Publication: The Journal of Bone & Joint Surgery; JBJSExpress: F
Type: Scientific Articles; Volume: ; Issue:

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Degrees are correct; Fagnani and

Comment [RO4]: Please provide degrees, if appropriate, to be added for all authors. (Some degrees have already been added [here and in the byline] from your information in Editorial Manager; please confirm those.)

Ok, Orthopaedics

Comment [d5]: Should this be "Orthopaedics" (plural), here and in the Investigation line?

Ok email address

Comment [RO6]: OK to publish your e-mail address?

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Comment [d7]: Please provide a complete mailing address (including street and postal code).

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Does Overuse or Genetics Play a Greater Role in Determining Subacromial Space Width?

An MRI Study on Elderly Twins

Comment [d8]: OK as clarified?

"SUBACROMIAL SPACE WIDTH. DOES OVERUSE OR GENTICS PLAY A GREATER ROLE IN DETERMINING IT? AN MRI STUDY ON ELDERLY TWINS." This is our favourite title.

S. Gumina, MD, PhD, V. Arceri, MD, C. Fagnani, T. Venditto, MD, C. Catalano, MD, PhD, V. Candela, MD, and L. Nisticò
Investigation performed at the Departments of Orthopaedic and Traumatology, Rehabilitation, and Radiologic Sciences, University of Rome Sapienza, Rome, Italy

Comment [RO9]: Correct for where the work was performed?

Correct

Background:

Age and peripheral microcirculation disorders are the main causes of rotator cuff degeneration. A variant acromion shape may affect the width of the subacromial space, resulting in a pathological narrowing of the space that may compromise the cuff integrity. It is not clear whether the subacromial space width is genetically determined or changes according to loading conditions. To clarify this unresolved question, we performed an MRI (magnetic resonance imaging) study with the aim of evaluating the acromiohumeral distance in a group of elderly monozygotic and dizygotic twins, and we analyzed the obtained data using the twin design to separate the contributions of shared and unique environments.

Methods:

We identified twenty-nine pairs of elderly twins. On MRI scans, we evaluated the acromiohumeral distance and health status of the rotator cuff tendons. Heritability, defined as the proportion of total variance of a specific characteristic in a particular population due to a genetic cause, was estimated as twice the difference between the intraclass correlation coefficients for monozygotic and dizygotic pairs. The influence of shared environment, due to environmental factors that contribute to twin and sibling similarity, was calculated as the difference between the monozygotic correlation coefficient and the heritability index. One-way ANOVA (analysis of variance) was used to estimate the differences among job categories, both in the total cohort and within zygosity groups.

Results:

The intraclass correlation coefficient was substantially higher for monozygotic than for dizygotic twins, indicating a high degree of concordance of the acromiohumeral distance in pairs of individuals who shared 100% of their genes. The heritability index was 0.82, and shared and unique environmental contributions were both 0.09. There were no significant differences among subjects in different job categories, either in the total cohort ($p = 0.685$) or within the monozygotic ($p = 0.719$) and dizygotic groups ($p = 0.957$).

Conclusions:

The acromiohumeral distance is mainly genetically determined and only marginally influenced by external factors.

Level of Evidence:

Prognostic Level III. See Instructions for Authors for a complete description of levels of evidence.

Comment [d10]: OK as clarified?

No;
"Although in
a lower

Comment [d11]: OK as clarified?

Ok

Publication: The Journal of Bone & Joint Surgery; JBJSExpress: F
Type: Scientific Articles; Volume: ; Issue:

Rotator cuff tendinopathy occurs as a result of intrinsic and extrinsic factors. Age[1-3], altered biology[4,5], tendon hypovascularity[6-9], smoking[10,11], and tendon overloading and overuse[12,13] are generally accepted intrinsic factors. The latter are responsible for a series of cellular changes, particularly increases in matrix metalloproteinases and reductions in tissue inhibitors of metalloproteinases[14,15], nitric oxide synthases[16], and chondroid metaplasia[17]. All of these changes disturb the turnover rate and proliferation of collagen, leading to tendon degeneration and tenocyte apoptosis[18-20].

