prevalence of metal hypersensitivity in patients with shoulder pathologies

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Background: To date, medical history and dedicated questionnaires are the fastest and easiest way to assess risks of joint metal hypersensitivity. No published studies determined the overall prevalence of hypersensitivity to metals in patients with shoulder pathologies. The purpose of this study was therefore to estimate the prevalence of metal hypersensitivity reported by patients with shoulder pathologies, and to identify patients at risk of joint metal hypersensitivity based on a dedicated questionnaire.

Methods: The authors prospectively asked all adult patients consulting for shoulder pathologies between September 2018 and February 2019 at 10 centers to fill in a form. The main outcome was ''reported hypersensitivity to metals,'' comprising belt buckles, coins, earrings, fancy jewelry, keys, leather, metallic buttons, piercings, spectacles, watch bracelets, or zips.

Results: A total of 3217 patients agreed to fill in the survey, aged 55 ± 16 (range, 18-101) with equal proportions of men (51%) and women (49%), and a majority of patients consulting for cuff pathology (55%). A total of 891 (28%) patients had professions considered at risk for metal hypersensitivity. The most frequently reported metal hypersensitivities were fancy jewelry (15%), earrings (13%), and watch bracelets (9%). A total of 629 (20%) patients, of which the vast majority were women, reported hypersensitivity to 1 or more metals.

Conclusions: This survey of 3217 patients identified 20% who reported metal hypersensitivities, though only 2.2% had done patch tests. Matching profiles of those with positive patch tests to those with no patch tests revealed that 9.4% of the total cohort had similar sex and self-reported metal hypersensitivities. Factors associated with a positive patch test were female sex, self-reported cutaneous allergy, and self-reported metal hypersensitivity. The clinical applicability of these estimates remains uncertain as there is insufficient evidence that allergy to metal implants can be predicted by questionnaires or patch tests.

Level of Evidence: Level III; Cross-Sectional Design; Epidemiology Study

Keywords: Metal hypersensitivity; allergy; shoulder pathology; metal implant; cutaneous patch test; total shoulder arthroplasty; reverse shoulder arthroplasty; hemi-shoulder arthroplasty

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Implants for anatomic and reverse shoulder arthroplasty are largely successful, yet a small number of patients experience unexplained pain or instability, sometimes requiring revision. Some of these complications might be due to metal hypersensitivity, defined as an immunologic response to the intra-articular release of metal ions.[6,16] To date, the mechanism underlying metal sensitization is debated. It could be a reaction to implant failure, triggering substantial particulate wear, or to normal wear, triggering subsequent aseptic loosening.[12,15,19] Cutaneous hypersensitivity to metal affects 10%-20% of the population, most often to nickel (17% in women and 3% in men).[8,22,23] Patients with a medical history of metal hypersensitivity were shown to be 4 times more likely to experience implant failure after total knee arthroplasty.[7] It is therefore essential to diagnose metal hypersensitivity preoperatively to warn patients and consider the use of hypoallergenic implants.[16]

There is no standard method to diagnose joint metal hypersensitivity.[1] In their guidelines, the American Contact Dermatitis Society recommends that patients with a history of metal hypersensitivity be evaluated by cutaneous patch testing before implant surgery.[20] Cutaneous patch testing, which is most often used, is performed by exposing the skin to metal ions for 2-4 days, and thereafter grading skin reactions from ''no response'' to ''severe rash.'' Alternatively, hypersensitivity can be tested using blood samples with the memory lymphocyte immunostimulation assay, which is costly and only available in specialized laboratories.[9,13] Controversies exist about the validity of cutaneous patch testing to determine joint hypersensitivity, whereas the applicability of blood testing remains to be proven.[5] To date, medical history and dedicated questionnaires are the fastest and easiest way to assess risks of joint metal hypersensitivity. Two overlapping questionnaires, respectively designed by the French Hip and Knee Society (SFHG) and Study Group for Bone Surgery (GECO), are available for practitioners, although none have been validated for shoulder arthroplasty patients.

To the authors' knowledge, no published studies determined the overall prevalence of hypersensitivity to metals in patients with shoulder pathologies. The purpose of this study was therefore to estimate the prevalence of metal hypersensitivity reported by patients with shoulder pathologies, and to identify patients at risk of joint metal hypersensitivity based on a dedicated questionnaire. This information would be useful in addressing patient expectations and preventing risks by offering adapted hypoallergenic implants.