Rotator cuff tendinopathy related to distinct anatomical variants of the scapular shape is usually also considered to be due to extrinsic factors. According to the extrinsic theory, anatomical structures are responsible, in a dynamic fashion, for degenerative changes observed in shoulders with subacromial impingement[21].

In the absence of a rotator cuff tear, narrowing of the subacromial space may be the consequence of a tight posterior glenohumeral capsule[22], aberrant scapular muscle activity in the shoulder girdle[23-25], scapular dyskinesis[26], thoracic hyperkyphosis[27], adaptive shortening of the pectoralis minor[28-30], or acromioclavicular joint arthritis[31]. However, extrinsic mechanisms for rotator cuff tendinopathy mostly involve anatomical variables (primarily in the anterior aspect of the acromion) that may pathologically influence the subacromial space. The literature includes a huge number of articles regarding the shape[32,33] and slope[34,35] of the acromion, the acromion index[36], and the degree of acromial coverage[37]; however, even today, it remains unclear whether the subacromial space width is primarily genetically determined (and only in part influenced by external factors) or changes over time according to the loads to which the shoulder is subjected (regardless of genetic predisposition).

To clarify this unresolved question, we compared the subacromial space width between elderly monozygotic (identical) and dizygotic (fraternal) twins, and we used the twin study design[38] to separate the contributions of shared and unique environments.

Materials and Methods

Thanks to collaboration with the Genetic Epidemiology Unit of the National Institutes of Health, we recruited the study cohort from the Italian Twin Registry (ITR). This is a population-based registry established in 2001 with the main purpose of using twin data to investigate hereditary and environmental factors that contribute to phenotypic expression of normal and/or pathological human characteristics[39]. The ITR research activities have been approved by the Ethical Committee of the Istituto Superiore di Sanità.

From this database, we identified fifty pairs of twins in the same age range (fifty to seventy-five years) as most patients who are treated surgically for a rotator cuff tear[40].

"the latter" is referred to the INTRINSIC FACTORS

Comment [d12]: "These extrinsic factors"? (If not, please specify how many of the factors at the end of the list in the previous sentence "latter" refers to.)

Comment [d13]: As phrased, "reductions in" appears to refer to all three of the subsequent phrases in the sentence.
Is that correct, or do you mean "reductions in tissue inhibitors of metalloproteinases[14,15], increases in nitric oxide synthases[16], and chondroid metaplasia[17]"?

CORRECT: "reductions in tissue inhibitors of metalloproteinases14,15

Comment [d14]: OK as changed from "synthetases", per the title of ref. 16?

ok

Comment [d15]: This appears to state that atomic structures dynamically cause generation. Is that correct, or do you mean ynamically caused changes in anatomical uctures are responsible"?

The sentence is well written.

Comment [d16]: Clarification correct as dded?

Ok

Comment [d17]: "Register", per the title of ref. 39?

Register

Twin pairs in which at least one member had a history of glenohumeral or moderate to severe acromioclavicular arthropathy, shoulder fracture, rheumatoid disease or other autoimmune disease, glenohumeral or acromioclavicular instability, adhesive capsulitis, or rotator cuff tear were excluded. Twin pairs in which one or both members had been retired for more than five years were also excluded from the study, as were opposite-sex dizygotic twin pairs. The remaining twins who were willing to sign an informed consent form describing the aims and procedures of the study were included in the analysis. Zygosity was ascertained by comparing the genotypes of nine tetranucleotide multiallelic markers between the twins of each pair (accuracy, 99.98%).

The acromiohumeral distance and rotator cuff status (structural and qualitative condition) of the dominant shoulder were assessed by MRI (magnetic resonance imaging) (MAGNETOM Avanto Medical 76x32; Siemens). Oblique coronal, oblique sagittal, and axial T2-weighted spin-echo MRI scans (repetition time, 3200 ms; echo time, 85 ms) were obtained for the shoulders of all subjects. Coronal oblique shoulder images were in a plane parallel to the supraspinatus tendon. The patients were examined in the supine position with the arm at the side, the palm facing up, and the hand under the hip to keep the shoulder motionless.