Material and methods

The authors prospectively enrolled all adult patients consulting for shoulder pathologies between September 2018 and February 2019 at 10 centers. While waiting for their appointment, patients who consented to participate in the survey filled in a form.

The form compiled questions from 2 forms designed by French orthopedic scientific societies. The SFHG form was designed to detect and evaluate the risk of metal hypersensitivity prior to hip or knee arthroplasty. Similarly, the GECO form was designed to evaluate the risk of allergic reaction to metal implants. Our form comprised 52 questions under 6 themes: demographics (age, sex, body mass index), profession, family and personal medical history, cutaneous allergies, cutaneous tests, and surgical history (Supplementary Appendix S1).

The main outcome was ''reported hypersensitivity to metals,'' comprising belt buckles, coins, earrings, fancy jewelry, keys, leather, metallic buttons, piercings, spectacles, watch bracelets, or zips.

Statistical analysis

Descriptive statistics were used to summarize the data. Shapiro-Wilk tests were used to assess the normality of distributions. For quantitative data, differences between groups were evaluated using Wilcoxon rank-sum tests (Mann-Whitney U test). For categorical data, differences between groups were evaluated using Fisher exact tests. Based on existing studies reporting a 10%-20% prevalence of cutaneous hypersensitivity to metal,[4,8,22,23] a sample size calculation indicated that a minimum 186 patients are needed to observe a 15% prevalence of cutaneous metal hypersensitivity, with an accuracy of 5%, and that a minimum of 1157 patients are needed to observe a 15% prevalence of cutaneous metal hypersensitivity, with an accuracy of 2%. Univariable logistic regression analysis was performed to determine the likelihood of reporting metal hypersensitivity, expressed as odds ratios (ORs), in relation to the following factors: patient age, body mass index, sex, smoking, tattoo, piercing, allergies, and hypersensitivity to metals. Each patient who had a positive patch test was matched with up to 10 patients who had not done patch tests, based on patient sex and self-reported metal hypersensitivity, using propensity scores and nearest neighbor–matching algorithm without replacement (caliper width equal to 0.2 of the standard deviation of the logit score). Standardized differences were estimated for all the baseline covariates to assess imbalance before matching and balance after matching. A standardized difference of less than 10% indicates appropriate balance.[2] P values $<.05$ were considered statistically significant. Statistical analyses were performed using R, version 3.3.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

A total of 3217 patients agreed to fill in the survey, aged 55 ± 16 years (range, 18-101 years) with equal proportions of men (51%) and women (49%), and a majority of patients were consulting for cuff pathology (55%) (Table I). A total of 891 (28%) patients had professions considered at risk for metal hypersensitivity. The most prevalent risk factors were dental implants in 754 patients (23%), smoking in 602 (19%), and tattoos in 516 (16%). The most prevalent allergies were respiratory in 915 patients (28%), cutaneous in