The acromiohumeral distance was measured for each subject by three different physicians to assess inter-rater reliability. The assessors performed their evaluations one to twenty-four hours apart without knowledge of each others' assessments. The acromiohumeral distance was calculated in the coronal oblique projection as the distance between the most caudal point of the lower surface of the acromion and the most cranial point of the proximal aspect of the humerus.

One of the authors interviewed all participants about employment, recording specific information regarding both type and duration. Occupations were divided in three groups: "heavy manual workers" (cleaners, laborers, craft workers, transportation workers, and equipment operators), "administrative support workers" (administrative workers, technicians, and housewives), and "professional workers" (professionals and managers).

A flowchart of enrolled participants is shown in Figure 1.

Statistical Analysis

Power calculations were based on the correlation coefficient of the acromiohumeral distance. Assuming a Pearson correlation coefficient of 0.7, a two-tailed α value of 0.05 (sensitivity = 95%), and a β value of 0.20 (study power = 80%), we determined that at least fourteen twin pairs were required in the study (G*Power software, version 3; Universität Düsseldorf).

All data were analyzed by a single blinded researcher with use of SPSS software (version 18; SPSS, Chicago, Illinois). Calculated p values were two-sided, with $p < 0.05$ considered

"Or" is correct

Comment [d18]: Please confirm that "or" is correct here and elsewhere in this sentence. (You had "and".)

Ok,Correct as edited

Comment [d19]: Correct as edited, per Fig. 1? (Your original phrasing implied that *all* of the remaining twins consented to inclusion.)

Comment [d20]: Please confirm; I was not able to find this portion of the product name on the Siemens web site.

Confirmed

Comment [O21]: Were the assessors blinded to which group the twin belonged to?
-Marc Swiontkowski, MD

Yes, they were blinded.

Ok, correct.

Comment [d22]: The group names have been changed from A, B, and C since you did not refer to those letters again later. Correct as edited?

Comment [d23]: Correct as added?

Ok, correct.

Correct as it is.

Comment [d24]: Correct as is, or should "of each type" be added here?

Comment [d25]: Correct as edited and expanded?

ok, correct as edited.

significant, and all results are reported with a 95% confidence interval (CI).

The intraclass correlation coefficient (ICC), with a 95% CI, was calculated to assess reliability. In particular, the ICC(3,2,1) was used to determine inter-rater reproducibility. The ICC, which is the most suitable statistical test for the assessment of reliability, can range from 0 to 1; 0.00 to 0.25 indicates little or no correlation, 0.26 to 0.49 indicates low correlation, 0.50 to 0.69 indicates moderate correlation, 0.70 to 0.89 indicates high correlation, 0.90 to 0.99 indicates very high correlation, and 1 indicates perfect reliability[41-43].

Differences in means according to zygosity were evaluated with a pooled t test.

Heritability (h2), defined as the proportion of total variance of a specific characteristic in a particular population due to a genetic cause, was estimated as twice the difference between the intraclass correlation coefficient (r) for monozygotic (MZ) pairs and that for dizygotic (DZ) pairs ($h2 = 2[r_{MZ} - r_{DZ}]$)[44]. The shared environmental influence (c2), due to environmental factors that contribute to twin and sibling similarity, was estimated as the difference between the monozygotic intraclass correlation coefficient and the heritability index ($c2 = r_{MZ} - h2$). The unique environmental influence (e2), due to environmental factors that contribute to differences between twins and between siblings, was estimated as the difference between 1 and the monozygotic intraclass correlation coefficient ($e2 = 1 - r_{MZ}$).

We divided the subjects into three categories of employment: heavy manual workers, administrative support workers, and professionals. One-way ANOVA (analysis of variance) was used to estimate the differences among the three job types, both in the total cohort and within the monoyzgotic and dizygotic twin groups.

Source of Funding

No external funding was received for this study.

Results

Twenty-nine of the fifty twin pairs met the inclusion criteria and were analyzed. Their mean age (and standard deviation) was 63.72 ± 3.37 years (range, fifty-three to seventy-two years). Fifteen were monozygotic pairs (mean age, 63.66 ± 4.32 years; range, fifty-three to seventy-two years), and fourteen were dizygotic pairs (mean age, 63.78 ± 1.96 years; range, sixty to sixty-six years). The baseline characteristics of the subjects are reported in Table I.

The inter-rater reproducibility was high, with an ICC(3,2,1) value of 0.784 (95% CI, 0.692 to 0.856). The mean of the three acromiohumeral distance measurements was 10.20 ± 1.53 mm in the monozygotic twin pairs and 9.61 ± 1.86 mm in the dizygotic twin pairs (p = 0.197).

The sentence is ok.

Comment [d26]: You also refer to reliability, including "inter-rater reliability". If you would prefer to make such phrasing more consistent, please indicate the desired changes.

Ok, as edited.

Comment [d27]: "correlation", for consistency?

Comment [d28]: In the tables you refer to heritability as "H".
Should this be "h" (or "H"), "h2" (or "H2"), or "h^2" (or H^2") in this section?

Similarly, please indicate if any changes in c2 and e2 are needed.

Ok, it can be deleted.

Comment [d29]: OK to delete this sentence, since it was described in more detail at the end of the previous section?

Comment [d30]: OK?

Ok

Comment [d31]: Table I gives slightly different values. Please make consistent.

The correct values are those of Table I.

Intraclass correlation coefficients of the acromiohumeral distance for the monozygotic and the dizygotic twins are reported in Table II. The intraclass correlation coefficient was consistently high for the monozygotic twins, indicating a high degree of concordance for the acromiohumeral distance in individuals who shared 100% of their genes. The dizygotic twins showed a lower correlation, which indicated a lower concordance in this group of twins who shared, on average, 50% of their genes. The difference in correlation between monozygotic and dizygotic twins suggested strong genetic influences on the acromiohumeral distance. In accordance with that result, the calculated heritability index was 0.82, while the contributions of shared and unique environment were both 0.09.

The acromiohumeral distance value was 9.91 ± 1.88 mm in the twenty-seven subjects in the heavy manual worker group, 9.70 ± 1.66 mm in the nineteen subjects in the administrative support worker group, and 10.26 ± 1.50 mm in the twelve subjects in the professional worker group; the differences among the groups were not significant ($p = 0.685$). In the monozygotic twins, the acromiohumeral distance was 10.25 ± 1.88 mm in the heavy manual worker group, 9.88 ± 2.30 mm in the administrative support worker group, and 10.60 ± 1.31 mm in the professional worker group ($p = 0.719$). In the dizygotic twins, the acromiohumeral distance was 9.55 ± 1.89 mm in the heavy manual worker group, 9.60 mm ± 0.80 mm in the administrative support worker group, and 9.80 ± 1.79 mm in the professional worker group ($p = 0.957$) (Table III).

Discussion

Our understanding of the role of extrinsic factors in the genesis of rotator cuff impingement syndrome and tears is changing, strengthening the hypothesis that tendon degeneration, principally caused by age and peripheral microcirculation disorders, is the primary cause of the rotator cuff tear[1-3,6-9].

Anatomical variants of the scapular apophysis may affect the width of the subacromial space, in extreme cases resulting in a pathological narrowing of the space that may jeopardize the health status of the rotator cuff tendons.

More than forty years ago, Neer hypothesized that the presence of a spur at the anteroinferior aspect of the acromion might be the main cause of mechanical abrasion between the rotator cuff and the coracoacromial arch[45]. Subsequently, Bigliani et al.[32] classified the acromion shape into three patterns that were more or less prone to rotator cuff tendinopathy. A higher prevalence of rotator cuff tears was also attributed to a flatter slope of the acromion and to a decreased lateral acromial angle[34,35]. Oh et al.[46] classified acromial spurs into distinct morphologies and suggested that the most common heel-type spur might be a risk factor for full-thickness rotator cuff tears.

Comment [d32]: Correct as added?

ok, correct as added.