Table I Demographics and allergy profile of the population

	All patients (N = 3217)	No patch tests (n = 3147)	Positive patch tests (n = 51)	Negative patch tests (n = 19)
Age, mean ± SD	55.5 ± 15.9	55.5 ± 16.0	53.6 ± 17.6	55.9 ± 11.6
BMI, mean ± SD	26.1 ± 4.6	26.1 ± 4.5	27.3 ± 6.3	25.7 ± 5.1
Women	1580 (49)	1526 (48)	45 (88)	9 (47)
Men	1617 (52)	1601 (51)	6 (12)	10 (53)
High-risk professions	891 (28)	874 (28)	11 (22)	6 (32)
Farmer	225 (7)	219 (7)	4 (8)	2 (11)
Builder	438 (14)	430 (14)	5 (10)	3 (16)
Hairdresser	40 (1)	37 (1)	3 (6)	0 (0)
Jewelry	13 (0)	13 (0)	0 (0)	0 (0)
Metallurgy	265 (8)	260 (8)	3 (6)	2 (11)
Polishing	34 (1)	33 (1)	1 (2)	0 (0)
Painter	124 (4)	122 (4)	2 (4)	0 (0)
Tanner	11 (0)	11 (0)	0 (0)	0 (0)
Indications				
Cuff pathology	1767 (55)	1721 (55)	34 (67)	12 (63)
Instability	310 (10)	305 (10)	2 (4)	3 (16)
Arthropathy	181 (6)	177 (6)	2 (4)	2 (11)
Capsulitis	127 (4)	122 (4)	4 (8)	1 (5)
Omarthrosis	371 (12)	364 (12)	6 (12)	1 (5)
Biceps pathology	84 (3)	80 (3)	3 (6)	1 (5)
Fracture/trauma	190 (6)	189 (6)	1 (2)	0 (0)
Prosthesis	412 (13)	401 (13)	7 (14)	4 (21)
1 or more reactions	52 (2)	48 (2)	2 (4)	2 (11)
2 or more reactions	41 (1)	37 (1)	2 (4)	2 (11)
Osteosynthesis	382 (12)	373 (12)	6 (12)	3 (16)
1 or more reactions	202 (6)	198 (6)	3 (6)	1 (5)
2 or more reactions	87 (3)	86 (3)	1 (2)	0 (0)
Risk factors				
Allergic parents	328 (10)	306 (10)	16 (31)	6 (32)
Dental implant	754 (23)	736 (23)	10 (20)	8 (42)
Piercing	217 (7)	210 (7)	6 (12)	1 (5)
Smoking	602 (19)	590 (19)	11 (22)	1 (5)
Tattoos	516 (16)	498 (16)	15 (29)	3 (16)
Vascular implant	115 (4)	114 (4)	0 (0)	1 (5)
Allergies				
Cosmetics	111 (3)	95 (3)	15 (29)	1 (5)
Cutaneous	751 (23)	701 (22)	41 (80)	9 (47)
Food	264 (8)	247 (8)	15 (29)	2 (11)
Insect bites	542 (17)	529 (17)	10 (20)	3 (16)
Medication	696 (22)	668 (21)	23 (45)	5 (26)
Mites	554 (17)	519 (16)	25 (49)	10 (53)
Respiratory	915 (28)	877 (28)	28 (55)	10 (53)
Metal hypersensitivity				
Belt buckles	169 (5)	136 (4)	31 (61)	2 (11)
Coins	26 (1)	18 (1)	8 (16)	0 (0)
Earrings	407 (13)	368 (12)	36 (71)	3 (16)
Fancy jewelry	479 (15)	435 (14)	41 (80)	3 (16)
Keys	18 (1)	12 (0)	6 (12)	0 (0)
Leather	22 (1)	18 (1)	0 (0)	4 (21)
Metallic buttons	122 (4)	90 (3)	28 (55)	4 (21)
Piercings	24 (1)	20 (1)	3 (6)	1 (5)
Spectacles	45 (1)	33 (1)	12 (24)	0 (0)
Watch bracelets	300 (9)	265 (8)	32 (63)	3 (16)
Zips	70 (2)	46 (1)	23 (45)	1 (5)

SD, standard deviation; *BMI*, body mass index.

Table II Reported metal hypersensitivity in patients with no patch tests or positive patch tests

	No patch tests (n = 3147)	Positive patch tests (n = 51)	*P* value
Reported hypersensitivity ≥1 metal	629 (20)	47 (92)	<.001
Women	537 (17)	43 (84)	
Men	92 (3)	4 (8)	
Reported hypersensitivity to ≥2 metals	363 (12)	42 (82)	<.001
Women	340 (11)	40 (78)	
Men	23 (1)	2 (4)	
Reported hypersensitivity to ≥3 metals	199 (6)	35 (69)	<.001
Women	187 (6)	34 (67)	
Men	12 (0)	1 (2)	

751 (23%), and to medication in 696 (22%). The most frequently reported metal hypersensitivities were fancy jewelry (15%), earrings (13%), and watch bracelets (9%).

A total of 629 (20%) reported hypersensitivity to 1 or more metals, 363 (11%) reported hypersensitivity to 2 or more metals, and 199 (6%) reported hypersensitivity to 3 or more metals. The vast majority of patients who reported hypersensitivity to 1 or more metals were women (Table II).