Even though many years have passed since these milestone publications, we still debate whether the subacromial space width (primarily the result of the acromion shape) is influenced by possible overloading or is genetically determined. Wang and Shapiro[47] were proponents of the first hypothesis, observing that the shape of the acromion progressed from flat to curved or hooked as age increased. Analogously, in 2001, Shah et al.[48] conducted a macroscopic, radiographic, and histologic study on eighteen cadaveric shoulders (twelve pairs from six cadavers and six unpaired) and observed a common pattern of degeneration of collagen, fibrocartilage, and bone in all of the curved and hooked acromions. Therefore, they concluded that the shape of the acromion is acquired in response to traction forces applied via the coracoacromial ligament and is not congenital in origin. However, the results of both publications lacked supporting statistical analysis and did not provide information on the impact of the various acromion shapes on the subacromial space. In addition, the authors did not provide information on the limb dominance or occupation of the subjects. Mahakkanukrauh and Surin[49] supported the same theory. They performed an anatomical study on 346 skeletons and observed that occurrence of acromial osteophytes and increasing age were significantly correlated; furthermore, no sex differences were noted in the frequency of osteophytes.

The main purpose of our study was to assess the influence of genetic factors on the acromiohumeral distance; therefore, we conducted an MRI study on elderly monozygotic and dizygotic twins. Studies on twins provide a useful tool to evaluate the contribution of genes and environment on the disease or trait of interest[50].

As the reliability of acromiohumeral distance measurements made using radiographs has not been supported by the studies that we reviewed[50], an MRI assessment was preferred. Furthermore, a recent study found that the acromiohumeral distance better reflected the clinical status of patients with subacromial impingement than the acromial shape did[51].

We evaluated dizygotic twins as the control rather than a common control group, because this is required to estimate the heritability according to the twin methodology[38] and also because non-twin siblings would have posed an additional issue of age differences, which could influence the results.

In the case of quantitative traits, the phenotypic similarity between twins is estimated by the intraclass correlation coefficient. For the acromiohumeral distance, we determined this by the correlation of the values within each pair of twins. The resulting heritability index showed genetic factors to be the main cause of the variability of the acromiohumeral distance, with shared and unique environmental factors contributing only slightly to the variability.

The role of genetic factors is also supported by the results of the acromiohumeral distance comparisons of the three groups of

Comment [d33]: Should this be ref. 38? (Ref. 50 is a systematic review on the best way to perform AHD measurements.)

Yes, it is reference 38.

Comment [d34]: "more general"? "more typical"?

"more general"

workers. No significant differences were found among groups who performed or had performed different types of labor. This was confirmed both in the whole study cohort and within the monozygotic and dizygotic subjects. These data appear to be partially in contrast with those of Frost and Andersen[52], who observed that shoulder-intensive work was a risk factor for impingement syndrome. Analogously, van Rijn et al.[53] noted that highly repetitive work was associated with the occurrence of subacromial impingement, and Roquelaure et al.[54] observed that skilled blue-collar workers were more likely to develop subacromial impingement, especially if forced to abduct the arm repeatedly. Finally, in a longitudinal study, Svendsen et al.[55] showed that forceful work, work with elevated arms, and repetitive work each doubled the risk of surgery for subacromial impingement.

Our study suggests that the anatomical features that influence the width of the subacromial space are mainly genetically determined. However, if the subacromial space is already constitutionally narrow, external factors would strongly contribute to further reduction of the space, making it too tight. This might occur as a consequence of the ossification of the acromial insertion of the coracoacromial ligament[45]; of contracture of the posterior capsule of the glenohumeral joint, which would lead to upward migration of the humeral head[22,56,57]; or of scapular muscle performance deficits[26].

The low number of twin pairs in our study did not allow us to apply quantitative genetic models[58] to estimate the heritability by taking into account individual differences in age and sex as well as relevant environmental exposures such as work activities. It would be interesting to evaluate the results of our study according to genre belonging, but the sample size would be too small. This heterogeneity is not considered a potential source of error, as the aim of the study was to evaluate the differences between monozygotic and dizygotic twins.

In conclusion, the acromiohumeral distance is primarily genetically determined and is less influenced by external factors.

It was impossible

Yes, the

Comment [d35]: Please clarify.

Comment [d36]: Please clarify. ("The heterogeneous nature of the study cohort"?)

Comment [d37]: OK as changed from "homozygotic"?

Ok, as changed

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Comment [d38]: Correct as added?