Only 70 (2.2%) had done cutaneous patch tests, of which 51 (1.6%) tested positive to at least 1 metal (Figure 1). Compared with patients who tested negative, patients who tested positive comprised a greater proportion of women (84% vs. 42%; $P = .001$) but did not differ significantly in terms of age (55 ± 12 vs. 53 ± 18; $P = .937$), body mass index (26 ± 5 vs. 27 ± 6; $P = .387$), allergies to medication (45% vs. 26%; $P = .180$), or respiratory allergies (55% vs. 53%; $P > .99$) (Table III). Furthermore, patients who tested positive had a greater prevalence of cutaneous allergies (80% vs. 47%; $P = .015$), and reported more frequently hypersensitivity to belt buckles (61% vs. 11%; $P < .001$), earrings (71% vs. 16%; $P < .001$), fancy jewelry (80% vs. 16%; $P < .001$), metallic buttons (55% vs. 21%; $P = .015$), spectacles (24% vs. 0%; $P = .028$), watch bracelets (67% vs. 16%; $P = .001$), and zips (80% vs. 16%; $P = .002$).

Univariable analysis of patients who had done patch tests confirmed association of positive patch tests with cutaneous allergies (OR, 4.56; $P = .009$) and with hypersensitivity to belt buckles (OR, 13.18; $P = .001$), earrings (OR, 12.80; $P < .001$), fancy jewelry (OR, 21.87; $P < .001$), metallic buttons (OR, 4.57; $P < .001$), watch bracelets (OR, 8.98; $P = .002$), and zips (OR, 14.79; $P = .011$) (Table IV). Matching the 51 patients who had a positive patch test to the 3147 patients who had not done patch tests yielded 297 patients (9.4%) with similar profiles in terms of sex and self-reported metal hypersensitivity.

Discussion

The present survey of 3217 patients consulting for shoulder pathologies identified 20% who reported hypersensitivity to 1 or more metals (subjective), the majority of whom were women (Table II), though only 2.2% had done cutaneous patch tests (objective) that could affirm their beliefs. Matching the profiles of patients who had positive patch tests to those who had not done patch tests revealed that 9.4% of the total cohort had similar characteristics in terms of sex and self-reported metal hypersensitivities, and could therefore be considered at risk of allergic reaction to metal implants. The clinical applicability of these estimates remains to be confirmed, however, as there is insufficient evidence that allergy to metal implants can be predicted with any certainty, by either the questionnaires used or the cutaneous patch tests.

With the increasing number of shoulder replacements, metal hypersensitivity is progressively being recognized as

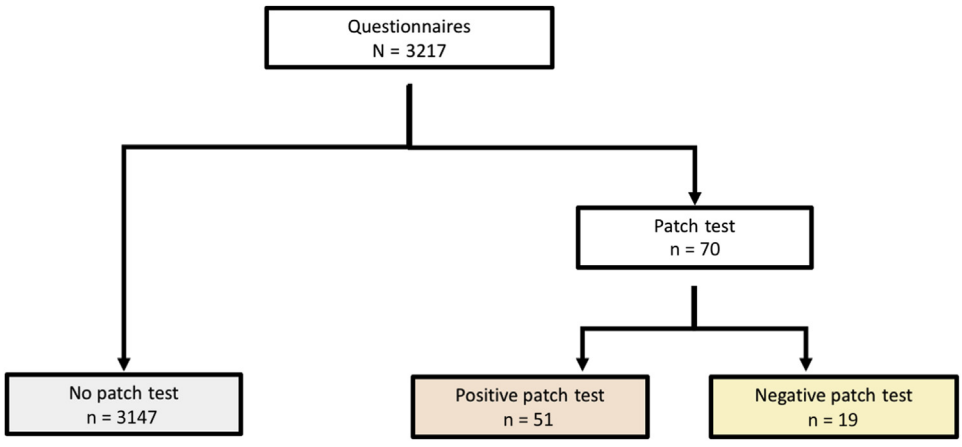

Figure 1 Flowchart of the study.

Table III Comparison of patients with positive patch tests and negative patch tests

	Positive patch tests (n = 51)	Negative patch tests (n = 19)	*P* value
Age, mean ± SD	55.6 ± 11.6	53.4 ± 17.6	.937
BMI, mean ± SD	25.7 ± 5.1	27.3 ± 6.3	.387
Women	45 (88)	9 (47)	.001
Jobs at risk			
Agriculture	4 (8)	2 (11)	.660
Builder	3 (6)	5 (26)	**.030**
Hairdresser	3 (6)	0 (0)	.557
Jewelry	0 (0)	0 (0)	NA
Metallurgy	3 (6)	2 (11)	.608
Painting	2 (4)	0 (0)	>.99
Polishing	1 (2)	0 (0)	NA
Tannery	0 (0)	0 (0)	NA
Risk factors			
Allergic parents	16 (31)	6 (32)	>.99
Dental implant	10 (20)	8 (42)	.070
Piercing	6 (12)	1 (5)	.665
Smoker	11 (22)	1 (5)	.159
Tattoo	15 (29)	3 (16)	.360
Vascular implant	0 (0)	1 (5)	.271
Allergies			
Cosmetics	15 (29)	1 (5)	.052
Cutaneous	41 (80)	9 (47)	**.015**
Food	15 (29)	2 (11)	.127
Insect bites	10 (20)	3 (16)	>.99
Medication	23 (45)	5 (26)	.180
Mites	25 (49)	10 (53)	>.99
Respiratory	28 (55)	10 (53)	>.99
Reported metal hypersensitivity			
Belt buckles	31 (61)	2 (11)	**<.001**
Coins	8 (16)	0 (0)	.097
Earrings	36 (71)	3 (16)	**<.001**
Fancy jewelry	41 (80)	3 (16)	**<.001**
Keys	6 (12)	0 (0)	.180
Leather	4 (8)	0 (0)	.568
Metallic buttons	28 (55)	4 (21)	**.015**
Spectacles	12 (24)	0 (0)	**.028**
Piercings	3 (6)	1 (5)	>.99
Watch bracelets	32 (63)	3 (16)	**.001**
Zips	23 (45)	1 (5)	**.002**

SD, standard deviation; *BMI*, body mass index; *NA*, not available.
Bold values indicate statistically significant differences.

a factor that could contribute to implant failure, although its clinical significance is still controversial.[6] Positive patch tests are estimated at 25% after lower limb arthroplasty and at 60% in patients with implant failure, whereas actual complications due to metal hypersensitivity are estimated to range between 0.1% and 5%.[8,10,14,18] It is worth noting that most of the published evidence is relevant to hip or knee arthroplasty, which involves different etiologies and wear patterns to shoulder arthroplasty, because of the weight-bearing function of the implants.

Complications due to metal allergies are, however, likely underdiagnosed and miscategorized as implant loosening. In the general population, the incidence of metal allergy, defined by positive patch tests, is approximately 10%-20%, with nickel, cobalt, and chromium hypersensitivities most frequently detected.[8,22,23] In this series, 9% of patients who did not have patch tests before filling in the survey could be matched with patients who had positive patch tests based on sex and reported hypersensitivity to metals, whereas 20% of patients reported hypersensitivity to 1 or more metals, thus confirming the estimate of 10%-20% at risk of metal allergy.

The environmental, genetic, and behavioral factors that contribute to risks of postoperative complications due to metal hypersensitivity following joint arthroplasty are still unknown.[4] Consequently, no reliable methods exist to identify patients at risk of metal hypersensitization, which can be investigated using cutaneous and/or in vitro testing methods.[8,14,18] Despite concerns with subjective grading, risks of sensitization to metals,[25,27,28] and lack of evidence that cutaneous hypersensitivity reflects periprosthetic hypersensitivity, its low costs and availability make cutaneous patch testing the method most frequently used by orthopedists to identify patients at risk.[18,27,28] In this series, 2% of patients had cutaneous patch tests previous to filling in the survey, of whom 73% tested positive to at least 1 metal. Lymphocyte transformation testing (LTT) and the memory lymphocyte immunostimulation assays (a specific type of LTT, 8–11) are in vitro tests used to investigate metal sensitivity to evaluate the proliferative response exhibited by lymphocytes after activation.[8] Today, besides clinical inaccessibility, high costs, and rapid decay of T cells, concerns about the diagnostic accuracy, clinical validity, and significance of the results restrain the use of LTT.[7,11,21,26]