Correct as added

Fig. 1
Flow of participants through the trial. GH = glenohumeral, AC = acromioclavicular, MZ = monozygotic, and DZ = dizygotic.

TABLE I Baseline Characteristics of the Cohort

	MZ Twins* (N = 30†)	DZ Twins* (N = 28‡)	P Value
Age *(yr)*	63.66 ± 4.32 (53-72)	63.78 ± 1.96 (60-66)	
Female	62.40 ± 6.3 (53-72)	63.77 ± 2.03 (60-66)	0.264
Male	64.30 ± 2.86 (61-71)	63.80 ± 1.83 (61-66)	0.978
Acromiohumeral distance *(mm)*	10.13 ± 1.70	9.69 ± 1.74	0.197

*The values are given as the mean and standard deviation, with or without the range in parentheses. †10 female and 20 male. ‡18 female and 10 male.

Comment [d39]: All tables OK as edited for clarity?

Ok as edited.

Comment [d40]: Correct as transposed? (For example, you has had 18 female + 10 male MZ twins = 28.)

Ok as edited

TABLE II Summary of Acromiohumeral Distance Heritability Analysis*

MZ Twins				DZ Twins				
	P Value of Mean Squares				P Value of Mean Squares			
Mean Difference *(mm)*	Within Pairs	Among Pairs	ICC	Mean Difference *(mm)*	Within Pairs	Among Pairs	ICC	Heritability
−0.13	<0.001	0.450	0.91	0.10	<0.001	0.849	0.50	0.82

*MZ = monozygotic, DZ = dizygotic, and ICC = intraclass correlation coefficient.

Comment [d41]: Correct as added?

Correct as added

TABLE III: Acromiohumeral Distance (AHD) Differences According to Occupation

	Monozygotic Twins		Dizygotic Twins	
Occupation*	AHD† *(mm)*	P Value	AHD† *(mm)*	P Value
HMW	10.25 ± 1.88	0.842 vs. ASW	9.55 ± 1.89	1.00 vs. ASW
ASW	9.88 ± 2.30	1.00 vs. PW	9.60 ± 0.80	1.00 vs. PW
PW	10.60 ± 1.31	1.00 vs. HMW	9.80 ± 1.79	1.00 vs. HMW

*HMW = heavy manual workers, ASW = administrative support workers, and PW = professional workers. †The values are given as the mean and standard deviation.

Comment [d42]: Please check whether the p values in this table are correct.
Five of the six are >0.995.
Also, you indicate p = 0.842 for the difference between 9.88 and 10.25, but 1.00 for the larger difference between 9.88 and 10.60.

p values are correct

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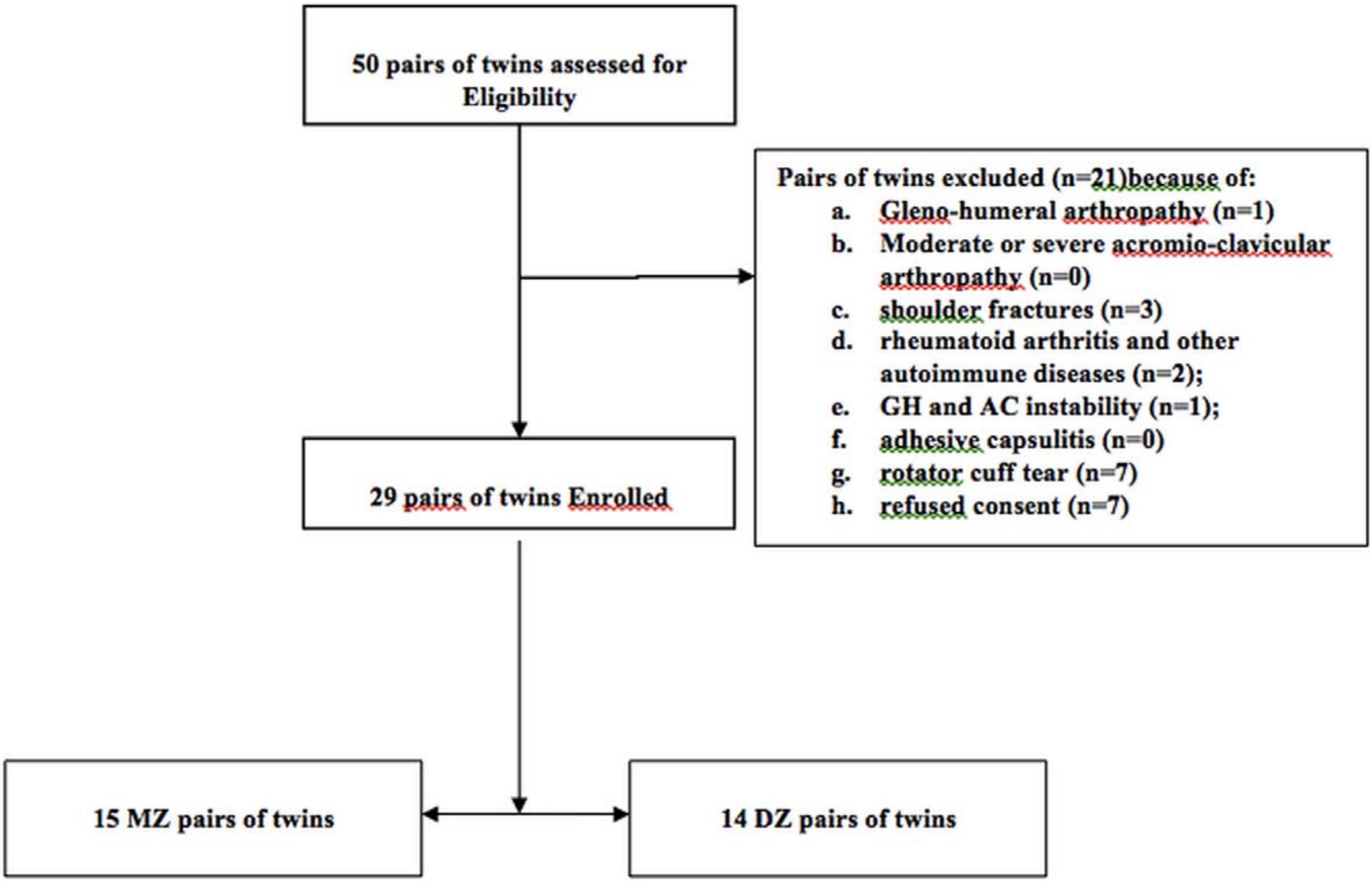

50 pairs of twins assessed for Eligibility
Pairs of twins excluded (n=21)because of:
a. Gleno-humeral arthropathy (n=1)
b. Moderate or severe acromio-clavicular arthropathy (n=0)
c. shoulder fractures (n=3)
d. rheumatoid arthritis and other autoimmune diseases (n=2);
e. GH and AC instability (n=1);
f. adhesive capsulitis (n=0)
g. rotator cuff tear (n=7)
h. refused consent (n=7)
29 pairs of twins Enrolled
15 MZ pairs of twins
14 DZ pairs of twins