Until validated screening tests are developed to identify patients at risk of symptomatic metal allergy after arthroplasty, the use of questionnaires to identify patients with a history of metal hypersensitivity is the easiest and most cost-effective strategy to detect patients at risk. Although discrepancies exist between history taking, cutaneous patch testing, and LTT,[5] patient-reported metal hypersensitivity was shown to be associated with decreased functional outcomes and mental health scores after joint arthroplasty.[17] Among hip and knee surgeons, the scientific community demonstrates increased awareness of risks for patients presenting hypersensitivity to metals. Still, most surgeons overlook the issue and use standard implants that contain cobalt, chromium, or nickel in all patients, although hypoallergenic implants could be used to prevent poorer outcomes and/or complications in patients identified to be at risk of metal hypersensitivity.[3,15,24]

Two dedicated questionnaires designed by the SFHG and GECO have been made available to surgeons, although they are yet to be scientifically validated. This study constitutes a first step toward designing and

Table IV Univariable analysis for positive patch tests

Variable	Patch test (n = 70)		
	Odds ratio	95% CI	*P* value
Continuous			
Age	1.01	0.97, 1.05	.531
BMI	0.95	0.86, 1.05	.282
Categoric			
Women	5.38	0.58, 50.57	.117
Smoker	4.95	0.86, 93.92	.140
Tattoo	2.22	0.62, 10.55	.254
Piercing	2.40	0.37, 47.02	.433
Allergies			
Cosmetics	7.50	1.35, 140.92	.060
Cutaneous	4.56	1.48, 14.64	**.009**
Food	3.54	0.87, 24.10	.118
Insect bites	1.30	0.34, 6.35	.715
Medication	2.30	0.75, 7.99	.160
Mites	0.87	0.30, 2.50	.788
Respiratory	1.10	0.38, 3.17	.865
Hypersensitivity to metals*			
Belt buckles	13.18	3.31, 88.94	**.001**
Fancy jewelry	21.87	5.96, 108.31	**<.001**
Metallic buttons	4.57	1.43, 17.76	**.016**
Piercings	1.13	0.13, 23.55	.921
Watch bracelets	8.98	2.59, 42.36	**.002**
Zips	14.79	2.73, 276.00	**.011**

* None of the patients with a negative patch test reported hypersensitivity to coins, keys, spectacles, or leather.
Bold values indicate statistically significant differences.

validating a short questionnaire adapted to identify patients at risk of intra-articular metal allergy among shoulder arthroplasty patients. In our series, the comparison of patients with cutaneous patch tests and patients with negative patch tests suggests that sex, reported cutaneous allergy, and hypersensitivity to metals are the 3 most important factors to consider when analyzing patient history. We suggest that patients with cutaneous allergy or reported hypersensitivity to 1 or more metals be referred to an allergist and/or offered a hypoallergenic implant.

More than 85% of patients reporting hypersensitivity to 1 or more metals were female, corroborating the higher prevalence of women among allergic patients reported in other studies.[4,7] As most shoulder hypoallergenic implants are available in limited sizes, manufacturers should consider extending their range of hypoallergenic, non–cobalt-chromium alloy implants to smaller sizes.

The limitations of this study include lack of data on the prevalence of patients who refused to fill in the form, possibly because of its length, as well as heterogeneity in patient indications. Another limitation is that many of the assumptions and questions raised in this study are based on evidence from lower extremity arthroplasty, which involves different etiologies and wear patterns, because the implants bear full body weight. Notwithstanding these limitations, this is the largest prospective study reporting the prevalence of metal hypersensitivity among patients with shoulder pathologies.

Conclusion

The present survey of 3217 patients identified 20% that reported hypersensitivity to 1 or more metals, the majority of whom were women, though only 2.2% had done cutaneous patch tests that could affirm this. Matching profiles of patients who had positive patch tests to those with no patch tests revealed that 9.4% of the total cohort had similar sex and self-reported metal hypersensitivities and could therefore be considered at risk of allergic reaction to metal implants. The factors associated with a positive cutaneous patch test were female sex, self-reported cutaneous allergy, and self-reported metal hypersensitivity. The clinical applicability of these estimates remains to be confirmed, however, as there is insufficient evidence that allergy to metal implants can be predicted with any certainty, by either the questionnaires used or the cutaneous patch tests.

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Supplementary Data

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