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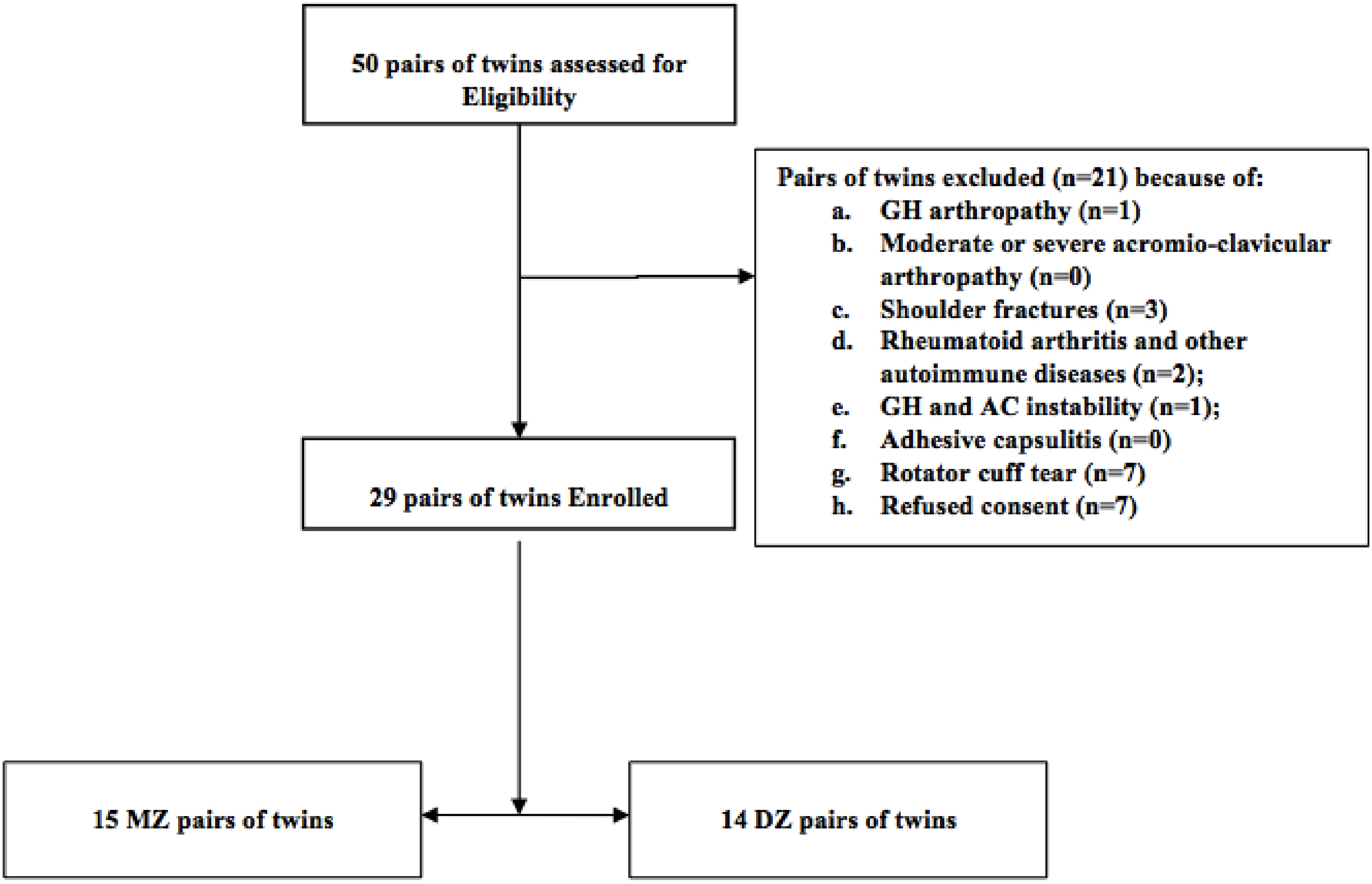

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Does Overuse or Genetics Play a Greater Role in Determining Subacromial Space Width? An MRI Study on Elderly Twins

1. The adaptive shortening of which muscle is responsible for narrowing of the subacromial space?

A. deltoid

B. pectoralis major

C. pectoralis minor

D. biceps long head

Location of Answer: In the absence of a rotator cuff tear, narrowing of the subacromial space may be the consequence of a tight posterior glenohumeral capsule, aberrant scapular muscle activity in the shoulder girdle, scapular dyskinesis, thoracic hyperkyphosis, adaptive shortening of the pectoralis minor, or acromioclavicular joint arthritis.

2. The ossification of which ligament is responsible for a narrowing of the subacromial space?

A. coracoacromial ligament

B. superior glenohumeral ligament

C. coracoclavicular ligaments

D. superior acromioclavicular ligament

E. inferior glenohumeral ligament

Location of Answer: Our study suggests that the features of the anatomical structures that influence the subacromial space width are mainly genetically determined. However, if the subacromial space is already constitutionally narrow, external factors would strongly contribute to further reduce the space, making it too tight. This might occur as a consequence of the ossification of the acromial insertion of the coracoacromial ligament; through the contracture of the posterior capsule of the glenohumeral joint, which would lead to upward migration of the humeral headl or because of scapular muscle performance deficits.